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Abstract

Adding emollient bath additives to standard eczema management for children with eczema: the BATHE RCT

Miriam Santer,[1]* Kate Rumsby,[1] Matthew J Ridd,[2] Nick A Francis,[3] Beth Stuart,[1] Maria Chorozoglou,[4] Amanda Roberts,[5] Lyn Liddiard,[2] Claire Nollett,[6] Julie Hooper,[1] Martina Prude,[1] Wendy Wood,[7] Emma Thomas-Jones,[3] Taeko Becque,[1] Kim S Thomas,[5] Hywel C Williams[5] and Paul Little[1]

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Background: Childhood eczema is very common. Treatment often includes emollient bath additives, despite there being little evidence of their effectiveness.

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

Design: Pragmatic, randomised, open-label, multicentre superiority trial with two parallel groups.

Setting: Ninety-six general practices in Wales, the west of England and southern England. Invitation by personal letter or opportunistically.

Participants: Children aged between 12 months and 12 years fulfilling the UK Diagnostic Criteria for Atopic Eczema. Children with inactive or very mild eczema (a score of ≤ 5 on the Nottingham Eczema Severity Scale) were excluded, as were children who bathed less than once per week or whose parents/carers were not prepared to accept randomisation.

Interventions: The intervention group were prescribed 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 standard eczema management, including regular leave-on emollients and topical corticosteroids (TCSs) when required.

Main outcome measures: The primary outcome was eczema control measured by Patient Oriented Eczema Measure [POEM, 0 (clear) to 28 (severe)] weekly for 16 weeks. The secondary outcomes were eczema severity over 1 year (4-weekly POEM), number of eczema exacerbations, disease-specific quality of life (QoL) (Dermatitis Family Impact Questionnaire), generic QoL (Child Health Utility-9 Dimensions) and type and quantity of topical steroid/calcineurin inhibitors prescribed. Children were randomised (1 : 1) using online software to either bath additives plus standard eczema care or standard eczema care alone, stratified by recruiting centre, and there was open-label blinding.

Results: From December 2014 to May 2016, 482 children were randomised: 51% were female, 84% were white and the mean age was 5 years ($n = 264$ in the intervention group, $n = 218$ in the control group). Reported adherence to randomised treatment allocation was > 92% in both groups, with 76.7% of participants completing at least 12 (80%) of the first 16 weekly questionnaires for the primary outcome. Baseline POEM score was 9.5 [standard deviation (SD) 5.7] in the bath additives group and 10.1 (SD 5.8) in the no bath additives group. Average POEM score over the first 16 weeks was 7.5 (SD 6.0) in the bath additives group and 8.4 (SD 6.0) in the no bath additives group, with no statistically significant difference between the groups. After controlling for baseline severity and confounders (ethnicity, TCS 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% confidence interval –0.27 to 1.10), which is well below the published minimal clinically important difference of 3 points. There was no difference between groups in secondary outcomes or in adverse effects such as redness, stinging or slipping.

Limitations: Simple randomisation resulted in an imbalance in baseline group size, although baseline characteristics were well balanced between groups.

Conclusion: This trial found no evidence of clinical benefit of including emollient bath additives in the standard management of childhood eczema.

Future work: Further research is required on optimal regimens of leave-on emollients and the use of emollients as soap substitutes.

Trial registration: Current Controlled Trials ISRCTN84102309.

Funding: This project was funded by the NIHR Health Technology Assessment Programme and will be published in full in *Health Technology Assessment*; Vol. 22, No. 57. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

Glossary

Bath additive/bath emollient Emollients to be added to bath water. Not to be confused with leave-on emollients (applied directly to the skin) or soap substitute emollients (used instead of soap).

CFH Docmail Ltd A company that provides secure mass mailing at reduced cost. Compliant with the latest international data security standards, Docmail has been used extensively within the NHS for many years.

Clinical studies officer/research nurse Staff employed by the academic/health-care institutions that are hosting the study to recruit participants. Research nurses also have clinical qualifications.

Confidence interval In statistics, a range around a measurement that estimates its precision.

Good clinical practice for clinical trials An international system of accreditation whereby the rights, safety and well-being of research participants are protected and research data are of the highest quality.

Health Technology Assessment programme A National Institute for Health Research funding stream that supports research of immediate benefit to patients, clinicians and policy-makers.

LifeGuide Customisable online software to support health interventions, established by the Department of Psychology at the University of Southampton.

National Institute for Health Research A division of the Department of Health and Social Care that supports health-care research in the UK.

National Institute for Social Care and Health Research Now Health and Care Research Wales, this organisation of the Welsh Government supports health-care research and development in Wales.

No bath additives Standard eczema care without bath additives (control group).

Serious adverse event In human drug trials, any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalisation or causes prolongation of existing hospitalisation. A serious adverse event is not necessarily related to the product under investigation.

Standard deviation A statistical measurement that quantifies the dispersion of measurements around the mean.

List of abbreviations

A&E	accident and emergency
ANOVA	analysis of variance
BATHE	Bath Additives for the Treatment of Eczema in cHildren
CCG	Clinical Commissioning Group
CEBD	Centre for Evidence-Based Dermatology
CHU-9D	Child Health Utility-9 Dimensions
CI	confidence interval
CRN	Clinical Research Network
CSO/RN	clinical studies officer/research nurse
CSRI	Client Service Receipt Inventory
DFIQ	Dermatitis Family Impact Questionnaire
EEACT	economic evaluations alongside clinical trials
EQ-5D	EuroQol-5 Dimensions
FbC	family-borne cost
GP	general practitioner
HEAP	health economics analysis plan
HOME	Harmonising Outcome Measures for Eczema
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ITT	intention to treat
MMLM	mixed multilevel model
NESS	Nottingham Eczema Severity Score
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NISCHR	National Institute for Social Care and Health Research
NR	notes review
NSGCCE	Nottingham Support Group for Carers of Children with Eczema
OR	odds ratio
POEM	Patient Oriented Eczema Measure
PPI	patient and public involvement
PSP	Priority Setting Partnership
QALY	quality-adjusted life-year
QoL	quality of life
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedure
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
UKDC	UK Diagnostic Criteria for Atopic Dermatitis

Plain English summary

Eczema is very common in children and can have a significant impact, causing itching and sleep problems. The main treatments are emollients, which are used to moisturise the skin, and steroid creams or ointments to treat flare-ups. Guidelines have suggested that people with eczema should use 'complete emollient therapy', including an emollient for washing (soap substitute), an emollient applied directly to the skin (leave-on emollient) and an emollient liquid added to the bath (bath additive). However, there is little evidence to show that using bath additives is helpful. This trial measured whether or not bath additives help children with the symptoms of eczema.

Children with eczema aged between 1 and 11 years were all given standard eczema management. Half of the children were also asked to use a bath additive, and this was decided at random. Bath additives were prescribed by the child's general practitioner (GP). We suggested that children used Oilatum® (Stiefel Skin Science Solutions, a GlaxoSmithKline company, Middlesex, UK), Balneum® (Almirall Ltd, Middlesex, UK) or Aveeno® (Johnson & Johnson Ltd, Maidenhead, UK) bath additives, as these are the most frequently prescribed, but parents/carers and GPs could choose an alternative.

Parents/carers completed short questionnaires about their child's eczema severity weekly for the first 16 weeks, then every 4 weeks from weeks 16 to 52. We asked parents/carers about any side effects or difficulties they had in using the treatment and whether or not they used any additional treatments. We also checked how many flare-ups of eczema were recorded in their GP records over 1 year and what treatments had been prescribed.

A total of 482 children from 96 general practices took part in the study. We found no difference between the two groups, either in eczema severity or in problems, such as stinging, redness or slipping.

The Bath Additives for the Treatment of Eczema in cHildren (BATHE) trial found that, although emollient bath additives are safe, they are not a useful additional treatment for children who are receiving standard eczema care, such as using leave-on emollients and emollients as soap substitutes.

Scientific summary

Background

Childhood eczema is a common condition that can have a substantial impact on quality of life for both the child and their family. Guidelines state that the regular application of emollients should form the mainstay of eczema treatment, with other treatments, such as topical corticosteroids (TCSs), used in addition for flare-ups. Emollients are thought to help by providing a barrier over the skin, decreasing moisture loss and protecting against skin irritants.

There are three methods of application of emollients: (1) leave-on emollients, in which emollients are applied to the skin and left to soak in; (2) soap substitutes, in which emollients are used instead of soap or other washing products; and (3) bath additives, which are oil and/or emulsifiers designed to be added to bath water. All three emollient types can be used together ('complete emollient therapy') and some emollient products can be used for more than one method of application. In this report the term 'bath additives' rather than 'bath emollients' is used in order to emphasise the differences between the three methods of application (i.e. these three methods differ in their proposed actions, and evidence relating to their effectiveness should also be considered separately).

Although there is widespread clinical consensus on, and some evidence for, the value of leave-on emollients and soap substitutes, there is less agreement regarding the potential additional benefits of bath additives and there is a dearth of evidence of their clinical effectiveness and cost-effectiveness. Systematic reviews have found no evidence of their effectiveness and one small study has suggested that they may indeed worsen eczema outcomes. However, despite the absence of evidence for their benefit, bath additives are widely prescribed for childhood eczema and cost the NHS > £23M annually.

Objective

We aimed to determine the clinical effectiveness and cost-effectiveness of bath additives in addition to standard management of atopic eczema in children.

Methods

Trial design

A pragmatic, randomised, open-label, multicentre superiority trial with two parallel arms.

Setting and recruitment

Ninety-six general practices in Wales, the west of England and southern England. Invitation was by personal letter or opportunistically by usual clinical team.

Eligibility criteria

Children were eligible to participate if aged between 12 months and 12 years and if they had eczema according to the UK Diagnostic Criteria for Atopic Eczema. Children with inactive or very mild eczema over the past 12 months, defined as a score of ≤ 5 on the Nottingham Eczema Severity Scale, were excluded, as were children who usually had a bath less than once per week or whose carers were not prepared for the child to be randomised. Only one child per family was enrolled.

Interventions

The intervention group members were prescribed bath additives by their usual clinical team and were asked to use them regularly for 12 months. We encouraged practices to issue Oilatum® (Stiefel Skin Science Solutions, a GlaxoSmithKline company, Middlesex, UK), Balneum® (Almirall Ltd, Middlesex, UK) or Aveeno® (Johnson & Johnson Ltd, Maidenhead, UK), which are the most frequently prescribed bath additives in the UK. Other bath additives could be issued on the basis of parent or prescriber preference, except for those products that contain antimicrobials or antipruritics as these can have an irritant effect greater than other bath additives. The control group were asked not to use any bath additives for 12 months. Both groups were advised to continue with standard eczema management, which includes the regular application of leave-on emollients and TCSs when required.

Outcomes

Primary outcome

Eczema severity was assessed by repeated measures of the Patient Oriented Eczema Measure (POEM), reported weekly, by parent/carer over 16 weeks. The POEM score range is from 0 (clear) to 28 (severe).

Secondary outcomes

- Eczema severity measured by POEM every 4 weeks from weeks 16 to 52.
- Disease-specific quality of life (QoL) at 16 weeks and at 1 year, measured by the Dermatitis Family Impact Questionnaire.
- Generic QoL at 16 weeks and at 1 year, measured by the Child Health Utility-9 Dimensions (CHU-9D).
- Number of eczema exacerbations resulting in a primary health-care consultation over 1 year [general practitioner (GP) notes review].
- Type (strength) and quantity of topical steroid/calcineurin inhibitors prescribed over 1 year (GP notes review).

Other outcomes

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

Sample size

The sample size was calculated for repeated measures analysis of variance in weekly POEM scores over 16 weeks. We aimed to detect a mean difference of 2.0 [standard deviation (SD) 7.0] between the intervention and control groups. An alpha of 0.05 and power of 90% with a correlation between repeated measures of 0.70 gave a sample size of 338 participants. Allowing for a 20% loss to follow-up, this gave a total sample size of 423 participants.

Early data suggested that approximately 80% of participants in both groups were strictly adherent to treatment allocation. Therefore, to report a per-protocol analysis with 90% power, in addition to the primary intention-to-treat analysis, we submitted an ethics amendment requesting recruitment of an additional 68 participants, giving a revised target recruitment of 491 participants.

Randomisation and blinding

Children were randomised in a 1 : 1 ratio to either standard eczema care plus bath additives or standard eczema care only, using online software following simple randomisation stratified by recruiting centre. This was an open-label trial.

Statistical methods

The primary analysis for the total POEM score was performed using a mixed multilevel model (MMLM) framework, with observations over time from weeks 1 to 16 (level 1) nested within participants (level 2) nested within centres (level 3). The primary outcome was based on adjusted results, controlling for baseline POEM, recruiting centre and any significant confounders. Unadjusted results are also reported.

Health economics

The aim of the health economic component was an assessment of the economic impact of the intervention on both the NHS and parents at 16 weeks and 52 weeks post randomisation. The costs included in the analysis relate to the primary and secondary care consultations, including accident and emergency, hospitalisations and use of medications. Family-borne costs (FbCs) were those associated with increased household expenditure because of the child's eczema. Quality-adjusted life-years (QALYs) were estimated using the paediatric QoL measure CHU-9D. Results were presented in the form of cost–consequences analysis and a MMLM framework was used and presented adjusted results for baseline POEM and recruiting centre.

Results

Invitations were sent to the parents/carers of 12,504 children and responses were received from 1451. There were 920 replies expressing a willingness to be contacted and including a completed screening questionnaire. Of these, 662 children met eligibility criteria and were approached regarding participation, with 483 children entering the trial. One carer subsequently withdrew permission to use their data. Analysis was thus carried out on data from 482 participants (intervention group, $n = 264$; control group, $n = 218$).

Baseline characteristics

The questionnaire completion rate was high, with 76.7% of participants completing > 80% of the time points for the primary outcome (12 out of 16 weekly questionnaires from week 1 to 16).

In the bath additives group, 73.8% of participants reported that they used a bath additive every time the participant had a bath and a further 19% reported using bath additives more than half of the time. In the no bath additives group, 87.4% of participants reported that they had never used a bath additive in the bath, and an additional 4.7% reported using them less than half of the time.

Primary outcome

The baseline POEM score was 9.5 (SD 5.7) in the bath additives group and 10.1 (SD 5.8) in the no bath additives group. The average POEM score over the 16-week period was 7.5 (SD 6.0) in the bath additives group and 8.4 (SD 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, TCS use and soap substitute use) and allowing for the clustering of patients within centres and responses within patients over time, the POEM score in the no bath additive group was 0.41 points higher than in the bath additive group [95% confidence interval (CI) –0.27 to 1.10], which is substantially lower than the published minimal clinically important difference of 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; 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].

There was no significant difference between groups in any of the secondary outcomes or in adverse effects such as redness, stinging or slipping.

Health economics

The individual costs were estimated alongside individual QALYS and presented in the form of mean (SD) values per study group. The 95% CIs around differences were also reported. The mean annual costs were estimated at £180.50 (SD £237) for the bath additives group and £166.12 (SD £293) for the no bath additives group. Similarly, the annual results for QALYs were 0.91 (SD 0.1) and 0.90 (SD 0.1) for the bath additives and the no bath additives group, respectively. The difference in mean cost was £14.38 (95% CI –£33.45 to £62.21) and in mean QALYs was 0.00 (95% CI –0.01 to 0.02). Across all the measures considered within the economic evaluation, there is only one statistically significant cost difference between the trial groups, relating to the 16-week result for which the cost difference was £20.89 (95% CI –£39.13 to –£2.65) in favour of the intervention group; this difference was not sustained in the 52-week results. The FbCs showed an annual increase in spending within the no bath additives group of £51.37 (95% CI –£118.49 to £15.74), which was not statistically significant. The economic analysis considered a comprehensive health profile to assess the cost-effectiveness of bath additives when used for childhood eczema. The analysis found no benefits that could be used to consider the intervention cost-effective. In fact, there were no significant differences observed in any economic outcome between the trial groups to alter this conclusion.

Discussion

This is the first large pragmatic trial on the role of bath additives. Published case series and case reports have not been strongly suggestive of beneficial effect. This trial provides the strongest evidence to date that emollient bath additives provide little additional benefit beyond standard eczema care in the management of childhood eczema.

The Bath Additives for the Treatment of Eczema in cHildren (BATHE) trial was an adequately powered randomised controlled trial, with high follow-up/questionnaire completion 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.

This was an open trial, as it is not possible to create a convincing placebo for bath additives, with a primary outcome measure that was participant reported, as our main concern was with the impact of symptoms. An unblinded trial with a participant-reported outcome could be biased in favour of finding a treatment effect because of a perception of positive benefits of treatment. However, the negative result of the trial suggests that this was not the case.

These findings are timely for clinicians and prescribing advisers in England, as many Clinical Commissioning Groups are currently reviewing emollient prescribing guidelines in order to reduce costs. However, there is currently very little research evidence to guide these discussions and there is concern from patient advocacy groups that decisions are being made solely based on cost in the absence of considerations around impact on quality of eczema care. There are also concerns that decisions concerning emollient bath additives could be erroneously extended to leave-on emollients. Data presented here suggest that adding bath emollients to bath water should be a low priority for prescribing, although we did not examine the use of these products as soap substitutes. It is important to note that, although more research is needed in this area, there is evidence that the regular use of leave-on emollients prevents flare-ups in eczema, and there is widespread clinical consensus around the role of emollients as soap substitutes. Promoting choice and adequate prescribing of these products is likely to improve QoL and reduce consulting and prescribing for flare-ups.

Conclusions

Implications for health care

This trial found no evidence of any clinical benefit of including emollient bath additives in the standard management of atopic eczema in children aged between 12 months and 12 years. These findings suggest that parents/carers can be advised that using emollient bath additives by pouring them into bath water is unlikely to provide any reduction in eczema symptoms, but that they should continue to use leave-on emollients regularly and to use emollients as a soap substitute as recommended by the National Institute for Health and Care Excellence (NICE) [National Institute for Health and Care Excellence. *Atopic Eczemain Under 12s: Diagnosis and Management*. Clinical guideline (CG57). London: NICE; 2007].

These trial results provide prescribing advisers and clinicians with good evidence on which to base decisions about bath additives for childhood eczema. The findings also provide parents/carers with useful information regarding those treatments that are unlikely to work as, anecdotally, bath additives may cause extra cleaning as well as rotting of rubber bath mats and toys.

Implications for research

Several questions around emollients and washing in eczema that were highlighted in the James Lind Alliance Priority Setting Partnership (Batchelor JM, Ridd MJ, Clarke T, Ahmed A, Cox M, Crowe S, *et al.* The Eczema Priority Setting Partnership: a collaboration between patients, carers, clinicians and researchers to identify and prioritize important research questions for the treatment of eczema. *Br J Dermatol* 2013;**168**:577–82) remain outstanding, including which emollient is the most effective and safe in treating eczema? Which should be applied first when treating eczema: emollients or topical steroids? Which is the best way for people with eczema to wash (frequency of washing, water temperature, bath vs. shower)?

We have not explored the role of leave-on emollients, and previous evidence suggests that these are of central importance to eczema management. However, there is little evidence regarding the leave-on emollients that are most effective and commissioners are increasingly restricting prescribing on the basis of cost alone. Further research would be needed to explore optimal emollient and bathing regimens.

Trial registration

This trial is registered as ISRCTN84102309.

Funding

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Chapter 1 Introduction

Scientific background

Eczema is very common, affecting > 20% of children at some point during their first 5 years of life.[1] Eczema has a significant impact on quality of life (QoL)[2] and can cause distress to affected children and their families because of sleep disturbance, itching and scratching.[3] The term 'atopic eczema' (synonymous with 'atopic dermatitis') is widely used to denote a clinical phenotype, rather than those who are truly atopic as defined by the presence of immunoglobulin E-specific antibodies to common environmental allergens. In this study, we use the term 'eczema' throughout to refer to the 'atopic eczema' clinical phenotype, in accordance with the recommended nomenclature of the World Allergy Organization.[4,5]

Skin complaints are the second most common reason for general practitioner (GP) consultations in children aged < 5 years.[6] Health and societal costs of eczema care are difficult to estimate as they vary widely by population under study, but eczema is thought to cause a similar economic burden to that for asthma.[7,8]

Emollients for the treatment of childhood eczema

Guidelines suggest that emollients form the mainstay of treatment for eczema and should be used regularly by all patients alongside other treatments, such as topical corticosteroids (TCSs), when necessary to treat flare-ups.[9] Emollients are thought to act by providing a protective layer over the skin, decreasing moisture loss and occluding against irritants.

There are three methods of application of emollients: (1) leave-on (directly applied) emollients, where emollients are applied to the skin and left to soak in, (2) soap substitutes, where emollients are used instead of soap or other washing products, and (3) bath emollients (or bath additives), which are oil and/or emulsifiers designed to disperse in the bath. All three approaches are often used together (referred to as 'complete emollient therapy').[5,9] In this report, the term 'bath additives' rather than 'bath emollients' is used to emphasise the differences between the three methods of application (i.e. these three methods differ in their proposed actions and evidence relating to their effectiveness should also be considered separately).

Although there is widespread clinical consensus on the need for leave-on emollients and soap substitutes, there is less agreement regarding the additional benefits of emollient bath additives.[10–13]

Bath additives for the treatment of childhood eczema

A previous systematic review has revealed no convincing evidence for the use of emollient bath additives in the treatment of eczema;[10,11] available data consist of case series and very small trials. One study[14] in which parents were asked to soak one of their child's arms for 15 minutes a day for 2 weeks in a basin containing water with bath additive found that clinical assessment by blinded observer was worse for the arm that was soaked daily than for the unsoaked arm in eight of the nine children, suggesting the possibility that bath additives may be harmful. No trials of emollient bath additives have been published since 2007[15] and trial registries reveal no ongoing studies.

In addition to concerns about cost-effectiveness, potential harms from using bath additives include skin irritation and greasier bath surfaces, which can increase the risk of slips and accidents[13] (listed in the Summary of Product Characteristics of leading brands). There is also a concern that people who use bath additives in place of leave-on emollients are receiving substandard emollient therapy.[12]

The effectiveness of adding bleach bath additives has also not been demonstrated in a small randomised trial, although 5 out of 18 participants in the bleach bath group experienced mild burning/stinging or dry skin.[16] Two small randomised studies[17,18] compared 'bath emollient' with 'bath emollient plus antiseptic' on a range of outcomes, but there were no significant differences between groups, including colony counts of *Staphylococcus aureus*.[19] For this reason, we chose to exclude bath additives that incorporate an antiseptic, because of the absence of benefit and the possible increased risk of skin irritation.[5,20]

In 2007, the Drug and Therapeutics Bulletin noted that the NHS spends > £16M per year on bath additives (at an average cost of £6.29 per item), representing 38% of the total cost of treatments prescribed for preschool children with eczema and matching the proportion spent on emollients for application directly to the skin.[9]

Despite the absence of evidence and the possibility of potential harms, bath additives are widely prescribed at a cost of > £23M per year to the NHS in England.[21] Currently, prescribing advice varies widely. An analysis of 216 formularies from Clinical Commissioning Groups in England and Local Health Boards in Wales[22] showed that 68% recommended the use of bath additives, 15% allowed their use but did not encourage it, 13% did not mention bath additives and 5% did not recommend their use.

Pragmatic trial design

Pragmatic clinical trials aim to test the effectiveness of an intervention in a real-life setting in order to recruit a study population that is as similar as possible to the population on which the intervention is meant to be used. Whereas an explanatory clinical trial aims to answer the question 'Can this intervention work under ideal conditions?', a pragmatic approach seeks to answer the question 'Does this intervention work under usual conditions?'.[23,24] Features of pragmatic trials include the use of clinically important outcomes and common participant-reported outcomes, long-term follow-up and encouragement of participants to adhere to the intervention only to the extent that would be anticipated in usual care.

Although relatively few pragmatic trials have been carried out in dermatology,[25] we felt that a definitive pragmatic clinical trial, including outcomes of relevance to participants and including long-term follow-up, was the most appropriate design to address the question of the effectiveness of bath additives in addition to standard eczema care in everyday care.[5]

Blinding

We chose an 'open-label' design as it would not be possible to create a convincing placebo for bath additives, which make the bath feel 'greasy', and many families of children with eczema will already have experience of using them. We wished to design a trial with a clinical outcome relevant to participants (as below). Ideally, we would also have included an objective assessment of eczema severity carried out by a blinded assessor. However, this would have increased burden for participants as additional face-to-face assessments would have been required, particularly as the relapsing and remitting nature of eczema means that follow-up assessment at a single time point is problematic. As our primary outcome was participant reported and, therefore, unblinded, incurring substantial additional costs for an objective secondary outcome did not seem warranted.

Participant-reported outcome measure

We wished to design a trial with a clinical outcome relevant to participants. In eczema, the appearance of the skin does not always closely reflect symptoms causing a major impact on the child and family, such as sleep disturbance and itch.[26] It was therefore particularly important to design a trial with a validated participant-reported primary outcome.[5]

We chose the Patient Oriented Eczema Measure (POEM)[27,28] as our participant-reported primary outcome measure. POEM comprises seven questions about eczema symptoms over the previous week that are summed to give a score from 0 (no eczema) to 28 (worst possible eczema). POEM is a patient-reported outcome that can be used by proxy (carer report), demonstrates good validity, repeatability and responsiveness to change[29] and is recommended by the National Institute for Health and Care Excellence (NICE)[9] and the international Harmonising Outcome Measures for Eczema (HOME) initiative.[30,31]

Capturing meaningful outcomes for people with eczema is complicated by the relapsing and remitting nature of the condition. Therefore, gathering information regularly over time is essential to understand disease burden[32] and to assess the impact of interventions. We therefore chose to collect POEM scores on a weekly basis from participants, as has been used successfully in other eczema trials.[33] An article reporting on the acceptability and practicality of weekly POEM completion is in preparation.[34]

Development of research priority

This trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme following a commissioned call advertised in February 2012. The research topic was suggested via the NIHR HTA website topic suggestion form and was approved in December 2011.

The James Lind Alliance Priority Setting Partnership (PSP) for Eczema published its top 10 priority topics in 2012.[35] Even though this call was not advertised directly as a result of the PSP, it does address some of the issues that patients, carers and clinicians highlighted, including priorities around bathing/washing and also around the best ways to use emollients.

Objectives

The objectives were to determine the clinical effectiveness and cost-effectiveness of adding bath emollient to the standard management of eczema in children, which includes regular application of leave-on emollients with use of TCSs as required.

The trial was registered before commencing on 13 December 2013 and the protocol was published online in August 2015.[5]

Chapter 2 Methods

Trial design

The Bath Additives for the Treatment of Eczema in cHildren (BATHE) trial was a pragmatic, randomised, open-label, multicentre, superiority trial with two parallel groups and a primary outcome of long-term control as measured by POEM weekly scores over 16 weeks. Children were randomised in a 1 : 1 ratio to either standard eczema care plus bath additives or standard eczema care only for 12 months (*Figure 1*).

Changes to trial protocol

As recruitment was ahead of target, and following discussion with the Trial Steering Committee, in October 2015 the decision was taken to increase the target sample size from 423 to 491 participants, to allow an analysis by treatment adherence in addition to an intention-to-treat (ITT) analysis. Assuming that 80% of participants were strictly adherent to their allocated treatment, recruitment of an additional 68 participants would be required to retain 90% power for a per-protocol analysis.

In addition, although not requiring an amendment to the trial protocol, concerns were raised that the participant information sheet was overly formal and text heavy and that this might be contributing to a lower than expected response rate. A colourful summary information leaflet was therefore designed, to be added to the patient invitation pack (see *Appendix 1*). The additional leaflet was included in mailshots from 12 June 2015 (63% of the invitations), but there is no evidence that its inclusion affected either the number of responses or the proportion of positive replies.

Participants

Participant identification

Participants were recruited exclusively through GP surgeries in Wales, the west of England and southern England. All recruiting sites were members of their local clinical research networks (CRNs) [NIHR CRN Wessex, NIHR CRN West of England and National Institute for Social Care and Health Research (NISCHR) in Wales] and were reimbursed for their time via the Service Support Costs scheme [Attributing the costs of health and social care Research and Development (AcoRD). URL: www.nihr.ac.uk/funding-and-support/study-support-service/early-contact-and-engagement/acord/ (accessed 10 September 2018)]. A total of 96 GP surgeries took part in the trial.

Postal invitation

Sites were provided with the instructions to conduct a search of their electronic records for potentially eligible children. The inclusion criteria were child aged between 12 months and 12 years, with a recorded diagnosis of eczema (Read Codes: eczema not otherwise specified, atopic eczema/dermatitis, infantile eczema) and who had obtained one or more prescriptions for drugs acting on the skin[36] within the past 12 months. The lists that were produced were then screened for further exclusions by the children's GPs (e.g. recent bereavement, child protection issues). When finalised, staff at the surgery merged the list of names and addresses with the trial invitation materials using a secure online mailing service. Trial staff were aware of how many invitation letters were being sent from each site, but did not have access to the details of the mailing list.

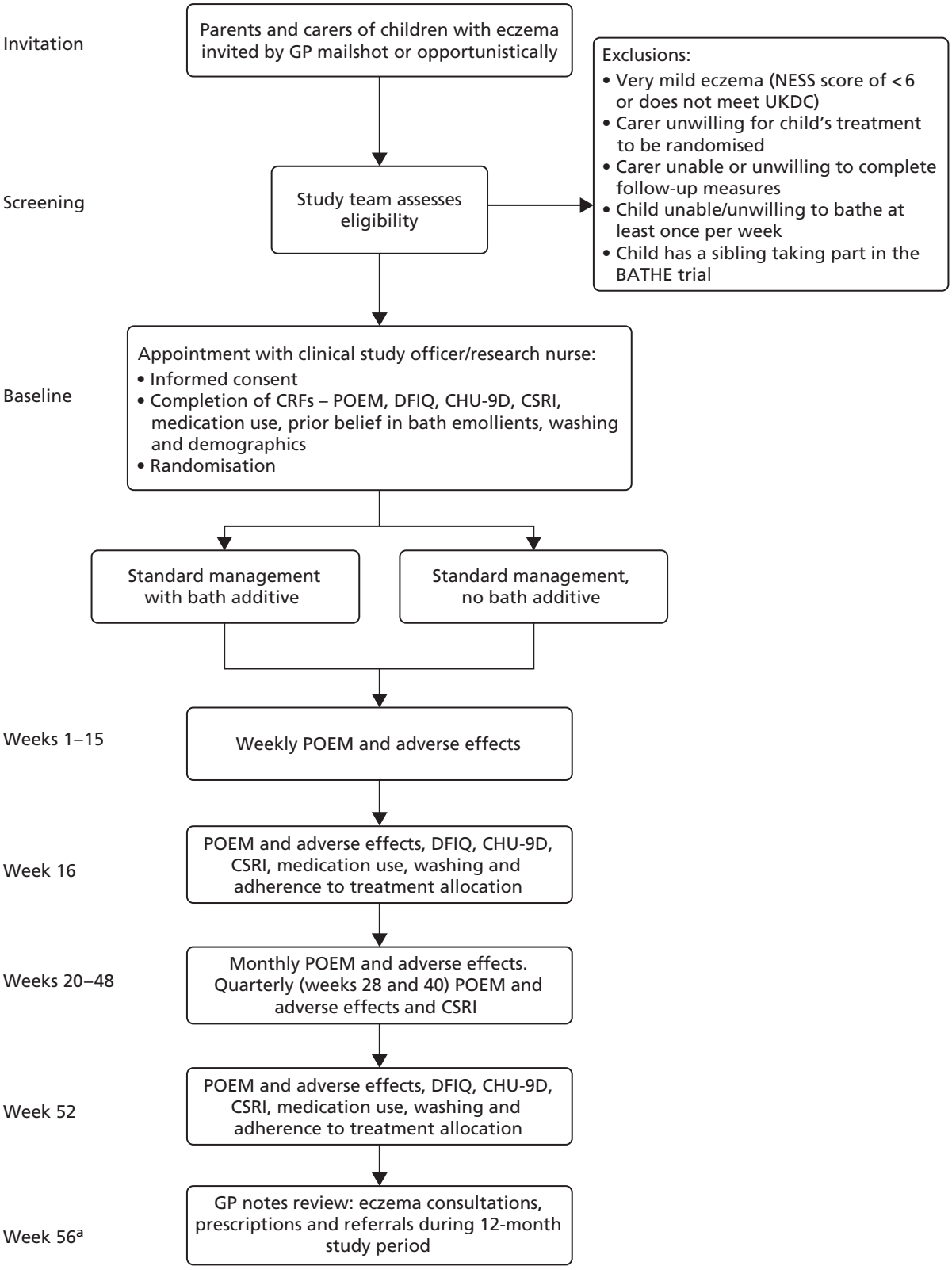


FIGURE 1 Participant flow through study. a, At least 4 weeks allowed for clinical letters to be received at surgery and scanned into patient record. CHU-9D, Child Health Utility-9 Dimensions; CRF, case report form; CSRI, client service receipt inventory; DFIQ, Dermatitis Family Impact Questionnaire; NESS, Nottingham Eczema Severity Score; UKDC, UK Diagnostic Criteria for Atopic Dermatitis.

The trial invitation pack consisted of a covering letter printed on the surgery's letterhead paper, an information sheet, a reply slip incorporating an eczema screening questionnaire (see *Appendix 2*) and a prepaid reply envelope. Children's names were used within the text of the letter and invitation letters were addressed 'to the parent/guardian' of the child. Patient identification numbers were assigned to each invitee when the mail merge was performed and were printed on the reply slip to permit anonymous replies. The participant identification number format (six digits consisting of centre number, site number and patient number, in the format X-XX-XXX) also enabled trial staff to monitor response rates at the surgery level.

Opportunistic invitation

Sites were also provided with invitation packs to hand out opportunistically to parents/carers of children with eczema. Although it was hoped that all eligible children would have received an invitation through the post, packs were provided in anticipation of new eczema diagnoses and families newly registered with participating surgeries. The trial team was not generally notified when an invitation pack had been handed out by surgery staff, and the overall number of opportunistic recruitment packs distributed is not known; however, 35 (2.4%) of the responses received were returned from opportunistic invitations, of which 34 were from children who were willing to take part, 19 (54%) of whom went on to participate in the trial.

All documents in the mailing pack were supplied in both English and Welsh to patients of those surgeries where Welsh is spoken, except for the screening questionnaire. This questionnaire was supplied only in English as neither of the measures it incorporates [UK Diagnostic Criteria for Atopic Dermatitis (UKDC) and Nottingham Eczema Severity Score (NESS)] have been validated in the Welsh language. Materials that were included in the patient invitation pack can be found in *Appendices 1–4*.

Reponses

Parents/carers could respond to the invitation letter by either returning the reply slip in the prepaid envelope or by entering the same data into a secure online questionnaire hosted by the University of Southampton (URL: www.iSurvey.soton.ac.uk; accessed 3 August 2018).

Eligibility

Children were eligible to participate if:

- they were aged between 12 months and 12 years
- they fulfilled UKDC (see following paragraphs)
- they scored mild to severe eczema severity over the past 12 months on the NESS (i.e. a score of > 5, excluding very mild eczema – see following paragraphs)
- they bathed at least once a week
- their parent/carer (or themselves) was willing for randomisation to either bath additive or no bath additive
- they had no sibling(s) participating in the trial
- they were not taking part in other clinical trials.

To avoid inviting ineligible children to baseline screening appointments, an initial assessment of eligibility was determined using a screening form, completed by the parent/carer, that combined the UKDC and the NESS, as below.

The UKDC are a refinement of the Hanifin and Rajka[37] clinical criteria for diagnosing eczema and are the most extensively validated way of diagnosing eczema; they have been widely used in epidemiological and clinical studies.[38] The UKDC questionnaire consists of a single inclusion/exclusion question ('in the last year, has your child had an itchy skin condition?') followed by a further five questions about the clinical course of the disease. Atopic dermatitis, or eczema, is indicated by a score of three or more positive responses from these five questions.

For the purposes of the BATHE trial, the requirement for visible flexural dermatitis was approximated by assessing the NESS body diagram for marks indicating the presence of eczema in the wrist, ankle, elbow and facial areas (see *Appendix 2*). In addition, the question relating to child or family history of atopy, being age adapted and involving some explanation, was not included on the screening questionnaire form. This question was asked by telephone or e-mail only if an additional point was required to reach eligibility (i.e. the child scored ≥ 5 on the NESS and ≥ 2 on the UKDC).

The NESS assesses eczema severity over the previous 12 months and comprises three questions: duration of eczema symptoms over past 12 months, frequency of sleep disturbance and current extent of eczema as represented by parental marking of a diagram[39] (see *Appendix 2*).

The NESS severity classifications are mild (score of 3–8), moderate (9–11) and severe (12–15).[39] However, the majority of children in primary care fall into the 'mild' category and a score of ≥ 9 would exclude 82% of children with eczema in primary care, whereas a cut-off point of ≥ 6 would exclude only 40% of children with 'very mild' eczema. Children with a score of ≤ 5 were excluded, as floor effects would make it unlikely that changes in eczema severity could be detected.

The screening forms were returned in a prepaid envelope to the trial centre in Southampton, where responses were entered into a secure database [Microsoft Access® (Microsoft Corporation, Redmond, WA, USA)]. The database calculated eligibility for each child using an algorithm (see *Appendix 5*). To be eligible to take part in the BATHE trial, children were required to meet the UKDC and to score ≥ 5 on the NESS. Those who reached eligibility on the NESS but scored only 2 on the UKDC were contacted by the clinical studies officer/research nurse (CSO/RN) in order to ask the additional question about atopy.

When screening forms did not meet eligibility criteria, parents/carers were sent a letter of thanks and explanation, together with a booklet explaining the best way to wash children with eczema. Children's details were not collected until the recruitment appointment and, therefore, children who were not recruited into the BATHE trial remained anonymous.

Recruitment

All contact with families regarding recruitment was conducted by a clinical studies officer or research nurse. In the Southampton and Bristol centres, the clinical studies officers were study-employed staff, whereas, in the Cardiff centre, recruitment was carried out by clinical studies officers or research nurses from the NISCHR, who may work across several research projects concurrently. The majority of trial staff were trained together at a whole-day workshop prior to the start of the recruitment period; however, the large number of staff in Wales meant that some new staff required handover training from trained research nurses.

Parents/carers of eligible children who expressed a willingness to take part in the trial were contacted by their local CSO/RN. After re-establishing eligibility, a recruitment appointment was made. The majority of appointments were held at the child's GP surgery, with a small number held at the child's home when this option was preferred by the family. The child did not need to attend the appointment, but whenever they were present efforts were made to include them in the discussion. Two summary child information leaflets were prepared to facilitate their understanding and assent forms were available for older children (see *Appendices 6* and *7*).

The mean number of days between completion of the screening form and the recruitment appointment was 24, and 370 (77%) participants were recruited within 30 days of the screening form completion date. When the time elapsed between completion of the screening form and the recruitment appointment was ≥ 30 days, the CSO/RN rechecked eligibility by asking parents/carers to confirm the time-sensitive questions from the NESS (questions five to seven of the screening form). Eligibility was recalculated by the CSO/RN and the data held in the trial management database were updated.

Baseline data were entered directly into the online software by the parent/carer wherever possible. This enabled the CSO/RN to familiarise the participants with logging in and using the software, but occasionally it added considerable time to the appointment. The recruitment process routinely took between 40 and 60 minutes and, therefore, parents/carers were reimbursed for their time and expenses with a £10 gift voucher.

Engagement

Following the baseline appointment, there were no other face-to-face meetings and so efforts were made to help participants to remain engaged with the trial throughout the full 12 months. A study logo of a rubber duck was adopted and used in many different ways: participating children (and their siblings) were invited to colour in and name a duck, which was then uploaded to a gallery on the study website. The logo was also used to identify small gifts, which were provided at the baseline appointment [a bath duck with study logo, Post-it® (3M, Bracknell, UK) notes and a novelty eraser] and birthday and Christmas cards and quarterly newsletters were sent about study progress. The newsletters were also uploaded to the study website, where participants were able to access key trial information and get in touch with the study team if required (URL: www.southampton.ac.uk/bathe; accessed 3 August 2018). No incentives were given to participants; however, a thank you card and a £10 voucher were sent to parents/carers shortly before each of the 16- and 52-week questionnaires were due in recognition of the time spent completing them, and all participants were eligible for inclusion in a prize draw for a tablet computer at the end of the study.

Interventions

Standard care with bath additive

In addition to the child's usual skincare regimen, parents/carers were asked to use one of the three most commonly used bath additives [Balneum® (Almirall Ltd, Middlesex, UK), Aveeno® (Johnson & Johnson Ltd, Maidenhead, UK) or Oilatum® (Stiefel Skin Science Solutions, a GlaxoSmithKline company, Middlesex, UK)] at least once per week, in accordance with the manufacturer's instructions. Having discussed any carer preferences, the CSO/RN asked staff at the surgery to set up a repeat prescription on the child's medical record. In the event of an adverse reaction to the bath additive, parents/carers were free to change the prescription to another of the recommended products at any point during the trial. Bath additives other than the three recommended products are also available and parents/carers were free to choose any bath additive they wished, provided that it did not contain any additional active ingredients, such as antipruritic or antimicrobial agents. A full list of acceptable bath additives was provided to the surgery in the study site file and was available on the study website (see *Appendix 8*). Both groups also received further advice (as below).

Standard care without bath additive

Parents/carers were requested to avoid using any emollient product that had been designed to be poured into the bath for the 12 months of their participation. It was reiterated that it was not known whether or not bath additives provided any benefit to children with eczema and that we did not believe that their child would experience any worsening of their eczema as a result of participating in this trial. Parents/carers in the no bath additive group were advised that they should treat their child's eczema exactly as they normally would, using leave-on emollients regularly and TCSs to treat flare-ups, and consulting health professionals as they normally would. As many participants had family members who also had eczema, and in accordance with the pragmatic nature of the trial, no specific instructions were given to parents/carers with regard to bath additives that might already be present in the home; instead, the main focus was on ensuring that parents/carers were in equipoise with and engaged with the aims of the research.

Advice given to both groups

We aimed for no difference in soap use between groups and both groups were therefore given the same advice about how to wash. Both groups were advised to use a leave-on emollient as a soap substitute. When parents/carers were keen to use existing wash products, they were advised that these could be used

for direct application to skin but should not be added to the bath water, as this could potentially have the same effect as a bath additive. All participants were provided with a copy of the BATHE trial Study Washing Leaflet that was based on best practice guidelines developed by the Nottingham Support Group for Carers of Children with Eczema (see *Appendix 9*).[40]

All parents/carers were reminded that they were free to use any other medications as they normally would and to visit their doctor or dermatologist as usual, if required. The standard operating procedure (SOP) that was used by recruiters during the baseline appointment is available in *Appendix 10*.

Data collection

Parents/carers were able to choose to complete the trial questionnaires either online or by post following discussion at the recruitment appointment, although online questionnaire completion was strongly encouraged. Online questionnaires became available on the seventh day following recruitment and every 7 days thereafter. Notifications were automatically sent by e-mail when the questionnaire went 'live' and reminders were sent after 48 hours if it had not been completed. Participants could also opt to receive the notifications and reminders by automated text. Both e-mails and text messages contained a hyperlink to the online questionnaire and participants were required to log in using their e-mail address and password in order to enter data. Of the 9784 times that parents/carers logged in to the website, 5963 logins (61%) were from mobile devices. A further 2909 logins (30%) were from computers or laptops, whereas 912 logins (9%) were from tablets.[34]

The 16-week questionnaire, and subsequent monthly questionnaires, remained available to complete online for 28 days. However, in order to encourage timely completion of the primary and secondary outcomes, a reminder letter and paper copy of the 16- and 52-week questionnaires were posted out if the online questionnaire had not been completed within 7 days. A total of 80 reminders were posted at week 16 and 107 reminders were posted at week 52.

Weekly paper questionnaires were printed in booklets of four. The first booklet, covering weeks 1–4, was marked with the day of the week on which the questionnaires should be completed and then handed to the parent at recruitment. Subsequent questionnaires were posted to participants shortly before they were due, together with a prepaid envelope. The data from the paper questionnaires were entered into a secure database and were merged with the data collected online prior to analysis.

Data management

The online data collection software was built using LifeGuide software (University of Southampton, Southampton, UK) and validated by Southampton Clinical Trials Unit. The clinical data were separated from the personally identifiable information and both data sets were stored on secure servers.

In the trial office, data from paper screening forms and questionnaires were entered into a password-protected Microsoft Access database. The clinical data were again stored separately from personally identifiable information in two data sets on a secure server. Paper forms were separated from each other and stored in locked filing cabinets in the trial office.

The data sets were merged and stripped of any identifying data prior to analysis.

Outcomes

Primary outcome

The primary outcome was eczema severity as measured by the POEM completed weekly for 16 weeks. The POEM is a patient-reported outcome that scores symptoms over the previous week. It consists of seven

questions that can be completed by the child's parent/carer and provides a severity score on a scale from 0 to 28. The published minimal clinically important difference of the POEM is 3.0.[41,42] The POEM was the only patient-reported outcome measure for eczema to demonstrate validity and repeatability in a systematic review by Schmitt *et al.*[29] and it was adopted as the preferred patient-reported outcome measure by the HOME initiative in 2015.[30,43] Our primary outcome measure is based on repeated measures of POEM data collected weekly over 16 weeks because these reflect the impact of this relapsing and remitting chronic condition better than comparing outcomes at a single follow-up point. Because of the burden of weekly data collection on participants, weekly data collection was limited to the first 16 weeks of the trial.

Secondary outcomes

1. The number of eczema exacerbations resulting in a primary health-care consultation over 1 year, assessed by a review of participants' primary care records. An exacerbation for this trial is defined as a consultation where there is mention of eczema and a topical steroid or topical calcineurin inhibitor (TCI) has been prescribed. The notes review form was based on those used in other recent eczema trials and recorded the number of consultations, prescriptions and referrals over the 12 months' trial participation (see *Appendix 11*). Notes reviews were carried out by members of the trial team at not less than 13 months after the recruitment date in order to allow time for clinic letters to be received and scanned into the patients' notes.
2. Eczema severity over 1 year as measured by POEM every 4 weeks, from 16 weeks to 12 months.
3. Disease-specific QoL at baseline, 16 weeks and 1 year, measured by the Dermatitis Family Impact Questionnaire (DFIQ).[44] The DFIQ is an internationally recognised validated instrument that measures the impact of a child's eczema on the family's QoL. The questionnaire consists of 10 questions and the total score ranges from 0 (no impact on family life) to 30 (maximum impact on family life).
4. Generic QoL as measured by the Child Health Utility-9 Dimensions (CHU-9D) at baseline, 16 weeks and 1 year. CHU-9D[45] is a paediatric QoL measure developed in children aged 7–11 years. It captures issues pertinent to childhood eczema, such as sleep disturbance and the child's mood, and is therefore more suitable for measuring the QoL in families affected by eczema than the EuroQol-5 Dimensions (EQ-5D). There are no suitable utility measures validated for very young children aged 1–4 years; however, personal communication (Dr Katherine Stevens, University of Sheffield, 2014) suggested guidance for using the CHU-9D in very young children. In addition, the CHU-9D performed well in children aged 1–4 years in the Supporting Parents and carers of Children with Eczema (SpaCE) trial and its use in younger age groups is currently being trialled elsewhere.[46,47]
5. Type (strength) and quantity of topical steroid/calcineurin inhibitors prescribed during trial participation, measured by GP notes review.

Sample size

The sample size was calculated for repeated measures analysis of variance (ANOVA) in weekly POEM scores over the 16-week observation period. Using weekly data from a similar population to that in the Softened Water Eczema (SWET) trial,[48] we aimed to detect a mean difference of 2.0 [standard deviation (SD) 7.0] between the intervention and control groups. The published minimal clinically important difference for POEM is 3.0,[41,42] but we wished to detect a difference of 2.0 because of the expectation of low baseline POEM scores in a population recruited entirely through primary care, and because we wished to be able to detect this small difference as the intervention is relatively inexpensive and even small effect sizes may be cost-effective. An alpha of 0.05 and a power of 90% with a correlation between repeated measures of 0.70 gives a sample size of 338 participants. Allowing for 20% loss to follow-up gave a total sample size of 423 participants.

We aimed to report a per-protocol analysis in addition to a primary ITT analysis, and early data suggested that approximately 80% of participants in both groups were strictly adherent to treatment allocation. We were concerned that if only 80% of participants were adherent to treatment allocation then we would

have usable data for only 270 participants. To get back up to 90% power for this group, we submitted an ethics amendment requesting recruitment of an additional 68 participants, giving a revised target recruitment of 491 participants.

Randomisation

Randomisation was performed using LifeGuide[49] software hosted by the University of Southampton and validated by Southampton Clinical Trials Unit. At the time of trial setup, LifeGuide was unable to easily perform block randomisation and the additional programming time would have resulted in delays to the trial. Simple randomisation was therefore used, stratified by centre. Although this can result in imbalances, it was felt that with strata of > 100 participants each, the overall balance between groups would be preserved.

A backup randomisation system was established for occasions when internet access to LifeGuide was not available or when the parent had opted to complete the trial questionnaires on paper. A second set of random treatment allocations was programmed into a Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) spreadsheet by the trial statistician. The spreadsheet similarly allocated treatments on a 1 : 1 basis, stratified by recruiting centre, and the treatment allocation was not revealed until the participant had been recruited. A total of 30 randomisations were conducted using this offline method.

Allocation concealment mechanism

Both the online and the offline randomisation procedures were conducted immediately at the end of the recruitment appointment, following completion of the baseline questionnaire. It was therefore impossible for the treatment allocation to be known prior to study entry. Once randomisation was complete, however, the participant, CSO/RN and the participant's clinical team were all aware of which group the child had been allocated to.

Implementation

Once recruitment and randomisation was complete, the lead GP at the site was notified of the child's enrolment into the study and their allocated treatment group was noted on a form completed by the recruiting CSO/RN. The form requested that repeat prescriptions be set up for children allocated to the bath additive group and it also recorded the parent/carer's preferred bath additive, if any. Practices were recommended to add a Read Code to the child's electronic record to indicate that they were enrolled in a clinical trial and/or to add an electronic alert or other notification to remind clinicians of their treatment allocation. This, however, was not enforced and the focus remained on ensuring that parents/carers were fully engaged with the aims and requirements of the study.

Blinding

Given the nature of bath emollient, which adds a greasy film to water, it was impossible to manufacture a convincing placebo treatment or to blind the participants to their treatment allocation. Participants were therefore fully aware of the treatment regime they were being asked to adhere to and report on. In order to support families throughout their 12-month participation, the trial team were also not blinded to the treatment allocated.

The trial statisticians carrying out the analysis were blind to allocation group and the statistical analyses were independently verified.

Statistical methods

The primary analysis for the total POEM score was performed using a mixed multilevel mixed model (MMLM) framework with observations over time from weeks 1–16 (level 1) nested within participants (level 2) nested within centres (level 3). Unadjusted results are reported, as well as results adjusting for baseline POEM, recruitment region as covariates and any significant confounders. Confounders were defined as variables associated with both the exposure and the outcome that significantly contribute to the multivariable model (defined as a p-value of < 0.05 or by modifying the effect estimate by $> 10\%$). The following variables were identified a priori as possible confounders: child age, child gender, carer age, carer gender, carer education, prior belief in bath emollients, type of emollient used, other medication used and other items used when washing (e.g. soap/shampoo/soap substitute).

The model used all of the observed data and made the assumption that missing POEM scores are missing at random. The model included a random effect for centre (random intercept) and patient (random intercept and slope on time) to allow for between-patient and between-centre differences at baseline and between-patient differences in the rate of change over time (if a treatment/time interaction was significant), and fixed effects for baseline covariates. An unstructured covariance matrix was used.

The assumptions of the normality of the residuals from the fixed part of the model and the normality of the random effects at the cluster level were checked.

For the analysis of secondary outcomes, repeated measures analysis in line with that used for the primary outcome was used for the monthly POEM up to 1 year.[5] 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, was used for count data. All analyses controlled for stratification variables and potential confounders. Preplanned sensitivity analysis and exploratory subgroup analyses were carried out as set out in the statistical analysis plan.

To test the sensitivity of the results to missing data, a chained equations multiple imputation model was used to impute the missing values. This analysis used 100 imputations and included all the outcomes and covariates included in the adjusted analysis of the primary outcome.

For all models, participants were analysed in the group to which they were randomised, regardless of their adherence to that allocation (ITT analysis). The only exception to this was the per-protocol analysis, for which participants were analysed on the basis of their reported use of bath additives. The reported use of bath additives was collected at 16 weeks and 52 weeks in both groups using the categorical response options ‘every time’, ‘more than half the time’, ‘less than half the time’ and ‘never’. This allows two possible definitions for adherence to the intervention.

Adherence definition one

Defined as the bath additive group using emollient bath additives ‘more than half the time’ or ‘every time’ and the no bath additive group using emollient bath additives ‘less than half the time’ or ‘never’.

Adherence definition two

These figures include only participants who reported using emollient bath additives ‘every time’ or ‘never’ (i.e. excluding participants who report using emollient both additives ‘more than half the time’ and ‘less than half the time’).

We report the effect sizes for the primary outcome based on both definitions of adherence. These can then be compared with the effect size in the ‘as randomised’ ITT population.

Chapter 3 Results

Participant recruitment

Invitation packs were sent to the parents/carers of 12,504 children and 1451 responses were received. A total of 1343 responses were returned by post; 832 respondents (62%) were willing to be contacted and 431 (32%) went on to participate in the trial. A total of 108 responses were received electronically; 88 respondents (81%) were willing to take part and 52 (48%) went on to be recruited. A total of 35 (2.4%) of the responses received were returned from opportunistic invitations; 34 respondents were willing to take part and 19 (54%) went on to participate in the trial.

A total of 237 parents/carers declined participation and returned a blank screening form. A further 104 answered 'No' to the first question of the UKDC ('In the last year, has your child had an itchy skin condition?') and did not fill in any other information about their child's condition. A total of 188 parents/carers indicated that they were unwilling or unable to take part but did complete the screening questionnaire. *Table 1* summarises the information received about these children's eczema, in comparison with children who went on to take part.

TABLE 1 Screening form characteristics of responders who declined participation compared with those of recruited participants

	Responder	
Respondent characteristic	Declined participation ($N = 185$)	Recruited ($N = 482$)
Age group, *n* (%)		
≤ 18 months	9 (5)	29 (6)
> 18 months but < 4 years	59 (32)	162 (34)
≥ 4 years	117 (63)	291 (60)
Eligibility, *n* (%)	($N = 186$)	($N = 482$)
Eligible	87 (47)	482 (100)
Query eligible	19 (10)	–
Not eligible	80 (43)	–
Eczema severity (eligible responders), mean (SD)	($N = 87$)	($N = 482$)
NESS (0–15)	9.14 (2.31)	9.52 (2.33)
UKDC score (0–4)	3.36 (0.48)	3.25 (0.61)
Belief in bath additives (1–9)[a]	($N = 183$)	($N = 475$)
Mean (SD)	5.6 (2.3)	4.6 (2.0)
Do not know	34 (18%)	97 (20%)
Bath additive use in past month, *n* (%)	($N = 180$)	($N = 481$)
Never	69 (38)	126 (26)
Less than half the time	36 (20)	109 (23)
More than half the time	23 (13)	96 (20)
Every time	52 (29)	150 (31)

a Where 1 is 'not at all effective' and 9 is 'very effective'.

There were 920 replies expressing a willingness to be contacted and these replies also included a completed screening questionnaire. Of these, 229 did not meet the clinical criteria required to enter the trial. Overall, 662 children met the clinical eligibility criteria and were approached regarding participation, of whom 483 entered the trial and 179 were not recruited for the reasons shown in *Figure 2*.

Figure 2 shows the flow of participants through the screening and recruitment process.

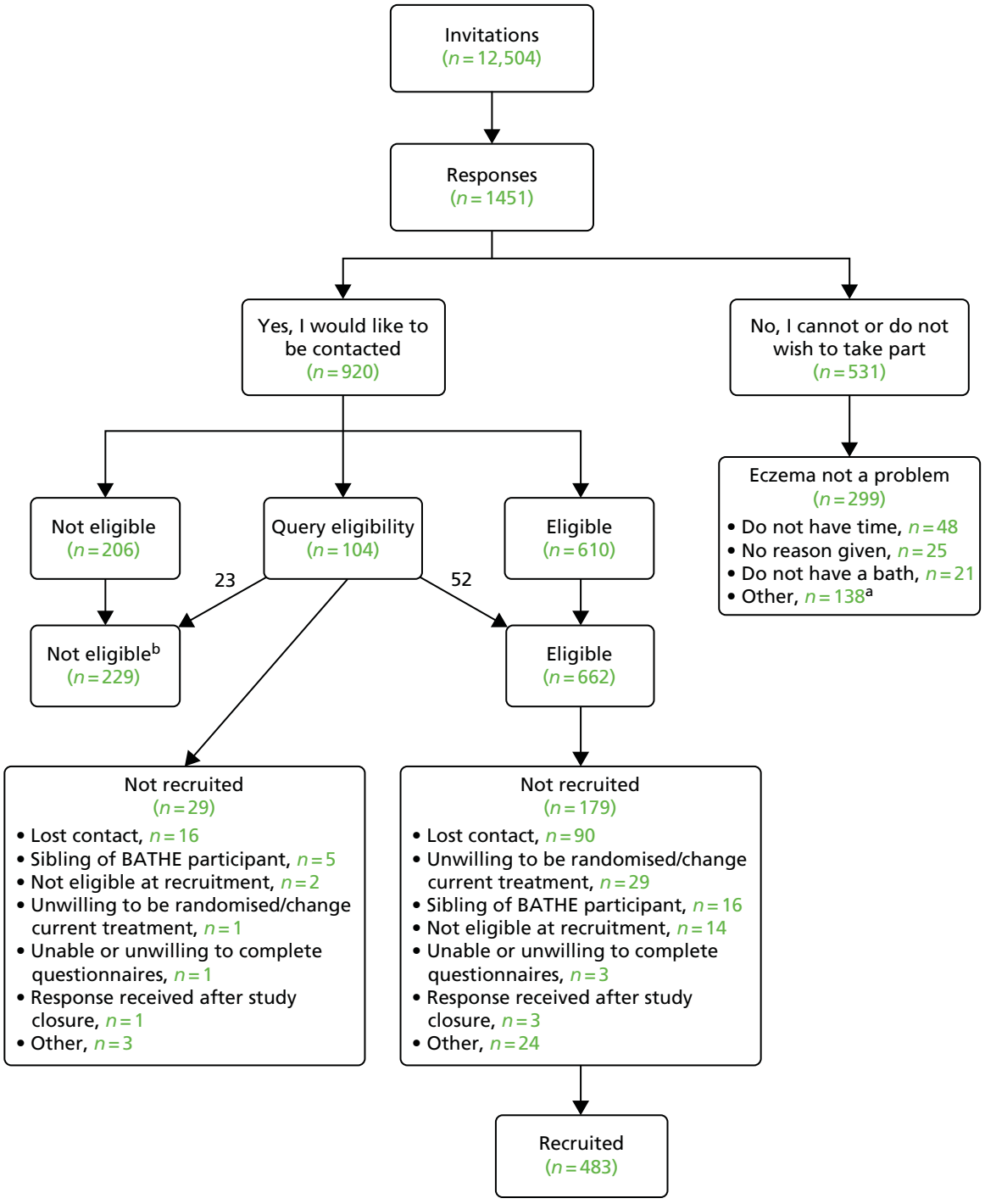


FIGURE 2 Recruitment flow chart. a, Unwilling to be randomised/change current treatment, $n = 58$; eczema no longer a problem, $n = 31$; child mostly showers, $n = 16$; child refused, $n = 2$; other/not specified reason, $n = 29$. b, Did not meet UKDC, $n = 65$; NESS score of < 6, $n = 76$; and did not meet either criterion, $n = 88$.

Figure 3 shows the number of participants who withdrew or who were lost to follow-up during the study period. Four participants formally withdrew during the 16-week primary outcome period, three from the Cardiff centre and one from the Bristol centre; all withdrawals were from the bath additive group. Permission was obtained from three parents to use the data already collected, and one requested that all data collected be removed. A total of 42 participants were lost to follow-up by the time of the 16-week primary outcome (22 in the bath additive group and 20 in the no bath additive group) and a further four 16-week questionnaires were not received from participants who remained enrolled.

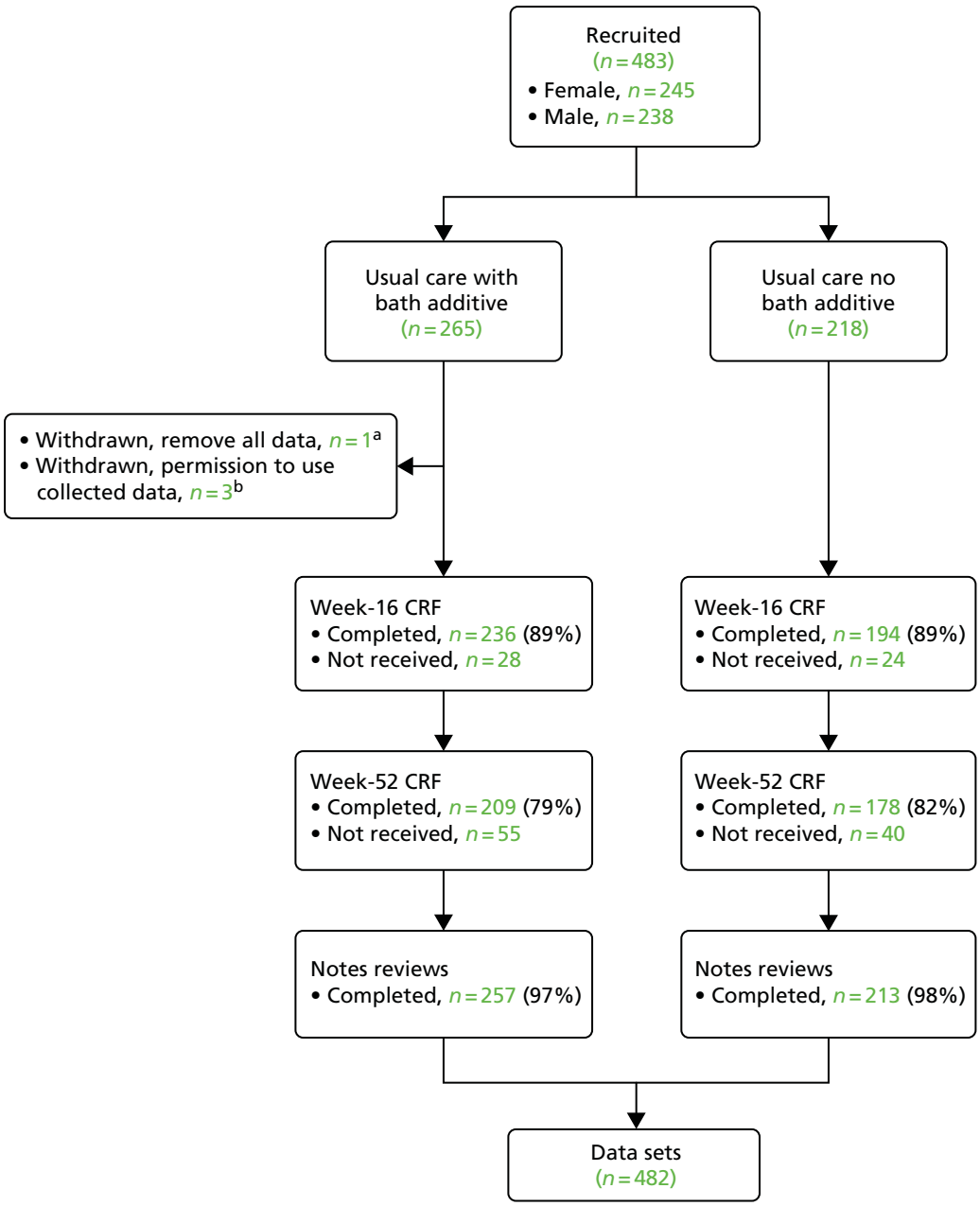


FIGURE 3 The BATHE participant flow chart. a, Reported eczema had not been a problem for some time, although screening form clearly indicated eligibility. b, One parent wished to bathe two children together but felt that bath additive was worsening the symptoms of the child not enrolled in the study; 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. CRF, case report form.

A total of 429 (89.6%) participants opted to complete their weekly questionnaire online. Of the remaining 51 participants, 27 (5.6%) requested the paper option at recruitment and 24 (5.0%) were switched from online to paper format after discussion with the study team. Reasons for this were primarily related to technical issues, as some parents/carers became discouraged after having problems logging in to the online database. Login problems were occasionally compounded by a failure to understand the automated nature of the system and the inability to complete POEMs retrospectively. This was particularly problematic for a small number of participants who experienced delays in obtaining their prescribed bath emollients and, therefore, did not 'start' participation in week 1. Although attempts were made to telephone all families during the first week, as a matter of courtesy and in order to address any problems, some parents could not be reached and it is not possible to determine how many participants were lost to follow-up because of technical or logistical problems.

The majority of trial participants needed no prompting to complete the trial and only 25% of the trial participants were contacted by telephone or e-mail during the 16-week primary outcome period because of failure to complete the questionnaires.

Recruitment dates

Recruitment took place from November 2014 to May 2016. The original target of 423 participants was reached in March 2016 and permission was obtained to continue recruiting participants up to an increased target of 491 participants as discussed in *Chapter 2*, *Changes to trial protocol*. Recruitment was stopped at the end of May 2016 as planned, with a total of 483 participants enrolled (*Figure 4*). The 52-week follow-up questionnaires and notes reviews of the last recruited participants were completed in June 2017.

Baseline data

Table 2 shows that, although there were more participants allocated to the bath additive group than the no bath additive group (see *Chapter 5, Discussion*), the key characteristics were well balanced at baseline.

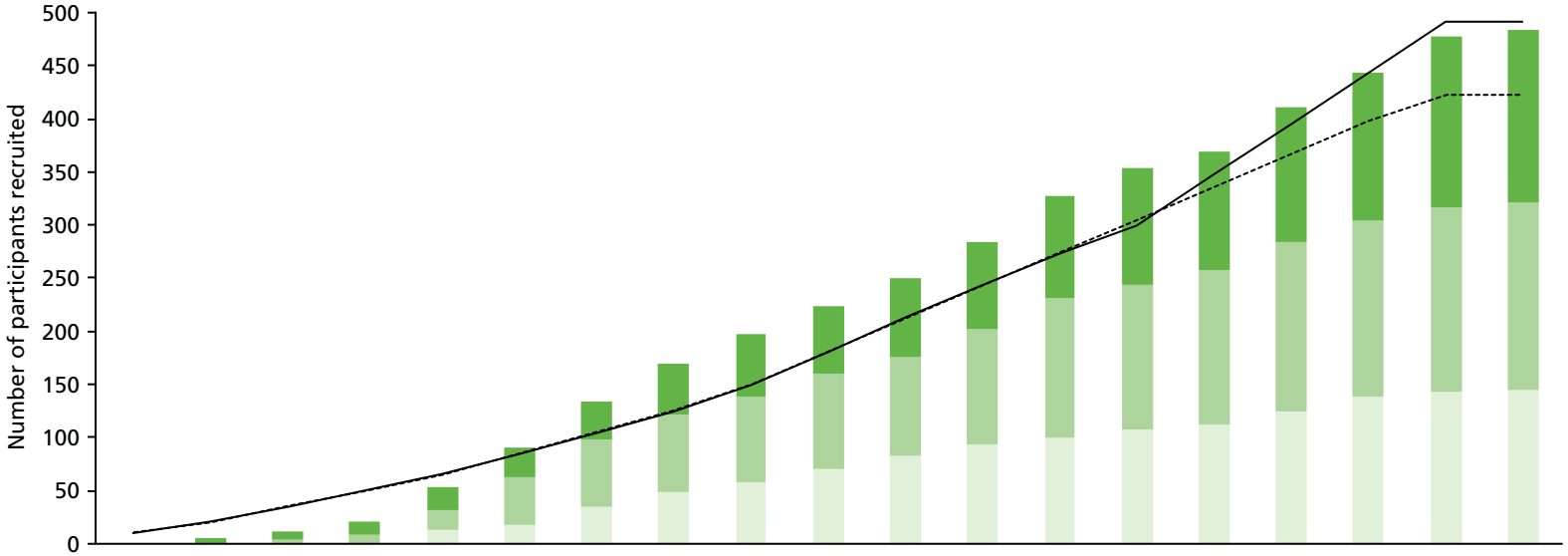
Numbers analysed

The questionnaire response rate was high, with 76.7% of participants completing questionnaires for > 80% of the time points for the primary outcome (12 out of 16 weekly questionnaires to 16 weeks). There were no marked differences in completeness of the data by randomisation group (see *Table 3* and *Figure 5*).

Outcomes

Primary outcomes

All 461 participants who had completed at least one POEM following baseline were included in this analysis. The results in *Table 4* indicate no statistically significant difference in weekly POEM scores between the two groups over the 16-week period. Of the prespecified potential confounders (child age, child gender, ethnic group, carer age, carer gender, carer education, prior belief in bath emollients, type of emollient used, other medication used, other items used when washing, such as soap/shampoo/soap substitute), only ethnic group, steroid use and soap substitute use were statistically significant and, therefore, retained in the models. After controlling for baseline severity and these confounders, and allowing for the clustering of patients within centres and responses within patients 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). Unadjusted POEM scores showed < 1 point difference between groups. These differences are not considered to be clinically meaningful, given the published minimal clinically important difference for POEM of 3.0.[41,42]



	November 2014	December 2014	January 2015	February 2015	March 2015	April 2015	May 2015	June 2015	July 2015	August 2015	September 2015	October 2015	November 2015	December 2015	January 2016	February 2016	March 2016	April 2016	May 2016
Southampton	0	5	7	13	21	28	36	48	59	64	75	82	97	110	111	127	140	161	162
Bristol	0	1	4	8	19	45	64	73	80	89	93	109	131	136	146	160	166	174	176
Cardiff	0	0	0	0	13	17	34	49	58	71	82	93	100	107	112	124	138	143	145
Cumulative actual accruals	0	6	11	21	53	90	134	170	197	224	250	284	328	353	369	411	444	478	483
Original cumulative target	10	20	35	50	65	85	105	125	150	181	212	243	274	305	336	367	398	423	423
Revised cumulative target	10	20	35	50	65	85	105	125	150	181	212	243	273	300	348	396	444	491	491

FIGURE 4 Recruitment by centre.

TABLE 2 Baseline characteristics of trial participants, by group

Participant characteristics	Treatment group		
	Bath additive (*N* = 264)	No bath additive (*N* = 218)	Total (*N* = 482)
Child age (years), mean (SD)	5.4 (2.9)	5.2 (2.9)	5.3 (2.9)
Child gender, *n* (%)			
Male	138 (52.3)	100 (45.9)	238 (49.4)
Female	126 (47.7)	118 (54.1)	244 (50.6)
Carer age (years), mean (SD)	36.5 (6.5)	35.9 (6.7)	36.2 (6.5)
Carer gender, *n* (%)			
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, *n* (%)			
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, *n* (%)			
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, *n* (%)			
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), *n* (%)	114 (43.2)	73 (33.5)	187 (38.8)
Moderate (8–16), *n* (%)	119 (45.1)	114 (52.3)	233 (48.3)
Severe (17–28), *n* (%)	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 level, Advanced level; GCSE, General Certificate of Secondary Education; IQR, interquartile range; O level, Ordinary level.
a Where 1 is 'not at all effective' and 9 is 'very effective'.

TABLE 3 Questionnaire return and completion during the study

Measure of completion	Treatment group		
	Bath additive (*N* = 264)	No bath additive (*N* = 218)	Total (*N* = 482)
Number of weekly questionnaires completed during the 16-week primary outcome period, mean (SD)	13.1 (4.5)	12.7 (4.7)	12.9 (4.6)
> 12 questionnaires completed, *n* (%)	209 (79.1)	161 (73.9)	370 (76.7)
Weekly questionnaire return, *n* (%)			
Week 1	224 (84.8)	191 (87.6)	415 (86.1)
Week 2	222 (84.1)	183 (83.9)	405 (84.0)
Week 3	223 (84.5)	176 (80.7)	399 (82.8)
Week 4	219 (83.0)	182 (83.5)	401 (83.2)
Week 5	216 (81.8)	175 (80.3)	391 (81.1)
Week 6	224 (84.8)	175 (80.3)	399 (82.8)
Week 7	209 (79.1)	173 (79.4)	382 (79.2)
Week 8	216 (81.8)	172 (78.9)	388 (80.5)
Week 9	221 (83.7)	163 (74.8)	384 (79.7)
Week 10	220 (83.3)	168 (77.1)	388 (80.5)
Week 11	203 (76.8)	161 (73.9)	364 (75.5)
Week 12	204 (77.2)	165 (75.7)	369 (76.6)
Week 13	203 (76.9)	165 (75.7)	368 (76.3)
Week 14	203 (76.9)	167 (76.6)	370 (76.8)
Week 15	207 (78.4)	173 (79.4)	380 (78.8)
Week 16	236 (89.4)	194 (89.0)	430 (89.2)
52-week questionnaire return, *n* (%)	209 (79.2)	178 (81.6)	387 (80.3)
Initial method of questionnaire completion, *n* (%)			
Online	235 (89.0)	196 (89.9)	431 (89.4)
By post	15 (5.7)	12 (5.5)	27 (5.6)
Switched method of completion during study, *n* (%)	14 (5.3)	10 (4.6)	24 (5.0)

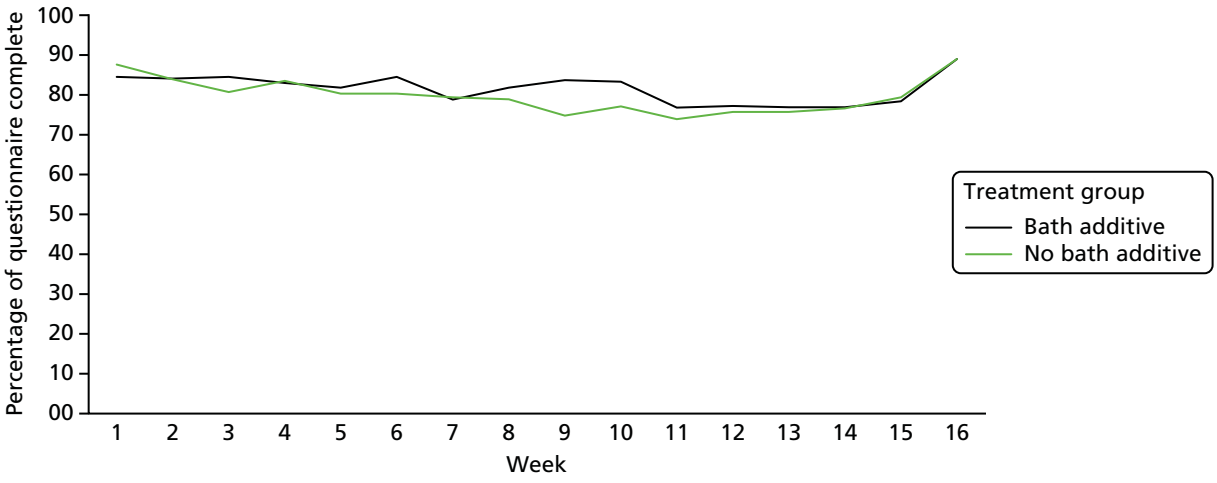


FIGURE 5 Questionnaire completion during the 16-week primary outcome period.

TABLE 4 Weekly POEM scores during the 16-week primary outcome period

Time period	Treatment group, mean (SD)	
	Bath additive	No bath additive
Baseline	9.5 (5.7)	10.1 (5.8)
Week 1	8.3 (5.6)	9.1 (5.9)
Week 2	7.8 (5.5)	8.2 (5.9)
Week 3	7.4 (5.3)	8.5 (5.9)
Week 4	7.6 (6.0)	8.6 (6.1)
Week 5	7.6 (5.9)	8.3 (6.0)
Week 6	7.8 (6.3)	8.4 (5.7)
Week 7	7.5 (6.1)	8.8 (6.1)
Week 8	7.3 (6.2)	8.2 (5.8)
Week 9	7.2 (5.9)	8.1 (5.8)
Week 10	7.3 (5.8)	8.5 (5.8)
Week 11	7.6 (6.1)	8.2 (6.0)
Week 12	7.7 (6.2)	7.9 (5.9)
Week 13	7.1 (5.9)	8.3 (6.2)
Week 14	7.2 (6.3)	7.9 (6.3)
Week 15	7.0 (6.3)	8.4 (6.5)
Week 16	7.1 (6.1)	8.2 (6.3)

There was no statistically significant interaction between treatment and time (interaction term 0.04, 95% CI –0.02 to 0.11; $p = 0.204$).

Patient Oriented Eczema Measure weekly for 16 weeks

There is some fluctuation in between-group differences in POEM score over the 16-week period, with some results statistically significant and others not. However, all the between-group differences are < 2 points, suggesting that even those that are statistically significant are not likely to be clinically meaningful as they are below the POEM minimal clinically important difference of 3.0 (*Tables 4* and *5* and *Figure 6*). Moreover, it is likely that some significant results may be found because of multiple testing (type I error).

TABLE 5 Patient Oriented Eczema Measure scores during the 16-week primary outcome period

POEM scores	Treatment group, mean (SD)		Univariate difference in mean POEM (95% CI)	Adjusted difference in mean POEM[a] (95% CI)
	Bath additive	No bath additive		
Primary outcome: 16-week repeated measures	–	–	–	–
Over the 16-week primary outcome period (repeated measures)	7.5 (6.0)	8.4 (6.0)	0.90 (–0.03 to 1.83)	0.41 (–0.27 to 1.10)

a Adjusted for baseline severity, clustering of participants within centre, ethnic group, steroid use and soap substitute use.

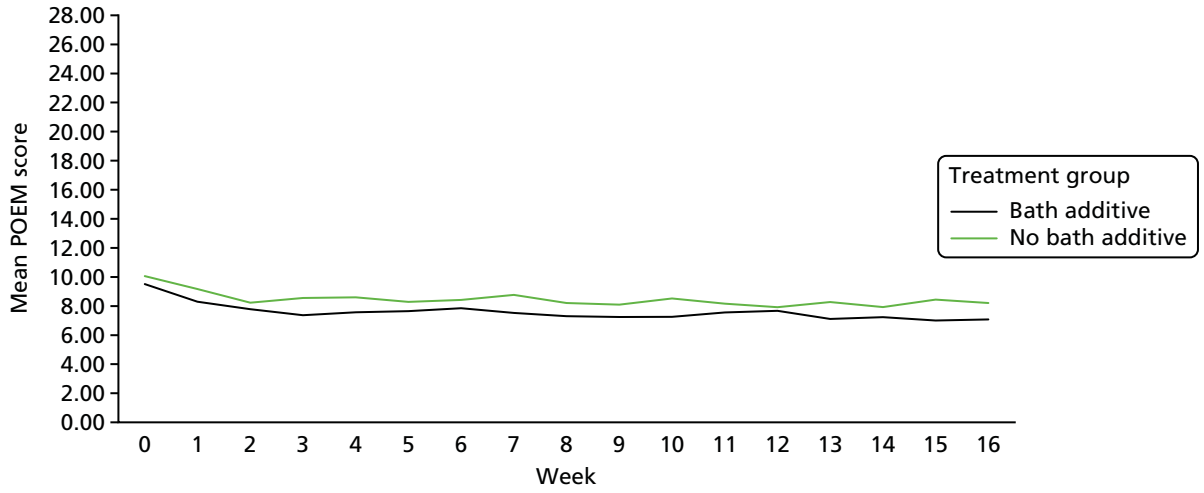


FIGURE 6 Mean POEM scores over the 16-week primary outcome period, by group.

Imputed analysis

As a sensitivity analysis, primary outcome was examined using imputed values for all missing weekly data using an individual chained equations multiple imputation model. *Table 6* shows that this produced an adjusted difference in mean POEM score between groups of 0.43 (95% CI –0.26 to 1.12). This is a very similar result to our primary analysis.

Adherence to allocated treatment (per-protocol analysis)

Parent/carer report of adherence to treatment allocation group at 16 weeks recorded 92.7% of participants in the bath additive group using bath additive 'every time' (73.8%) or 'more than half the time' (18.9%). Similarly, 92.1% of those in the no bath additive group said that they used bath additives either 'never' (87.4%) or 'less than half the time' (4.7%) (*Table 7*).

We considered two possible definitions of adherence and on neither basis was there a statistically significant difference between the groups (*Table 8*).

Participants were also asked about adherence at 52 weeks. *Table 9* shows that adherence remained high.

Secondary outcomes

Exacerbations

In total, we had exacerbations data for 470 (97.5%) children. Of these, 257 (54.7%) had at least one exacerbation as defined in the protocol (i.e. GP notes review recorded consultations in which there was mention of eczema and topical steroid or TCI was advised or prescribed).

TABLE 6 Patient Oriented Eczema Measure scores during the 16-week primary outcome period: results based on 100 imputations

Adherence to allocated treatment	Treatment group, mean (SD)		Univariate difference in mean POEM (95% CI)	Adjusted difference in mean POEM[a] (95% CI)
	Bath additive	No bath additive		
Primary outcome: 16 week repeated measures	–	–	–	–
Over the 16 week primary outcome period (repeated measures)	7.4 (6.0)	8.5 (6.0)	0.96 (0.05 to 1.87)	0.43 (–0.26 to 1.12)

a Adjusted for baseline severity, clustering of participants within centre, ethnic group, steroid use and soap substitute use.

TABLE 7 Adherence to allocated treatment during the 16-week primary outcome period

Adherence to allocated treatment	Treatment group, *n* (%)	
	Bath additive (*N* = 233)	No bath additive (*N* = 191)
Use of bath additives		
Every time	172 (73.8)	14 (7.3)
More than half the time	44 (18.9)	1 (0.5)
Less than half the time	15 (6.4)	9 (4.7)
Never	2 (0.9)	167 (87.4)
Number of baths per week	(*N* = 221)	(*N* = 176)
1–2	70 (31.7)	54 (30.7)
3–4	74 (33.5)	56 (31.8)
5–6	45 (20.4)	39 (22.2)
≥ 7, *n* (%)	32 (14.5)	27 (15.3)

TABLE 8 Patient Oriented Eczema Measure scores during the 16-week primary outcome period by adherence

Adherence to allocated treatment	Difference in mean POEM (95% CI)	
	Univariate	Adjusted
16-week repeated measures model		
'More than half' or 'every time' compared with 'less than half the time' or 'never'	0.35 (–0.58 to 1.28)	0.32 (–0.37 to 1.02)
'Every time' compared with 'never'	0.23 (–0.79 to 1.24)	0.38 (–0.39 to 1.15)

TABLE 9 Adherence to allocated treatment during the 52-week secondary outcome period

Exacerbations	Treatment group, *n* (%)	
	Bath additive (*N* = 203)	No bath additive (*N* = 176)
Use of bath additives		
Every time	118 (58.1)	9 (5.1)
More than half the time	55 (27.1)	4 (2.3)
Less than half the time	20 (9.9)	18 (10.2)
Never	10 (4.9)	145 (82.4)
Number of baths per week		
1–2	69 (36.5)	57 (35.6)
3–4	65 (34.4)	50 (31.3)
5–6	28 (14.8)	29 (18.1)
≥ 7	27 (14.3)	24 (15.0)

The distributions of the number of exacerbations is skewed and follows an approximately negative binomial distribution (*Figure 7*). As shown in *Table 10*, on average, the number of exacerbations was similar between groups. The unadjusted results indicated slightly more exacerbations in the no bath additive group, but in the adjusted model there was no significant difference in the number of exacerbations between groups.

Eczema severity over 1 year (from baseline to 52 weeks): monthly Patient Orientated Eczema Measure scores

The difference between groups in monthly POEM scores from baseline to 52 weeks was explored and tended to be non-significant (*Table 11* and *Figure 8*).

There was no statistically significant difference between the two groups at 52 weeks, based on monthly POEM scores over the period, and the CIs were well below 2 points (*Table 12*).

Dermatitis Family Impact Questionnaire

The distribution of the DFIQ was very skewed, with almost two-thirds of participants (62.9%) scoring ≤ 4 out of 27 on the scale. Therefore, a non-parametric approach has been used. The quantile regression compares the median values rather than the means. There was no statistically significant difference in the DFIQ at either 16 or 52 weeks (*Table 13*).

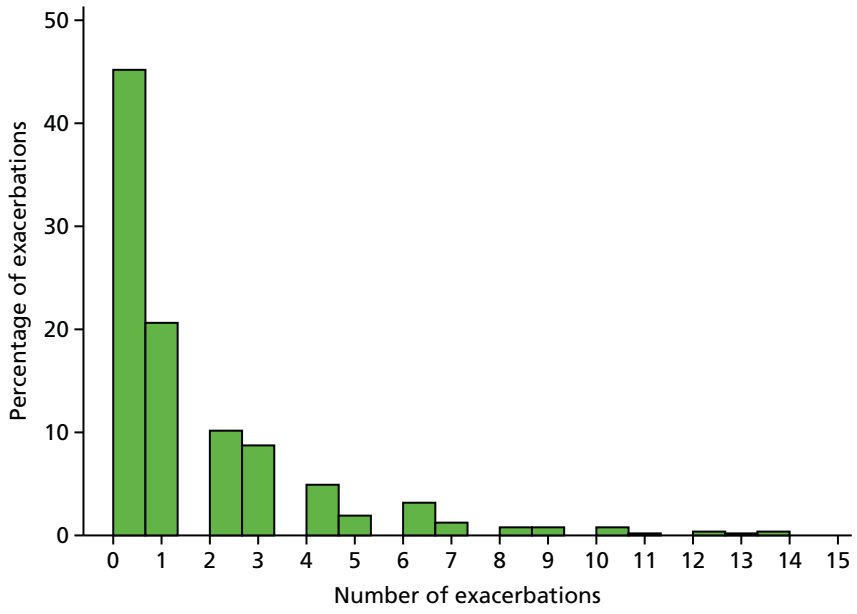


FIGURE 7 Distribution of exacerbations.

TABLE 10 Number of exacerbations of eczema over 52-week secondary outcome period

	Treatment group		RR exacerbations (95% CI)	
Time point	Bath additive	No bath additive	Univariate	Adjusted
Median number of exacerbations (IQR)	1 (0–2)	1 (0–3)	1.33 (1.02 to 1.75)	1.24 (0.96 to 1.60)

IQR, interquartile range.

TABLE 11 Mean monthly POEM scores during the 52-week secondary outcome period, by group

POEM scores	Treatment group, mean (SD)	
	Bath additive	No bath additive
Baseline	9.5 (5.7)	10.1 (5.8)
Week 4	7.6 (6.0)	8.6 (6.1)
Week 8	7.3 (6.2)	8.2 (5.8)
Week 12	7.7 (6.2)	7.9 (5.9)
Week 16	7.1 (6.1)	8.2 (6.3)
Week 20	6.9 (6.2)	8.7 (6.5)
Week 24	7.3 (6.5)	8.3 (6.7)
Week 28	7.4 (6.4)	8.8 (6.5)
Week 32	7.8 (6.7)	8.7 (7.0)
Week 36	7.2 (6.8)	8.8 (6.8)
Week 40	7.3 (6.4)	8.8 (6.7)
Week 44	6.9 (6.3)	8.2 (6.4)
Week 48	7.4 (6.6)	8.6 (6.9)
Week 52	7.1 (6.2)	8.0 (6.4)

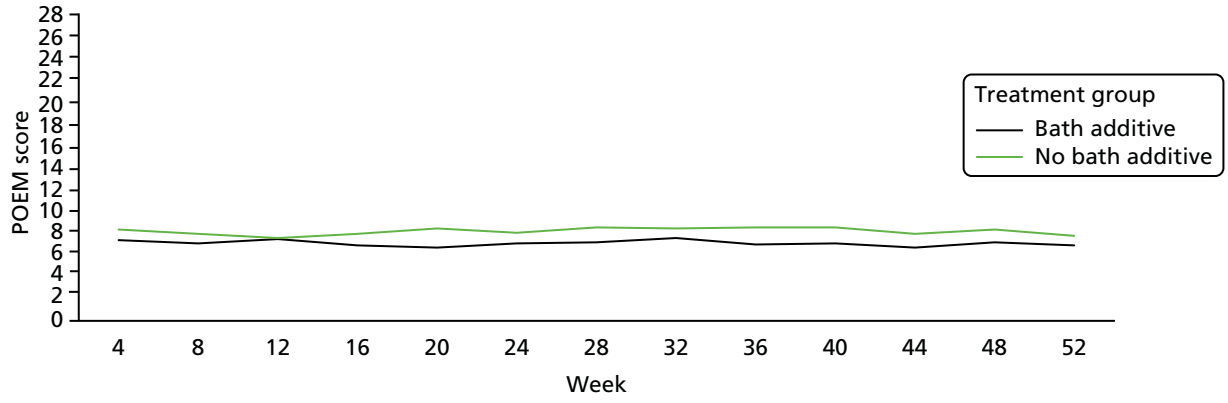


FIGURE 8 Patient Oriented Eczema Measure scores during the 52-week secondary outcome period, by group.

TABLE 12 Mean POEM scores during the 52-week secondary outcome period, by group

Time point	Treatment group, mean (SD)		Univariate difference in mean POEM (95% CI)	Adjusted difference in mean POEM (95% CI)
	Bath additive	No bath additive		
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)

TABLE 13 Dermatitis Family Impact Questionnaire at 16 and 52 weeks, by group

Prescriptions	Treatment group		Univariate difference in median DFIQ (95% CI)	Adjusted difference in median DFIQ (95% CI)
	Bath additive ($n = 230$)	No bath additive ($n = 186$)		
Median DFIQ at baseline (IQR)	2 (1–6)	3 (1–7)	–	–
Median DFIQ at 16 weeks (IQR)	2 (0–5)	3 (1–7)	1.00 (0.09 to 1.91)	0.29 (–0.57 to 1.14)
Median DFIQ at 52 weeks (IQR)	2 (0–5)	2 (0–6)	0.00 (–0.93 to 0.93)	–0.29 (–1.36 to 0.79)

IQR, interquartile range.

Health-related quality of life

See *Chapter 4*, *Health economic evaluation*, for a discussion of the CHU-9D.

Use of topical corticosteroids and topical calcineurin inhibitors

There were a total of 671 prescriptions for TCSs and 32 prescriptions for TCIs (*Table 14*). As shown in *Figure 9*, the distribution is skewed, with 44% children receiving no TCS or TCI prescription and 85% receiving fewer than five prescriptions over the 52-week study period.

Subgroup analysis

All of these analyses are intended to be hypothesis generating rather than hypothesis testing as the trial was not powered to explore the effect in subgroups and there is a risk of type I error, in which a statistically significant result is found simply because the data have been tested multiple times rather than because a genuine difference exists between the groups. However, there seems to be weak evidence in

TABLE 14 Prescriptions for TCSs/TCIs, by group

Number of prescriptions	Treatment group	
	Bath additive ($n = 258$)	No bath additive ($n = 164$)
Total number of TCS/TCI prescriptions	325	346
Median number of TCS/TCI prescriptions	0 (0–2)	1 (0–3)

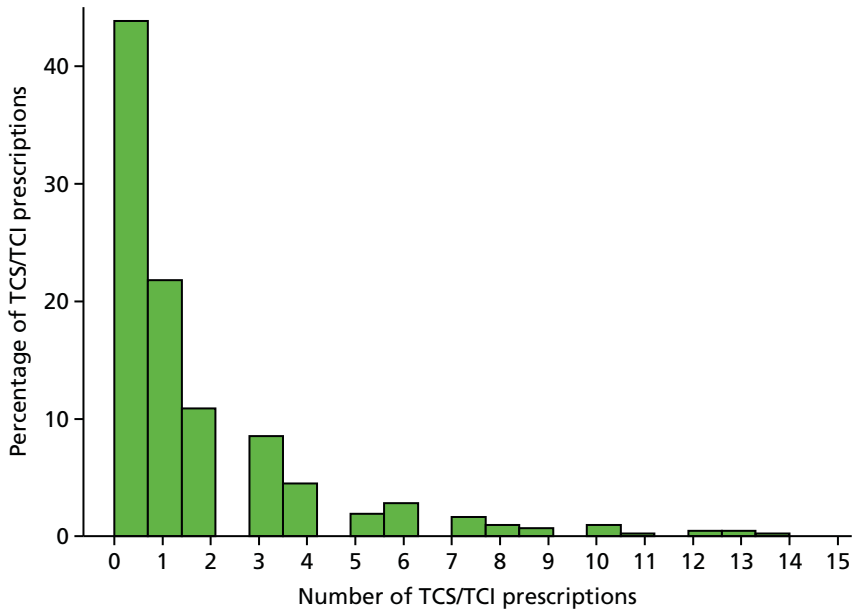


FIGURE 9 Prescriptions for TCSs and TCIs.

favour of an interaction with age. We cannot exclude the possibility of a small effect of bath additives among children aged < 5 years, as the no bath additive group had a POEM score 1.3 points higher than the group with bath additives. The upper limit of the 95% CI was 2.3, still below the now widely accepted POEM minimal clinically important difference of 3 points but reaching what we said would be considered clinically meaningful in this trial (i.e. 2 points).

A significant interaction effect was also seen in the frequency of bathing as reported at 16 weeks. There was no statistically significant difference in those children who bathed 1–4 times per week; however, in those children who bathed ≥ 5 times per week, the POEM score was 2.3 points higher (95% CI 0.63 to 3.91) in the no bath additive group. The upper CI reached 3.9, suggesting that there may be a clinically meaningful benefit to bath additives in this group, but this is a small group, with only 77 in the bath additive group and 66 in the no bath additive group (*Table 15*).

TABLE 15 Patient Oriented Eczema Measure scores during the 16-week primary outcome period, by group and subgroup

Primary outcome: 16-week repeated measures	*N* (%)	Treatment group, mean (SD)		Interaction term (95% CI)	Adjusted difference in mean POEM[a] (95% CI)
		Bath additive	No bath additive		
Age (years)					
< 5	256 (53.1)	6.99 (5.67)	9.09 (6.01)	–1.43 (–2.02 to –0.15)	1.29 (0.33 to 2.25)
≥ 5	226 (46.9)	7.97 (6.24)	7.52 (5.92)		–0.29 (–1.21 to 0.63)
Baseline severity					
Clear/mild (0–7)	187 (38.8)	4.78 (4.26)	5.22 (4.58)	–0.05 (–1.14 to 1.05)	–0.07 (–1.08 to 0.95)
Moderate (8–16)	233 (48.3)	8.14 (5.54)	9.18 (5.46)		0.65 (–0.45 to 1.74)
Severe/very severe	62 (12.9)	14.63 (6.16)	13.03 (6.92)		–1.16 (–3.62 to 1.32)
Use of leave-on emollient					
0–4 days per week	138 (28.6)	7.64 (6.68)	6.43 (5.42)	–0.02 (–2.05 to 2.01)	0.26 (–1.34 to 1.86)
5–7 days per week	344 (71.4)	8.61 (5.74)	7.93 (6.14)		0.69 (–0.39 to 1.76)
TCS use					
Any	241 (50.7)	8.40 (6.19)	9.35 (6.21)	0.52 (–1.35 to 2.40)	1.22 (–0.18 to 2.63)
None	234 (49.3)	6.63 (5.64)	7.39 (5.66)		0.58 (–0.64 to 1.81)
Frequency of bathing at 16 weeks					
1–4 times per week	255 (64.1)	7.93 (5.94)	8.00 (5.82)	2.14 (0.21 to 4.07)	–0.26 (–1.38 to 0.87)
≥ 5 times per week	143 (35.9)	6.30 (5.70)	8.75 (6.12)		2.27 (0.63 to 3.91)
Prior belief in bath additive					
1–3 low belief	106 (29.4)	7.93 (6.10)	9.27 (6.25)	0.85 (–0.52 to 2.21)	1.17 (–0.78 to 3.13)
4–6 moderate belief	158 (43.8)	8.37 (6.06)	8.68 (6.02)		–0.16 (–1.77 to 1.45)
7–9 high belief	97 (26.9)	5.70 (5.06)	7.09 (6.05)		1.80 (0.04 to 3.56)
Use of soap substitute at 16 weeks					
Any	89 (20.8)	8.09 (6.10)	9.31 (5.88)	1.30 (–0.97 to 3.57)	1.72 (–0.44 to 3.88)
None	340 (79.3)	7.17 (5.82)	7.99 (5.87)		0.36 (–0.63 to 1.35)

a Adjusted for baseline severity, ethnic group, steroid use and soap substitute use and allowing for the clustering of patients within centres and responses within patients over time.

Adverse events

No serious adverse events (SAEs) were reported during the trial period; however, one SAE, which occurred in the bath additive group and was unrelated to the trial intervention, was detected during the notes review process.

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. There was no statistically significant difference between the groups [odds ratio (OR) 1.40, 95% CI 0.79 to 2.47] (*Table 16*).

Over the full 52-week study period, 40.2% of the bath additive group and 41.3% of the no bath additive group reported at least one AE on questionnaires. As at 52 weeks, there was no statistically significant difference between the groups (OR 1.36, 95% CI 0.80 to 2.33).

TABLE 16 Adverse events by treatment allocation

	Treatment group, *n* (%)	
Adverse events	Bath additive	No bath additive
16 weeks		
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)
52 weeks		
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)

Chapter 4 Health economic evaluation

This chapter presents the economic analysis of the relative resource use, costs, clinical effectiveness and cost-effectiveness outcomes of emollient bath additives when used in addition to standard management versus standard management without bath additives for childhood eczema.

Introduction

Eczema is a skin condition that is very common in children. The economic implications of eczema in children are described in the introduction (see *Chapter 1*) of this report and are well documented in the literature.[33] Recommendations by the NICE guideline[9] on childhood eczema suggest the use of a 'complete emollient therapy' that includes bath emollient (bath additives) in addition to emollient cream and soap substitutes. However, the guideline also highlights the uncertainty from limited evidence on the benefit of including bath additives in this combination of treatments. In addition to the clinical question that this uncertainty generates, there is also an economic question to be addressed. This is even more important in the current economic climate in which NHS resources are extremely limited. Given that some estimates have suggested that bath additives account for more than one-third of the total costs treating eczema in childhood,[9,13] the relevance of the economic question becomes crucially important.

Economic evaluations alongside clinical trials (EEACT) provide timely information with high internal validity.[50] When conducting EEACT, the quality of the economic information derived depends on the features of the trial's design. However, it is generally acknowledged that pragmatic effectiveness trials are the best vehicle for economic studies.[50] For the economic analysis, the pragmatic nature of the trial means that the external validity of the economic results is increased by avoiding protocol-driven biases, such as artificial resource use.

Economic evaluations alongside clinical trials involve the comparative analysis of alternative interventions in terms of their costs and benefits.[51,52] Methodological guidelines for EEACT differ in their recommendations for the most appropriate perspective that should be adopted. As a minimum, it is recommended that analysts adopt a health system perspective for analysis. For England and Wales, this is currently considered to include the NHS and personal social services.[53]

The BATHE trial was a multicentre, pragmatic, non-blinded, randomised controlled trial with two parallel arms. The study population for the BATHE trial is described in *Chapter 3, Results*. Ideally, the economic evaluation would be factored into sample size calculations using standard methods, based on asymptotic normality, or by simulation.[54,55] However, it is common for the sample size of the trial to be based on the primary clinical outcome alone. As a consequence, sample size restrictions necessitate a focus on estimation rather than hypothesis testing for our economic evaluation.[56] The sample size in the BATHE trial was calculated for repeated measures ANOVA in weekly POEM scores over the 16-week observation period. In our protocol and the health economics analysis plan (HEAP) we stated our intention to conduct a cost-effectiveness analysis using the primary outcome, POEM, a cost–utility analysis using utility values obtained from the paediatric CHU-9D and to also report cost per exacerbation avoided. However, the economic results in this study reveal that none of these outcomes showed a clinically important difference. Therefore, our approach was to proceed by reporting our findings and ultimately presenting our economic evaluation in the form of cost–consequences analysis,[57] as per our HEAP. Following this, the economic evaluation was conducted from the NHS and Personal Social Services perspective; however, family-borne costs (FbCs), in the form of additional analyses, were also incorporated and the combined results are also reported in this chapter.

Methods

The range of cost and effectiveness outcomes used are described in this chapter. The economic evaluation used resource use, cost and effectiveness outcomes data collected for all of the participants enrolled in the BATHE trial as described in *Chapter 3, Results*. The time points of the evaluation were the 16- and 52-week follow-up periods used for the trial. The maximum 52-week follow-up period of the trial means that discounting of costs and outcomes was not relevant and was not conducted. The intervention was conducted in primary care settings; however, the setting for the economic evaluation covers both primary and secondary care resource use.

The analyses were carried out using the ITT approach, and individual patient data were estimated for each participant. All economic analyses were performed using Stata® version 14 (StataCorp LP, College Station, TX, USA) and Microsoft Excel.

Resource use and valuation, health-related quality of life and data collection tools

Resource use

The categories of resource use included in this study were determined by the perspective of the analysis (NHS). For each participant, health-care resource utilisation was measured using two data sources.

First, a modified version of the Client Service Receipt Inventory (CSRI) questionnaire[58] adapted for the BATHE trial was used to collect resources reported by parents/carers. The CSRIs were completed at baseline asking parents about resource use over the 3-month period prior to randomisation, at 16 weeks (the trial primary end point) and after that in 3-month intervals up to 52 weeks, as this is considered to be the most appropriate recall length for reporting.[59] The CSRI asked about resource use stemming from the child's eczema and, in addition to providing information on primary and secondary care resource use, it also allowed reporting of resources associated with salient clinical events, such as days lost from school for children and from work for parents because of their child's eczema as well as FbCs.

Second, GP electronic patient records were examined in order to record resource use on study case report forms called GP notes review (NR) throughout this report. The selection process for each resource variable was undertaken by assessors and the principal investigator (MS) identifying the 'eczema-related' items as opposed to 'other' resource use. The NR forms used in this study were designed to capture the frequency and intensity of care provided to each child, based on GP practice record and any complications experienced. The NR forms recorded GP and other primary care consultations, referrals to secondary care, as well as prescriptions and medications during the trial period for each participant.

We have used the triangulation of resource use data to validate our data by cross-verifying the same information. The data were used not in a complementary manner, integrating results, but for verification and better understanding of the data. Resource use, recorded using both approaches, is reported separately in the form of mean (SD) and 95% CIs, taking into account the skewness of the data.

Valuation

The valuation of resources used within the trial period involves quantifying each resource item used by multiplying it by the perspective unit cost of each item. The products estimated were summarised to calculate the individual cost for each participant. The principal costs are those associated with the use of bath additives and the primary and secondary health-care contacts and medications attributed to eczema. The comprehensive profile of resources captured for each participant was valued using national tariffs and expressed in Great British pounds, 2016 prices. The primary care resource use items were valued using the Personal Social Services Research Unit *Unit Costs of Health and Social Care 2016*.[60] The resource use items from the secondary care data were mainly valued using the *NHS Reference Costs for 2015 to 2016*.[61] When necessary, the unit costs were adjusted for inflation using the hospital and community health services index.[61]

Costs

Once resources were identified and valued, individual patient costs were estimated, mean estimates by group were calculated and differences in mean costs (ΔC) and mean effects (ΔE) between the groups were calculated. Arithmetic means were used to estimate differences between groups. Independent sample *t*-tests were used to test for differences in costs and effects observed between the groups; all statistical tests were two-tailed. However, cost data often do not conform to the assumptions for standard statistical tests for comparing differences in arithmetic means. They are usually right skewed and truncated at zero because of the small number of participants with high resource use and those participants who incur no costs. The assessment of uncertainty for each measure was estimated and reported in the form of SDs and CIs for point estimates using regression models.[50]

There were five main cost categories created from the data collection tools: (1) primary care resource use, (2) secondary care, including hospital admissions and accident and emergency (A&E), (3) medications for eczema, (4) prescriptions for eczema and (5) FbCs. Days lost from school for children and days lost from work because of their child's eczema for parents are also reported.

Effectiveness outcomes

Three alternative outcomes were identified as relevant and of interest to policy-makers, providers, funders of care and patients. These were:

1. the study primary outcome POEM, details of which are reported in *Chapter 3, Results*
2. exacerbations of eczema during the study period (see *Chapter 3, Results*)
3. a generic preference-based health-related quality of life (HRQoL) measure for paediatric populations (i.e. CHU-9D).

Health-related quality of life

Eczema has been shown to have a detrimental effect on children's QoL.[2,3] The paediatric QoL measure CHU-9D was used to collect data at baseline and at 16- and 52-week follow-up. In contrast to adult measures for HRQoL, for which there is widespread consensus in support of using the EQ-5D questionnaire, there is no consensus regarding the paediatric HRQoL measures. However CHU-9D, which is a relatively recently developed measure, has gained ground within the paediatric research community.[46] Responses obtained using the CHU-9D questionnaire were used to estimate utility values for each participant, reporting quality-adjusted life-years (QALYs) gained.

Analysis

Our analysis follows a prespecified HEAP. The purpose of the economic analysis was to estimate costs, cost and effectiveness outcome differences associated with the treatment, the variability of differences and whether or not the differences occurred by chance. Our economic results reported here are expressed in terms of net and incremental costs and effectiveness outcomes.

Regression models were used to estimate net and incremental cost and effectiveness outcomes and to adjust for confounders where appropriate. We used MMLMs controlling for baseline POEM and allowing for clustering of patients within centres, thereby following the same process undertaken for the statistical analysis for consistency of results.

Correlation and baseline covariates for costs and quality-adjusted life-years

We conducted correlation analysis to assess variables for inclusion as confounders in the analyses of cost and QALY outcomes. This allowed us to identify covariates for the outcomes of interest performing adjustment and including these variables in our analysis. Therefore, in addition to reporting unadjusted and adjusted results for baseline covariates, the effects of age and severity of eczema are also assessed and reported in the form of exploratory analysis.

Missing data

Extracts of health-care contact records were available from all trial sites; these were cross-checked against the CSRI questionnaires completed by parents/carers, ensuring that any conflicts or omissions were detected and corrected. The results of the economic evaluation were restricted to the observed data, making the assumption that any missing observations were missing at random. For the CSRI and the CHU-9D, this includes cases in which the parents failed to complete the questionnaires and for the NR data include cases of participants who left the participating GP surgery during the trial period and for whom the date of departure was unknown. However, the CSRI questionnaires were completed irrespective of any change in GP surgery occurring during the trial period. Therefore, the missing observations among the two data sources were compared and considered missing at random only when the observed data supported this assumption.

Addressing uncertainty

The sampling uncertainty of the economic outcomes were reported by estimating and reporting SDs for within-group estimates of costs and outcomes and CIs for between-group differences and comparison. To address potential threats arising from unrepresentative recruiting centres, we used hypothesis testing of homogeneous results across centres. The primary outcome (POEM) allowed us also to report costs by severity levels.[28] To avoid the danger of spurious subgroup effects and the probability of finding a difference due solely to random variation, we report these results in the form of exploratory MMLM analysis.

Results

The sample population for the economic analysis was 482 participants in total, the same as the statistical analysis. Missing values are indicated in each section below. In our sample, 264 participants were included in the bath additives group and 218 participants in the no bath additives group. The clinical and sociodemographic characteristics of the BATHE participants included in our economic study were well balanced between groups (see *Table 2*). The sections below report resource use and cost estimates from both data sources (i.e. CSRI and GP NR), and *Table 17* presents the unit costs used for the valuation of the resources used.

Resource use, costs and intervention costs

Resource use and costs source: Client Service Receipt Inventory

Resource use

Table 18 presents the eczema-related primary and secondary care consultations at baseline and at 16- and 52-week follow-ups as reported by parents completing the CSRI questionnaires. The baseline number of consultations showed no significant difference between the two groups. The total mean number of consultations was 0.89 (SD 1.4) and 0.95 (SD 1.6) for the bath additives and no bath additives groups, respectively, with a difference of –0.06 (95% CI –0.32 to 0.21). This difference indicated that there was no need to adjust for baseline resource use differences.

The mean number of primary and secondary care consultations at 16 weeks was 0.53 (SD 1.2) for the bath additives group and 0.88 (SD 1.7) for the no bath additives group, with a statistically significant difference of –0.35 (95% CI –0.62 to –0.08), indicating that fewer consultations were reported within the bath additives group. However, this statistically significant difference was not retained in the 52-week results (see *Table 18*).

TABLE 17 Unit costs

Resource or service	Unit cost (£)[a]	Source
GP	36.00	*Unit Costs of Health and Social Care 2016*[60]
GP telephone call	14.60	*Unit Costs of Health and Social Care 2016*[60]
Practice nurse	13.22	*Unit Costs of Health and Social Care 2016*[60]
Walk-in centre, out of hours	43.10	*Unit Costs of Health and Social Care 2016*[60]
Allergy clinic	168.67	*NHS Reference Costs 2015 to 2016*[61]
Child health	70.00	*NHS Reference Costs 2015 to 2016*[61]
Paediatric respiratory medicine	218.38	*NHS Reference Costs 2015 to 2016*[61]
Paediatric dermatology	135.41	*NHS Reference Costs 2015 to 2016*[61]
Dermatology nurse (specialist nurse)	86.00	*Unit Costs of Health and Social Care 2016*[60]
Paediatrics	194.36	*NHS Reference Costs 2015 to 2016*[61]
Nutrition and dietetics	71.17	*NHS Reference Costs 2015 to 2016*[61]
Out of hours	138.01	*Unit Costs of Health and Social Care 2016*[60]
Eye unit	96.34	*NHS Reference Costs 2015 to 2016*[61]
Health visitor	53.00	*NHS Reference Costs 2015 to 2016*[61]
Other outpatients	135.00	*Unit Costs of Health and Social Care 2016*[60]
Phototherapy unit	85.61	*NHS Reference Costs 2015 to 2016*[61]
Paediatric clinical immunology	235.69	*NHS Reference Costs 2015 to 2016*[61]
A&E	98.00	*Unit Costs of Health and Social Care 2016*[60]
A&E by ambulance	146.86	*NHS Reference Costs 2015 to 2016*[61]
Hospital admissions (dermatology)	987.50	*NHS Reference Costs 2015 to 2016*[61]
Non-specified hospital admissions	236.00	*NHS Reference Costs 2015 to 2016*[61]
Clinical genetics	439.45	*NHS Reference Costs 2015 to 2016*[61]
Microbiology	7.63	*NHS Reference Costs 2015 to 2016*[61]
Phlebotomy	3.37	*NHS Reference Costs 2015 to 2016*[61]
Hospital pharmacist	72.00	*Unit Costs of Health and Social Care 2016*[60]
Chinese herbal specialist consultation	35.00	Private appointment (web)
NHS 111, cost per call	8.41	*Unit Costs of Health and Social Care 2016*[60]
Prescription cost	8.00	*Unit Costs of Health and Social Care 2016*[60]
Bath additives (costed by item)	–	BNF 68 (2016)[36]
Various medications (costed by item)	–	BNF 68 (2016)[36]

BNF, *British National Formulary*.
a 2016 prices.

TABLE 18 Eczema-related primary and secondary care resource use data from the CSRI

Resource or service	Treatment group, mean (SD)		Difference, mean (95% CI)
	Bath additives	No bath additives	
Baseline	*n* = 264	*n* = 218	
GP	0.70 (1.1)	0.75 (1.2)	–0.05 (–0.25 to 0.16)
Practice nurse	0.06 (0.4)	0.05 (0.3)	0.02 (–0.05 to 0.09)
Paediatric dermatologist	0.05 (0.2)	0.04 (0.2)	0.00 (–0.04 to 0.05)
Dermatology nurse	0.01 (0.1)	0.02 (0.2)	–0.01 (–0.04 to 0.01)
Paediatrics	0.02 (0.2)	0.01 (0.1)	0.01 (–0.02 to 0.04)
Allergy clinic	0.01 (0.1)	0.01 (0.1)	–0.01 (–0.02 to 0.01)
Other outpatients	0.00 (0.0)	0.00 (0.1)	0.00 (–0.01 to 0.00)
Out of hours	0.01 (0.1)	0.03 (0.2)	–0.02 (–0.06 to 0.01)
A&E	0.00 (0.0)	0.01 (0.2)	–0.01 (–0.03 to 0.00)
Dermatology admissions	0.00 (0.0)	0.00 (0.0)	0.00 (0.00 to 0.00)
Other	0.03 (0.3)	0.02 (0.1)	0.02 (–0.02 to 0.05)
Total number of consultations	0.89 (1.4)	0.95 (1.6)	–0.06 (–0.32 to 0.21)
16 weeks	*n* = 236	*n* = 194	
GP	0.40 (0.9)	0.68 (1.3)	–0.29 (–0.50 to –0.08)
Practice nurse	0.03 (0.2)	0.01 (0.2)	0.01 (–0.02 to 0.05)
Paediatric dermatologist	0.05 (0.3)	0.07 (0.4)	–0.02 (–0.08 to 0.05)
Dermatology nurse	0.02 (0.1)	0.01 (0.1)	0.00 (–0.02 to 0.03)
Paediatrics	0.01 (0.1)	0.01 (0.1)	0.00 (–0.02 to 0.02)
Allergy clinic	0.01 (0.1)	0.04 (0.3)	–0.04 (–0.07 to 0.00)
Other outpatients	0.00 (0.0)	0.00 (0.0)	0.00 (0.00 to 0.00)
Out of hours	0.01 (0.1)	0.03 (0.2)	–0.02 (–0.05 to 0.01)
A&E	0.01 (0.1)	0.00 (0.0)	0.01 (–0.01 to 0.02)
Dermatology admissions	0.00 (0.0)	0.00 (0.0)	0.00 (0.00 to 0.00)
Other	0.02 (0.1)	0.03 (0.2)	–0.01 (–0.05 to 0.03)
Total number of consultations	0.53 (1.2)	0.88 (1.7)	–0.35 (–0.62 to –0.08)
52 weeks	*n* = 203	*n* = 184	
GP	1.19 (2.0)	1.67 (2.4)	–0.48 (–0.92 to –0.05)
Practice nurse	0.10 (0.6)	0.04 (0.3)	0.05 (–0.03 to 0.14)
Paediatric dermatologist	0.18 (0.8)	0.14 (0.8)	0.03 (–0.13 to 0.20)
Dermatology nurse	0.08 (0.7)	0.06 (0.3)	0.03 (–0.08 to 0.13)
Paediatrics	0.02 (0.2)	0.05 (0.3)	–0.03 (–0.08 to 0.02)
Allergy clinic	0.03 (0.3)	0.10 (0.6)	–0.07 (–0.15 to 0.02)
Other outpatients	0.00 (0.1)	0.02 (0.1)	–0.01 (–0.03 to 0.01)
Out of hours	0.06 (0.4)	0.06 (0.3)	0.00 (–0.07 to 0.08)
A&E	0.01 (0.1)	0.00 (0.0)	0.01 (–0.01 to 0.03)
Dermatology admissions	0.00 (0.0)	0.01 (0.1)	–0.01 (–0.02 to 0.00)
Other	0.05 (0.3)	0.18 (1.1)	–0.13 (–0.29 to 0.03)
Total number of consultations	1.73 (3.1)	2.32 (3.7)	–0.59 (–1.27 to 0.08)

Costs

Following valuation (see *Table 17*) of the resources used, *Table 19* presents the costs estimated from the parent-reported CSRI, for baseline and 16- and 52-week follow-ups. The mean estimates for the bath additives group and the no bath additives group at 16 weeks were £26.52 (SD £74.4) and £47.42 (SD £116.6), respectively, showing a statistically significant difference of –£20.89 (95% CI –£39.13 to –£2.65), indicating a decrease in the bath additives group in the costs of primary and secondary care consultations. As with the resource use data, the statistical significance of the difference was not retained in the 52-week costs of primary and secondary care consultations, which showed a difference of –£28.38 (95% CI –£80.06 to –£23.30).

TABLE 19 Eczema-related primary and secondary care costs from the CSRI

Resource or service	Treatment group, mean (SD)		Difference, mean (95% CI)
	Bath additives	No bath additives	
Baseline	*n* = 264	*n* = 218	
GP	25.23 (39.2)	26.92 (43.8)	–1.69 (–9.12 to 5.74)
Practice nurse	0.85 (5.4)	0.61 (4.4)	0.24 (–0.65 to 1.14)
Paediatric dermatologist	6.16 (32.8)	5.59 (30.0)	0.56 (–5.11 to 6.24)
Dermatology nurse	0.98 (11.8)	1.97 (12.9)	–1.00 (–3.21 to 1.22)
Paediatrics	4.42 (41.3)	1.78 (18.6)	2.63 (–3.30 to 8.57)
Allergy clinic	1.28 (14.7)	2.32 (19.7)	–1.04 (–4.12 to 2.03)
Other outpatients	0.00 (0.0)	0.62 (9.1)	–0.62 (–1.72 to 0.49)
Out of hours	1.02 (16.6)	4.33 (30.1)	–3.31 (–7.57 to 0.94)
A&E	0.00 (0.0)	1.35 (14.8)	–1.35 (–3.14 to 0.44)
Dermatology admissions	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)
Other	1.18 (15.4)	1.53 (12.0)	–0.35 (–2.86 to 2.16)
Total costs of consultations	41.11 (86.5)	47.02 (100.1)	–5.92 (–22.61 to 10.78)
16 weeks	*n* = 236	*n* = 194	
GP	14.44 (33.1)	24.74 (46.4)	–10.30 (–17.85 to –2.75)
Practice nurse	0.37 (2.5)	0.18 (2.5)	0.19 (–0.29 to 0.67)
Paediatric dermatologist	6.89 (41.9)	9.31 (51.1)	–2.42 (–11.24 to 6.40)
Dermatology nurse	1.46 (12.9)	1.18 (11.6)	0.28 (–2.07 to 2.62)
Paediatrics	1.10 (16.9)	1.34 (18.6)	–0.24 (–3.60 to 3.13)
Allergy clinic	0.95 (14.6)	6.96 (45.3)	–6.00 (–12.15 to 0.14)
Other outpatients	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)
Out of hours	0.76 (11.7)	3.71 (31.5)	–2.95 (–7.31 to 1.41)
A&E	0.55 (8.5)	0.00 (0.0)	0.55 (–0.65 to 1.75)
Dermatology admissions	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)
Other	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)
Total costs of consultations	26.52 (74.4)	47.42 (116.6)	–20.89 (–39.13 to –2.65)

continued

TABLE 19 Eczema-related primary and secondary care costs from the CSRI (*continued*)

Resource or service	Treatment group, mean (SD)		Difference, mean (95% CI)
	Bath additives	No bath additives	
52 weeks	*n* = 203	*n* = 184	
GP	43.03 (70.9)	60.33 (85.8)	–17.29 (–32.97 to –1.62)
Practice nurse	1.28 (7.3)	0.55 (3.4)	0.73 (–0.43 to 1.89)
Paediatric dermatologist	26.68 (117.2)	19.38 (108.3)	7.30 (–15.32 to 29.92)
Dermatology nurse	7.20 (60.6)	4.99 (24.6)	2.22 (–7.20 to 11.63)
Paediatrics	4.15 (47.4)	9.86 (56.2)	–5.71 (–16.07 to 4.65)
Allergy clinic	5.26 (44.3)	16.50 (95.3)	–11.24 (–25.87 to 3.40)
Other outpatients	0.67 (9.5)	2.20 (17.1)	–1.54 (–4.27 to 1.20)
Out of hours	8.20 (54.9)	7.58 (43.6)	0.62 (–9.35 to 10.59)
A&E	1.13 (11.4)	0.00 (0.0)	1.13 (–0.53 to 2.78)
Dermatology admissions	0.00 (0.0)	5.37 (72.8)	–5.37 (–15.41 to 4.68)
Other	0.85 (9.7)	0.08 (1.1)	0.77 (–0.64 to 2.18)
Total costs of consultations	98.45 (235.1)	126.83 (281.5)	–28.38 (–80.06 to 23.30)

Resource use and costs source: general practitioner notes review

Resource use

Table 20 presents resource use data for eczema, recorded from the electronic GP notes review for the 52-week follow-up. As for the CSRI estimates, these estimates are resources used for eczema-related consultations. In the 52-week follow-up, participants in the bath additives group had a mean of 1.01 (SD 1.8) consultations and the no bath additives group had a mean of 1.43 (SD 2.8) consultations. The difference between the two groups, however, as seen in the data from the CSRI for the same period, was not statistically significant: –0.42 (95% CI –0.83 to 0.00) (see *Table 20*). The annual mean number of prescriptions related to eczema were 5.47 (SD 8.4) for the bath additives group and 6.40 (SD 8.6) for the no bath additives group, with a non-significant difference of –0.93 (95% CI –2.47 to 0.61). As expected, the number of prescriptions for bath additives showed a statistically significant difference of 3.55 (95% CI 2.99 to 4.10).

The primary and secondary care number of consultations for health issues other than eczema (see *Table 20*) showed very similar results, with a non-statistically significant difference of –0.69 (95% CI –1.59 to 0.22) between the two groups during the 52-week trial follow-up.

Costs

Following valuation of the resources used, *Table 21* presents the costs at the 52-week follow-up. Similar results to CSRI data were obtained using the NR data, with the total costs of consultations estimated as £54.63 (SD £133.20) and £73.00 (SD £210.20) for the bath additives group and the no bath additives group, respectively, with a non-statistically significant difference of –£18.37 (–£49.57 to –£12.84). The difference between the two groups in cost of prescriptions for eczema was –£7.41 (–£19.72 to £4.91), whereas the difference in cost of medications for eczema was –£6.36 (–£15.91 to £3.19); none reached statistical significance. The results presented in *Tables 18–25* have not been adjusted for potential baseline covariates.

TABLE 20 Eczema-related primary and secondary care resource use from the GP NR

Resource or service	Treatment group, mean (SD)		Difference, mean (95% CI)
	Bath additives ($n = 261$)	No bath additives ($n = 214$)	
52 weeks			
GP	0.54 (1.0)	0.67 (1.2)	–0.13 (–0.33 to 0.07)
GP telephone call	0.10 (0.4)	0.13 (0.5)	–0.03 (–0.11 to 0.06)
Practice nurse	0.11 (0.4)	0.26 (0.9)	–0.15 (–0.27 to –0.03)
Walk-in centre/out of hours	0.04 (0.2)	0.08 (0.5)	–0.04 (–0.11 to 0.03)
Total primary care consultations	0.79 (1.4)	1.14 (2.0)	–0.35 (–0.66 to –0.05)
Allergy clinic	0.01 (0.1)	0.02 (0.1)	–0.01 (–0.03 to 0.01)
Child health	0.00 (0.0)	0.01 (0.2)	–0.01 (0.04 to 0.01)
Respiratory–asthma clinic	0.00 (0.1)	0.00 (0.0)	0.00 (0.00 to 0.01)
Paediatric dermatologist	0.15 (0.6)	0.13 (0.7)	0.02 (–0.10 to 0.14)
Dermatology nurse (specialist nurse)	0.00 (0.1)	0.02 (0.2)	–0.01 (–0.04 to 0.01)
Paediatrician	0.02 (0.2)	0.03 (0.2)	–0.01 (–0.04 to 0.03)
Dietitian	0.01 (0.1)	0.01 (0.1)	0.00 (–0.02 to 0.02)
Out of hours	0.00 (0.1)	0.02 (0.1)	–0.01 (–0.03 to 0.00)
Eye unit	0.00 (0.0)	0.00 (0.1)	0.00 (–0.01 to 0.00)
Health visitor	0.00 (0.0)	0.00 (0.1)	0.00 (–0.01 to 0.00)
Other outpatients	0.00 (0.0)	0.00 (0.1)	0.00 (–0.01 to 0.00)
Phototherapy	0.00 (0.1)	0.00 (0.0)	0.00 (0.00 to 0.01)
Paediatric clinical immunology	0.00 (0.1)	0.00 (0.0)	0.00 (0.00 to 0.01)
A&E	0.00 (0.0)	0.01 (0.2)	–0.01 (–0.03 to 0.00)
A&E by ambulance	0.00 (0.0)	0.00 (0.1)	0.00 (–0.01 to 0.00)
Emergency	0.00 (0.0)	0.01 (0.1)	–0.01 (–0.03 to 0.01)
Dermatology admissions	0.01 (0.1)	0.00 (0.1)	0.00 (–0.01 to 0.02)
Hospital nights (> 1)	0.00 (0.1)	0.00 (0.1)	0.00 (–0.01 to 0.01)
Total secondary care consultations	0.22 (0.8)	0.29 (1.2)	–0.07 (–0.25 to 0.12)
Total number of consultations	1.01 (1.8)	1.43 (2.8)	–0.42 (–0.83 to 0.00)
Prescriptions related to eczema	5.47 (8.4)	6.40 (8.6)	–0.93 (–2.47 to 0.61)
Bath additives prescriptions	3.96 (3.9)	0.41 (1.6)	3.55 (2.99 to 4.10)

TABLE 21 Eczema-related primary and secondary care costs from the GP NR

Resource or service	Treatment group, mean cost (£) (SD)		
	Bath additives ($n = 261$)	No bath additives ($n = 214$)	Difference, mean (95% CI)
52 weeks			
GP	17.70 (34.5)	22.05 (38.6)	–4.35 (–10.95 to 2.25)
GP telephone call	1.07 (4.2)	1.35 (5.5)	–0.28 (–1.16 to 0.59)
Practice nurse	1.47 (5.3)	3.46 (11.9)	–1.99 (–3.60 to –0.37)
Walk-in centre/out of hours	1.65 (8.3)	3.42 (22.8)	–1.77 (–4.76 to 1.22)
Total primary care consultations	21.89 (38.6)	30.29 (54.7)	–8.40 (–16.84 to 0.05)
Allergy clinic	1.94 (18.0)	2.36 (19.9)	–0.43 (–3.85 to 2.99)
Child health	0.00 (0.0)	1.31 (19.1)	–1.31 (–3.64 to 1.02)
Respiratory–asthma clinic	0.84 (13.5)	1.02 (14.9)	–0.18 (–2.75 to 2.38)
Paediatric dermatologist	20.49 (85.1)	19.29 (107.7)	1.20 (–16.18 to 18.58)
Dermatology nurse (specialist nurse)	0.99 (11.9)	2.41 (16.5)	–1.42 (–3.99 to 1.14)
Paediatrician	4.37 (28.6)	6.59 (50.5)	–2.23 (–9.47 to 5.02)
Dietitian	0.55 (8.8)	0.67 (6.9)	–0.12 (–1.57 to 1.33)
Out-of-hours emergency	0.53 (8.5)	3.87 (26.5)	–3.34 (–6.76 to 0.08)
Eye unit	0.00 (0.0)	0.45 (6.6)	–0.45 (–1.25 to 0.35)
Health visitor	0.00 (0.0)	0.25 (3.6)	–0.25 (–0.69 to 0.19)
Other outpatients	0.00 (0.0)	0.63 (9.2)	–0.63 (–1.75 to 0.49)
Phototherapy	0.33 (5.3)	0.00 (0.0)	0.33 (–0.38 to 1.04)
Paediatric clinical immunology	0.90 (14.6)	0.00 (0.0)	0.90 (–1.06 to 2.86)
A&E	0.00 (0.0)	2.06 (22.4)	–2.06 (–4.78 to 0.67)
A&E by ambulance	0.00 (0.0)	0.69 (10.0)	–0.69 (–1.91 to 0.53)
Dermatology admissions	1.81 (20.6)	1.10 (16.1)	0.71 (–2.69 to 4.10)
Hospital nights (> 1)	0.00 (0.1)	0.00 (0.1)	0.00 (–0.01 to 0.01)
Total secondary care consultations	32.74 (114.8)	42.71 (179.2)	–9.97 (–36.67 to 16.73)
Total costs of consultations	54.63 (133.2)	73.00 (210.2)	–18.37 (–49.57 to 12.84)
Prescriptions (any eczema, no bath additives)	43.76 (66.9)	51.17 (69.1)	–7.41 (–19.72 to 4.91)
Bath additives prescriptions	31.66 (31.1)	3.29 (12.8)	28.37 (23.91 to 32.84)
Medications related to eczema	30.28 (49.4)	36.64 (56.3)	–6.36 (–15.91 to 3.19)
Bath additives	20.22 (19.5)	2.03 (7.6)	18.19 (15.41 to 20.97)
Intervention costs	51.88 (50.2)	5.32 (20.4)	46.56 (39.37 to 53.75)
Health system costs	180.50 (237.0)	166.12 (293.0)	14.38 (–33.45 to 62.21)
FbCs	90.93 (276.6)	142.30 (390.1)	–51.37 (–118.49 to 15.74)
Total costs (health system and family-borne)	281.78 (426.0)	306.23 (513.9)	–24.45 (–119.06 to 70.17)

Intervention costs

The intervention costs were estimated from the NR data and are presented in *Table 22*, for the 52-week follow-up. The intervention cost includes the actual prescription costs in addition to the cost of the bath additives. The total mean intervention cost for the bath additives group was £51.88 (SD £50.20). As stated in *Resource use*, a small number of participants in the no bath additives group received prescriptions for bath emollients and the mean cost of these was estimated to be £5.32 (SD £20.40). The cost of bath additives during the 52-week follow-up for the bath additives group was £20.22 (SD £19.50) and the cost of prescriptions for bath additives was £31.66 (SD £31.10).

Family-borne costs

Table 23 presents estimates of the FbCs as reported by parents within the CSRI questionnaire. The FbCs were estimated at baseline and at 16-week and 52-week follow-up, but none of the differences assessed at each time period reached statistical significance. Overall, parents within the no bath additives group annually spent £51.37 (95% CI –£118.49 to £15.74) more on household items for their child's eczema than parents within the bath additives group (see *Table 23*), but this difference was not statistically significant.

TABLE 22 Non eczema-related primary and secondary care costs from the GP NR

Resource or service	Treatment group, mean cost (£) (SD)		Difference, mean (95% CI)
	Bath additives ($n = 261$)	No bath additives ($n = 214$)	
52 weeks			
GP	1.48 (2.0)	1.86 (2.8)	–0.38 (–0.81 to 0.06)
GP telephone call	0.58 (1.2)	0.68 (1.5)	–0.10 (–0.35 to 0.14)
Practice nurse	0.82 (1.2)	0.77 (1.3)	0.05 (–0.18 to 0.27)
Walk-in centre, out of hours	0.30 (0.6)	0.43 (1.0)	–0.13 (–0.27 to 0.01)
Allergy clinic	0.00 (0.1)	0.01 (0.2)	–0.01 (–0.03 to 0.01)
Child health	0.00 (0.1)	0.00 (0.0)	0.00 (0.00 to 0.01)
Asthma clinic	0.00 (0.1)	0.00 (0.0)	0.00 (0.00 to 0.01)
Paediatric dermatologist	0.01 (0.1)	0.01 (0.1)	0.00 (–0.02 to 0.01)
Paediatrician	0.07 (0.4)	0.08 (0.4)	–0.01 (–0.09 to 0.06)
Dietitian	0.00 (0.0)	0.00 (0.1)	0.00 (–0.01 to 0.00)
Out-of-hours emergency	0.06 (0.2)	0.12 (0.6)	–0.06 (–0.14 to 0.01)
Eye casualty	0.00 (0.1)	0.00 (0.1)	0.00 (–0.01 to 0.01)
Paediatric clinical immunology	0.00 (0.1)	0.00 (0.0)	0.00 (0.00 to 0.01)
A&E	0.06 (0.3)	0.07 (0.3)	–0.01 (–0.07 to 0.05)
A&E by ambulance	0.00 (0.0)	0.00 (0.1)	0.00 (–0.01 to 0.00)
Emergency	0.00 (0.0)	0.01 (0.1)	–0.01 (–0.02 to 0.00)
Dermatology admissions	0.04 (0.2)	3.74 (4.8)	0.00 (–0.04 to 0.03)
Paediatric admissions	0.00 (0.1)	0.00 (0.1)	0.00 (–0.01 to 0.01)
Hospital nights (> 1)	0.06 (0.3)	0.00 (0.0)	–0.01 (–0.07 to 0.05)
Other outpatients	0.71 (1.3)	0.68 (1.2)	0.03 (–0.19 to 0.25)
Total number of non-eczema consultations	4.14 (4.0)	4.75 (5.5)	–0.61 (–1.47 to 0.25)

TABLE 23 Family-borne costs from the CSRI

Household items[a]	Treatment group, mean cost (£) (SD)		
	Bath additives (*n* = 264)	No bath additives (*n* = 218)	Difference, mean (95% CI)
Baseline			
Clothes	7.09 (63.3)	4.45 (15.5)	2.64 (–5.99 to 11.27)
Food	4.13 (16.9)	5.39 (19.4)	–1.26 (–4.51 to 1.99)
Over-the-counter products	7.15 (15.7)	9.02 (19.9)	–1.87 (–5.06 to 1.31)
Laundry	7.64 (20.5)	8.47 (18.2)	–0.83 (–4.33 to 2.68)
Equipment	1.92 (12.8)	0.83 (12.2)	1.09 (–1.15 to 3.34)
Travel costs	0.78 (6.6)	0.66 (3.3)	0.12 (–0.84 to 1.08)
Complementary medicine	2.56 (37.0)	0.47 (3.4)	2.10 (–2.84 to 7.04)
Other	2.27 (36.9)	0.07 (0.8)	2.20 (–2.72 to 7.12)
Total family-borne extra costs	33.54 (105.6)	29.35 (49.5)	4.19 (–11.09 to 19.47)
16 weeks	**n = *236***	**n = *194***	
Clothes	3.42 (11.5)	4.38 (16.7)	–0.96 (–3.64 to 1.72)
Food	2.60 (10.1)	4.19 (20.4)	–1.59 (–4.56 to 1.39)
Over-the-counter products	6.23 (14.5)	7.35 (17.2)	–1.12 (–4.13 to 1.89)
Laundry	4.98 (11.7)	8.01 (19.0)	–3.03 (–5.97 to –0.09)
Equipment	0.71 (5.6)	0.86 (5.7)	–0.15 (–1.23 to 0.92)
Travel costs	0.85 (8.9)	0.49 (2.9)	0.35 (–0.96 to 1.67)
Complementary medicine	6.32 (95.5)	0.93 (6.5)	5.39 (–8.11 to 18.89)
Other	0.05 (0.6)	0.23 (2.2)	–0.18 (–0.46 to 0.11)
Total family-borne extra costs	25.15 (112.6)	26.44 (52.7)	–1.29 (–18.55 to 15.97)
52 weeks	**n = *203***	**n = *184***	
Clothes	11.58 (29.8)	22.15 (99.1)	–10.57 (–24.90 to 3.76)
Food	12.86 (45.6)	26.57 (112.5)	–13.72 (–30.59 to 3.15)
Laundry	20.11 (45.3)	28.70 (73.3)	–15.86 (–35.98 to 4.27)
Over-the-counter products	23.23 (42.3)	39.09 (138.9)	–8.59 (–20.64 to 3.46)
Equipment	2.46 (12.8)	6.99 (47.5)	–4.53 (–11.33 to 2.28)
Travel costs	2.87 (21.7)	4.10 (20.8)	–1.24 (–5.49 to 3.02)
Complementary medicine	8.44 (110.4)	7.93 (48.7)	0.51 (–16.84 to 17.86)
Other	9.24 (98.4)	6.76 (53.0)	2.48 (–13.55 to 18.51)
Total family-borne extra costs	90.93 (276.6)	142.30 (390.1)	–51.37 (–118.49 to 15.74)

a Parents were asked to report household items in excess of normal use attributable to their child's eczema.

Figure 10 highlights the skewed distribution of FbCs, showing that this difference is to a great extent driven by outliers. When these outliers were normalised by assigning mean values to them, the mean difference of the FbCs was reduced to –£40.28 (–£78.78 to –£1.78). *Figure 11* shows the normalised data, highlighting the similarities between the two groups.

Days lost from school for children and days lost from work for parents because of eczema

Table 24 shows days lost from school or nursery for children and days lost from work for parents because of their child's eczema. Overall, there is no statistically significant difference between the two groups at any time point, including baseline.

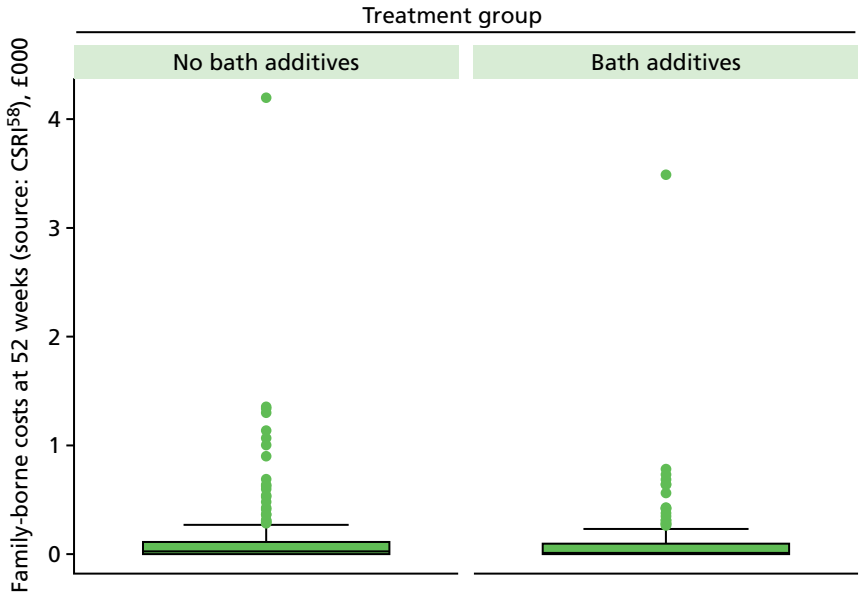


FIGURE 10 Family-borne costs. Data sourced from the CSRI.[58]

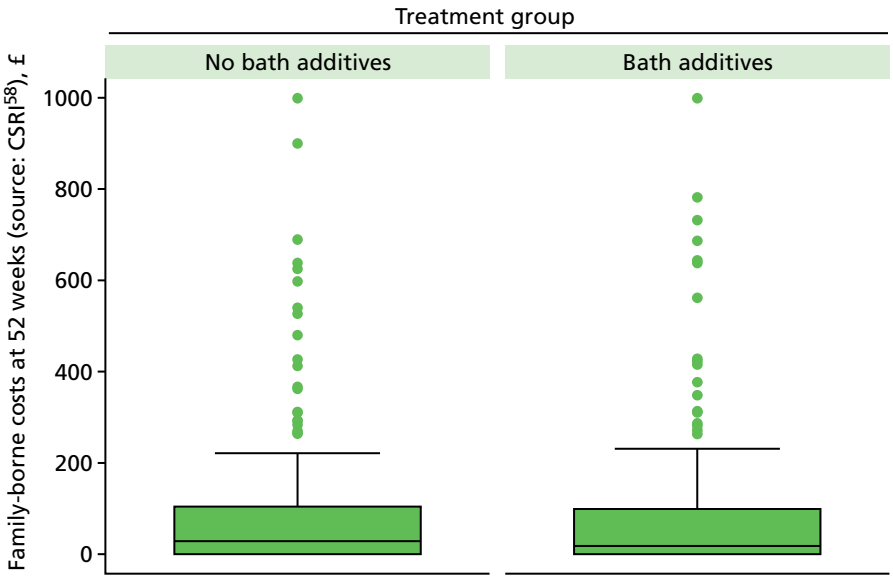


FIGURE 11 Family-borne costs (normalised outliers). Data sourced from the CSRI.[58]

TABLE 24 Days lost from school/nursery for children or work for parents because of a child's eczema

	Treatment group				
	Bath additives		No bath additives		
Days lost	*n*	Mean (SD)	*n*	Mean (SD)	Difference, mean (95% CI)
From school/nursery					
Baseline	264	0.36 (1.6)	218	0.19 (0.9)	0.17 (–0.07 to 0.40)
Week 16	236	0.25 (0.9)	194	0.17 (0.9)	0.07 (–0.10 to 0.25)
Week 52	210	0.67 (2.0)	189	0.51 (2.2)	0.16 (–0.25 to 0.58)
From work (parents)					
Baseline to week 16	264	0.51 (3.0)	218	0.43 (1.7)	0.07 (–0.38 to 0.52)
Week 16 to week 52	236	0.17 (0.8)	194	0.14 (0.7)	0.03 (–0.12 to 0.18)
52-week period	210	0.71 (2.3)	189	0.47 (1.7)	0.24 (–0.16 to 0.64)

Health-related quality of life, health profiles, utility scores and quality-adjusted life-years

Table 25 summarises the mean utility values generated using the data from the preference-based QoL measure CHU-9D at baseline and at 16 weeks and 52 weeks. There was no difference between the two groups at baseline and minimal differences in opposite directions at 16 weeks and 52 weeks. The 52-week mean QALY per participant was 0.90 (SD 0.1) for the bath additives group and 0.91 (SD 0.1) for the no bath additives group. Similarly, there was no significant difference detected at the 16-week follow-up. Therefore, in line with primary outcome POEM, both the utility values and the QALYs are extremely similar in both groups, indicating no effect of bath additives on HRQoL.

Analysis

Table 26 presents differences between groups for costs and QALYs: (1) controlling for centre and (2) adjusted for baseline severity (POEM) and allowing for the clustering of patients within centre. Both the unadjusted (*Table 25* and see *Tables 20* and *22*) the adjusted results (*Table 26*) present no statistically significant differences between the two groups. This was the case using both data sources for costs. The cost difference between the data sources reported here could be attributable to parents' different perspective classifying resources used as opposed to GP records (eczema related vs. other health issues).

Table 27 presents a summary of the key findings of the economic evaluation.

TABLE 25 Health-related quality of life and QALYs

	Treatment group				
	Bath additives		No bath additives		
QoL outcomes	*n*	Mean (SD)	*n*	Mean (SD)	Difference, mean (95% CI)
Utility values (CHU-9D)					
Baseline	264	0.90 (0.1)	218	0.90 (0.1)	0.00 (–0.02 to 0.02)
Week 16	211	0.91 (0.1)	173	0.89 (0.1)	0.01 (–0.01 to 0.03)
Week 52	177	0.90 (0.1)	150	0.91 (0.1)	–0.01 (–0.03 to 0.01)
QALYs					
Baseline to week 16	211	0.30 (0.0)	173	0.30 (0.0)	0.00 (0.00 to 0.01)
Week 16 to week 52	174	0.61 (0.1)	147	0.60 (0.1)	0.00 (–0.01 to 0.01)
52-week period	174	0.91 (0.1)	147	0.90 (0.1)	0.00 (–0.01 to 0.02)

TABLE 26 Costs and QALYs adjusted for baseline POEM and controlling for centre

Outcomes	*n*	Difference, mean (95% CI)	
		1[a]	2[b]
16 weeks			
HRQoL			
QALYs	384	0.00 (0.00 to 0.01)	0.00 (0.00 to 0.00)
Costs (£)			
HsC – CSRI	430	–22.57 (–40.66 to –4.47)	–20.80 (–38.64 to –2.95)
FbC – CSRI	430	–1.53 (–18.74 to 15.69)	0.15 (–16.83 to 17.14)
52 weeks			
HRQoL			
QALYs	321	0.00 (–0.01 to 0.02)	0.00 (–0.02 to 0.02)
Costs (£)			
HsC – CSRI	387	–33.50 (–84.48 to 17.49)	–28.85 (–78.58 to 20.88)
FbC – CSRI	387	–52.36 (–118.99 to 14.27)	–47.56 (–113.19 to 18.07)
Total health system costs – NR (£)	474	11.87 (–35.62 to 59.35)	19.18 (–26.33 to 64.70)

HsC, health system cost.
a Difference controlling for centre.
b Difference adjusting for baseline POEM and controlling for centre.

TABLE 27 Economic evaluation: key findings

Key findings at 52-week follow-up	Treatment group				Difference, mean (95% CI)
	Bath additives		No bath additives		
	n	Mean (SD)	*n*	Mean (SD)	
Full sample					
HsC (£)[a]	260	180.50 (237.0)	214	166.12 (293.0)	14.38 (–33.45 to 62.21)
QALYs	174	0.91 (0.1)	147	0.90 (0.1)	0.00 (–0.01 to 0.02)
Children < 5 years old					
HsC (£)[a]	132	190.58 (247.0)	118	188.55 (306.0)	2.03 (–66.94 to 71.0)
QALYs	88	0.91 (0.1)	73	0.90 (0.1)	0.01 (–0.01 to 0.03)
Children > 5 years old					
HsC (£)[a]	128	170.11 (226.6)	96	138.55 (275.2)	31.56 (–34.58 to 97.69)
QALYs	86	0.90 (0.1)	74	0.90 (0.1)	0.00 (–0.03 to 0.02)

HsC, health system cost.
a HsC source: NR, including medications and intervention costs.

For the purpose of the analysis that follows, the NR data source acted as the reference data source. *Table 27* presents the key findings for the full sample. However, because of uncertainties in measuring QoL for very young children, we have also presented our results according to whether participants were younger or older than 5 years. This was done in order to avoid any measurement issues affecting the very young group diluting the results of the older children group. Although potential limitations measuring QoL for very young children still remain, our results (QALYs) show that there were no different conclusions to draw.

Our sample was not powered to detect subgroup differences; however, in the form of the exploratory analysis that we report, *Table 28* shows that the most important factors determining costs and QALYs in children with eczema are the severity of their symptoms and their age, with younger children incurring higher costs. In our 52-week results, severity of symptoms was associated with increased costs up to £203 per year for the most severe cases. Similarly, severity of symptoms was associated with reduced QALYs from 0.09 for the most severe symptoms to 0.04 for the less severe symptoms. The results from our exploratory analysis should be interpreted with caution, but we consider them indicative.

Implications of the results

We aimed to assess whether or not bath additives, when used in addition to standard management versus standard management alone, could provide a cost-effective treatment option. The economic study shows that in children with eczema, the use of bath additives does not provide any additional economic or otherwise benefit. Therefore, bath additives cannot be considered value for money for the NHS. Given the amount spent annually on bath additives, this has important implications for the NHS and decision-makers alike.

Strengths and weaknesses

A strength of this economic study is the use of alternative data sources estimating the health system costs. This allowed us to present a comprehensive resource use profile for children with eczema. We also consider the pragmatic nature of this trial, which reinforces the external validity of our results, to be a strength.

The broad spectrum of the age of the children included in our trial is a limitation when assessing QoL, especially as there are no suitable measures to assess the QoL of very young children. Although we cannot eliminate this limitation, we have reported our results for the full sample alongside the two different groups (< 5 years/> 5 years) to avoid diluting the conclusions drawn by presenting only the full sample, which includes the very young age group and introduces additional uncertainty due to measurement limitations.

TABLE 28 Effect of bath additives, age < 5 years and severity of eczema on costs and QALYs

Explanatory variable	Cost, adjusted mean (95% CI); *p*-value		52-week QALYs; adjusted mean (95% CI); *p*-value ($n = 321$)
	16 weeks ($n = 430$)	52 weeks ($n = 474$)	
Bath additives group	–18.11 (–36.12 to –0.09); 0.049	25.16 (–21.16 to 71.48); 0.287	0.00 (–0.02 to 0.01); 0.878
Effect of other explanatory variables			
Severity of eczema[a]			
Mild	– – –	– – –	– – –
Moderate	14.03 (–5.23 to 33.29); 0.153	72.70 (23.09 to 122.31); 0.004	–0.04 (–0.06 to –0.02); 0.000
Severe	36.19 (7.42 to 64.96); 0.014	202.56 (128.49 to 276.62); 0.000	–0.09 (–0.11 to –0.06); 0.000
Age category			
< 5 years old	24.02 (–41.90 to –6.15); 0.008	41.63 (–87.72 to 4.46); 0.077	0.00 (–0.02 to 0.02); 0.901
Constant	40.11 (30.97 to 97.29); 0.021	51.90 (8.87 to 178.19); 0.245	0.94 (0.91 to 0.97); 0.000

a Severity defined as mild (0–7), moderate (8–16) and severe (≥ 17).

Conclusions

Given the finding of no clinical effectiveness of the intervention in this study, it could be argued that a full cost-effectiveness analysis has nothing to offer in addition to what is already presented in this chapter. We have, however, presented our results at length adopting a cost–consequences analysis format, in line with our HEAP. During this trial, we collected comprehensive data for both the costs and QoL, and we believe that these data present a valuable source of information for future studies and decision-making.

Comparing the alternative data sources, the difference between primary and secondary care consultations reported by parents (CSRI) and recorded within the GP electronic records (NR) perhaps shows the different perceptions classifying consultations as being for eczema or not, and this raises important questions for future economic studies. By comparing the two data sources, we also validated our assumption that missing data were missing at random.

Given that emollient bath additives account for more than one-third of the total costs of treating eczema in childhood,[9,13] we believe that the relevance of our economic results is essential.

Chapter 5 Discussion

Main findings

This trial found no evidence of any clinical benefit or cost-effectiveness of adding bath additive to the standard management of eczema in children aged between 12 months and 12 years. After controlling for baseline variables, the weekly POEM score over 16 weeks in the no bath additive group was 0.41 points higher than in the bath additives group (95% CI –0.27 to 1.10) on a scale of 0 (clear) to 28 (most severe). The narrow 95% CIs suggest that a clinically important treatment effect is unlikely to have been missed and is well within the meaningful difference of 2.0 between groups that we aimed to detect.

Although not powered to look at subgroups, prespecified exploratory subgroup analyses explored features that could plausibly modify the effectiveness of bath additives including age, baseline severity, use of leave-on emollient, use of TCSs/TCIs, use of soap substitute, frequency of bathing and prior belief in bath emollient. Although most of these showed no significant differences between groups, we could not exclude the possibility that younger children or children bathing ≥ 5 times per week might experience very modest benefit [1.29 (95% CI 0.33 to 2.25) and 2.27 (95% CI 0.63 to 3.91), respectively]. Although the published minimal clinically important difference for POEM is now widely regarded as being 3.0,[41,42] at the trial design stage we based our sample size calculation on a difference of 2.0, given that this could be regarded as meaningful for an inexpensive intervention in a population with mild eczema.

Primary analyses were carried out on an ITT basis. We carried out a per-protocol analysis in addition to this in order to explore the effect of adherence to randomised treatment allocation. This allowed an estimate of effectiveness for children whose carers reported that they had regularly used bath additives rather than the effectiveness of being allocated to the bath additive group; this also showed no statistically significant difference between groups.

Relevance to existing literature

Previous systematic reviews have noted the sparse randomised trial evidence for bath additives and have been unable to draw conclusions regarding their effectiveness.[9] Current prescribing guidelines vary, but a recent analysis of 216 formularies in England and Wales showed that 68% recommend their use.[22] This is the largest trial to date exploring the effectiveness of these widely used products.

In a large case series (post-marketing surveillance) of 3566 people,[62] most of whom had eczema and were aged ≤ 5 years, the tolerability of the bath additive was stated to be 'good' or 'very good' for 96.8% of participants. However, few data were presented on other treatments used and the absence of an experimental design meant that the effectiveness of the treatment cannot be inferred.

Although the addition of antiseptics to emollients is used by some for the prevention of infected eczema, there is no robust evidence for this.[63] There are some reports that irritant reactions are more frequent in individuals treated with bath additives with added antiseptics.[20] The trial reported here supports the finding that most bath additives are well tolerated but did not explore the effectiveness or tolerability of bath additives containing antiseptics/antimicrobials or antipruritics.

Strengths

This was an adequately powered randomised controlled trial, with high follow-up rates and good adherence to randomised trial allocations.

As an unblinded trial with a participant-reported measure as the primary outcome, there was a risk of bias in favour of the trial intervention, which is widely prescribed in childhood eczema in the UK. However, a convincing placebo is not possible for emollient bath additives and we wished to design a trial with a clinical outcome relevant to participants. As bath additives are a relatively inexpensive and widely used intervention, we felt that the risk of expectation of benefit leading to systematic bias in outcome reporting was less problematic. Having made this design decision, the finding of no significant difference between groups gives additional reassurance that we are very unlikely to be missing a meaningful benefit from the use of bath additives in childhood eczema.

Limitations

Adherence to allocation group

This trial aimed to test only the effectiveness of adding bath additives to bath water and aimed for no difference in soap use between groups. Standard advice for both groups was to use a leave-on emollient as a soap substitute. When parents/carers were keen to use an existing wash product, we advised that direct application to skin constituted use of the product as a soap substitute and this was compatible with their child entering the trial. However, if they wished to add an emollient or other bath additive product to bath water then they were not eligible to take part.

Self-report and NR data both suggest that most people adhered to this treatment allocation, but there are limitations in the strength of both of these data sources as participants may have potentially misreported. In addition, for NR data, receiving a prescription does not equate to use of a product and not receiving a prescription does not necessarily mean not using the product, given that bath additives are available to purchase over the counter. However, parents/carers were encouraged to report difficulties with allocation openly and we have no reason to believe that there was misreporting. Furthermore, to use bath additives regularly requires obtaining repeat prescriptions, which most participants in the bath additive group did. Purchasing bath additives over the counter is relatively unusual for children as all NHS prescriptions for under-16-year-olds are free in the UK.

Imbalance in group sizes at baseline

We used simple randomisation in this trial, stratified by centre. Simple randomisation preserves allocation concealment, which is often better than stratified randomisation and is less subject to technical errors.[64] Although achieving balance on key covariates may seem appealing, studies have shown that it adds little in terms of statistical efficiency to the approach taken in this study of adjusting in the analysis.[65,66]

Although simple randomisation can result in imbalances in the numbers recruited to each group, in a large trial, such as BATHE, the overall balance between groups should be preserved. The baseline characteristics showed that, although there were slightly more participants allocated to the bath additive group than the no bath additive group, the key characteristics were well balanced.

Participant-reported outcome measure: specific limitations

Given the young age group, the primary outcome (POEM) was recorded by proxy by parents/carers, although they were encouraged to involve children where possible. POEM is well validated for use by patient or by proxy (carer report).[29] POEM is recommended by NICE[9] and the international HOME initiative.[30]

Generalisability

Participants were recruited through primary care in southern England, the west of England and in Wales. As > 90% of eczema is managed in primary care in the UK, these findings would be applicable to most children with eczema. The response rate to letters of invitation from practices, although in keeping with similar studies,[67] was relatively low, suggesting that participating families may have been particularly motivated to be involved in research. However, of those who replied that they did not wish to participate, by far the most common reason for this was that their child's eczema was no longer a problem. It seems likely that many who did not respond would have not returned the reply slip for this reason.

Emollient bath additives are popular eczema treatments with some parents/carers and some prescribers in countries where baths, as opposed to showers, are the norm, although there is international lack of consensus about their role (Professor Masutaka Furue, Kyushu University, Japan, 13 October 2017; Dr Roberto Takaoka, University of São Paulo, Brazil, 12 October 2017; and Professor Eric Simpson, Oregon Health and Science University, USA, 12 October 2017; personal communication).

Chapter 6 Conclusions

Implications for health care

This trial provides useful information for parents/carers who are seeking to manage their child's eczema. Findings from this trial indicate that parents/carers can be advised that adding bath additive to bath water is unlikely to provide additional benefit over standard therapy in childhood eczema. Although we cannot completely exclude the possibility that children aged < 5 years who bath frequently might benefit, this is unlikely to be a clinically meaningful benefit.

Prescribers and policy-makers have already started to look at limiting the use of emollient bath additives in some Clinical Commissioning Group (CCG) areas as a potential cost saving, although an analysis of CCGs (England) and Local Health Boards (Wales) in 2016–17 showed that 68% still recommended the use of bath additives.[22] The findings of this trial would support the suggestion that adding emollients to bath water has no benefit, or minimal benefit at best, and prescribing budgets and parental energies may be best spent on more effective treatments. However, emollient products may be used for more than one purpose and some emollients marketed as bath additives are used as soap substitutes. Our study has not addressed the question of whether or not 'bath additives' are effective as soap substitutes, but it has found that advising parents/carers that pouring bath additives into bath water is not effective.

Anecdotal and qualitative evidence (Santer *et al.*[68] and Dr Miriam Santer, University of Southampton, 2015, personal communication) suggests that some families use emollient bath additives as an alternative to leave-on emollients as a response to child resistance. As there is good evidence for the effectiveness of leave-on emollients,[69] our findings suggest that families may be turning to an ineffective treatment (bath additives) because of barriers experienced in adhering to an effective eczema treatment (leave-on emollients). Barriers to regular application of topical treatments, such as leave-on emollients, include the time-consuming nature of such treatments and child resistance.[68] Some strategies to overcome barriers, such as involving the child in treatment, allowing them to choose an emollient that they like, distracting the child during treatment or using rewards, are likely to be more helpful than others, such as physically restraining the child or reducing the frequency of applications.[68] Promoting positive strategies to facilitate regular topical treatment use seems more likely to be helpful than using emollient bath additives as an alternative to leave-on emollients.

It is essential to highlight to prescribers and policy-makers that, although this trial found that pouring emollient bath additives into bath water was not beneficial, the role of emollients as soap substitutes or leave-on emollients has not been explored. Both soap substitutes and leave-on emollients have a much stronger a priori rationale for effectiveness than emollient bath additives and greater clinical consensus around their effectiveness, even though there are relatively few large trials in this area.[69] It is therefore important that policy-makers do not conflate the findings of this study, which relates to a specific method of delivering emollients to the skin via bath water, with the use of emollients as leave-on preparations or as soap substitutes as recommended by the NICE guideline on eczema in children.[9]

Recommendations for research

Some participants in this trial were using emollient bath additives as soap substitutes and further research is needed to explore what the best soap substitute is for use in eczema.

Several questions around emollients and washing in eczema that were highlighted in the James Lind Alliance PSP[34] remain outstanding, in particular the shared priority from patients and health-care professionals, 'which emollient is the most effective and safe in treating eczema?'. This is currently being

addressed by the NIHR HTA-funded Best Emollient for Eczema (BEE) study (15/130/07). The priority from patients and carers, namely 'what is the best way for people with eczema to wash: frequency of washing, water temperatures, bath versus shower?' remains unanswered. The priority from health-care professionals, namely 'how effective are interventions to reduce skin infections in the management of eczema?', is also related to the question of bathing and also remains unanswered.

Chapter 7 Patient and public involvement

In line with other NIHR research, patient and public involvement (PPI) was seen as a key element of the research from the outset. However, the PPI focus was secondary to the primary question of the effectiveness of bath additives and the Guidance for Reporting Involvement of Patients and the Public 2 short form checklist[70] are therefore used for reporting PPI activities rather than the Guidance for Reporting Involvement of Patients and the Public long form (see *Table 29*).[71]

TABLE 29 The GRIPP2 short form: brief description of BATHE PPI

Section and topic	Item	Reported in section
Aim	The aim of PPI in this study was to ensure that all aspects of trial design were acceptable to patients and parents/carers and to maximise dissemination of findings	See *Topic prioritisation*
	The study question had been prioritised by the NIHR HTA programme prior to funding	
Methods	Amanda Roberts, an experienced PPI co-applicant, was involved in all stages of trial design, management and interpretation	See details in *Trial design* and *Trial conduct*
	We consulted the CEBD Patient Panel at the study design stage and during recruitment and will feed back findings to this group	
	We carried out an online survey through social media at the study design stage, including > 200 parents/carers	
	We invited additional patient representatives (and paid travel expenses) to the end-of-study meeting for presentation and discussion of study findings. This included representatives of national patient advocacy groups (NSGCCE, NES, Eczema Outreach Scotland)	
Study results	We maintained good relationships with the PPI co-applicant and wider PPI links. Questions remain from some in the wider eczema community about why this trial was prioritised. All involved in the trial are keen that the findings should not be used to limit choice for people with eczema and their families around emollient prescriptions	See *End-of-study meeting*
Discussion and conclusions	We maintained good rates of recruitment and very good rates of retention in the trial and believe that this is related to the focus on keeping trial procedures as easy as possible for participating families, assisted by advice from PPI	See *Discussion and conclusions*
Reflections/critical perspective	The study went well but the dissemination and reception of findings will be crucial to its impact and we are at the very early stages of this process. However, the experience of our PPI co-applicant and other PPI input means that we hope to be in a strong position for anticipating and mitigating against potential negative impacts from the dissemination of study findings	–

CEBD, Centre for Evidence-Based Dermatology; NES, National Eczema Society; NSGCCE, Nottingham Support Group for Carers of Children with Eczema.

Topic prioritisation

This trial was funded by the NIHR HTA programme as the result of a commissioned call. The research topic had been suggested through the NIHR HTA website topic suggestion form. The NIHR HTA programme has PPI embedded in its prioritisation processes and Boards.

The James Lind Alliance PSP for Eczema[34] published its top 10 priority topics in 2012. Even though this call was not advertised directly as a result of the PSP, it addresses issues that patients, carers and clinicians highlighted as an outcome of the PSP, including priorities around bathing/washing and also around the best ways to use emollients.

Patient and public involvement co-applicant

Amanda Roberts has eczema, has two (grown-up) children with eczema and is an experienced PPI representative on a number of bodies, including the Centre for Evidence-Based Dermatology (CEBD) Patient Panel. Amanda is in contact with many carers of children with eczema through running the Nottingham Support Group for Carers of Children with Eczema (NSGCCE).

Trial design

The trial design benefited from having an experienced PPI representative as a member of our research team. Amanda Roberts contributed at all stages of trial design, including joining trial development telephone conferences, being copied in on all correspondence and drafts. Furthermore, between outline and full grant application, we carried out a workshop with members of the CEBD Patient Panel and carried out an online survey, including questions about information that parents/carers would like to receive in the trial information sheets and willingness to take part in the proposed trial. These provided useful feedback, although participants in both the survey and the workshop were typically caring for children with moderate or severe eczema, so it was noted at the time that, as the majority of study participants would have mild eczema, there was a possibility that their carers might hold different views.

We found that 33% (67 out of 203) of survey respondents would not be happy to participate if allocated to the 'usual-care' group and 9.3% (19 out of 204) would not wish to participate if allocated to the bath additive group. Two workshop members also had reservations about randomisation, one holding a strong view that one particular bath additive helped her child's eczema and another who felt that bath additives did not help her child's eczema.

These concerns highlighted the need for careful development of participant information leaflets, in consultation with patient/parent support groups, to communicate clinical equipoise about the benefits of bath additives. These concerns also confirmed the need for collection of 'prior belief' in bath additive prior to recruitment, as well as to ask invited participants if they would share reasons for declining to participate, so that we could seek to measure to what extent these concerns influenced recruitment.

Focus group members and survey respondents were also concerned about what would happen if their child's eczema deteriorated while they were in the study. Robust discussion and SOPs around consent processes were developed to ensure that carers were prepared to be randomised to either group. However, it was also made clear to parents/carers that they would receive all other treatment as usual, remain free to consult their usual clinical team as needed and could change bath additive if necessary. When these measures were insufficient, they could, of course, withdraw from the study.

We found that the duration of the study was perceived as a barrier by some completing the survey, supporting our decision to use weekly measures to 16 weeks as our primary outcome rather than 12 months. Furthermore, we found that a small proportion were not using baths, regardless of age, so we included bath use of at least once a week as an eligibility criterion.

Trial conduct

Amanda Roberts attended the team training day in 2014 and gave a presentation on patient/parent/carer perspectives to all trial staff. She attended further face-to-face meetings on trial conduct in 2016 and 2017.

Study materials: Amanda Roberts and members of the CEBD Patient Panel were involved in reviewing and revising the patient information sheet, child information sheet, consent form (see *Appendix 12*), assent form (see *Appendix 13*) and invitation letter.

Newsletters: Amanda Roberts was involved in providing content for quarterly newsletters to participants' families and reviewing the newsletters prior to them being circulated.

After the first few months of recruitment, we found that we were getting relatively low response rates. We therefore discussed recruitment at a CEBD PPI meeting in March 2015. Attendees responded that the patient information sheet was too dense and unfriendly. Using this feedback, a short and colourful summary leaflet was designed and included in the invitation pack from July 2015, but we were unable to detect any change in the response rate as a result of the additional information.

The independent Trial Steering Committee, appointed by the NIHR HTA programme, included independent PPI representative Rosemary Humphries.

End-of-study meeting for presentation and discussion on interpretation of findings

We invited additional patient representatives to the end-of-study discussion of findings, including representatives of national patient advocacy groups (NSGCCE, National Eczema Society, Eczema Outreach Scotland). Attendees included Amanda Roberts (PPI co-applicant), another member of the CEBD Patient Panel (a mother of children with severe eczema), the Chief Executive and Director of Services of the National Eczema Society and the PPI member of the BATHE Trial Steering Committee.

Patient representatives raised concerns that the trial results might be used to justify removing bath emollients from prescribing formularies and that some families rely on bath emollients as soap substitutes. Others acknowledged that understanding the likely effectiveness of these products was potentially useful for parents trying to work out how best to 'live with eczema'. The study team highlighted that the trial design was more likely to result in a false-positive result than a false-negative result, as it was an open trial with a participant-reported primary outcome measure (and was thus open to expectation bias). All felt that it was better for prescribers and commissioners to make prescribing decisions based on high-quality evidence, although they would not wish to see the use of emollient soap substitutes compromised through misinterpretation of trial findings.

The context of these concerns is that CCG formularies are increasingly restricting the availability of emollients in general, and bath additives in particular, and the National Eczema Society reports that patients are having problems accessing preferred products. Others were also concerned that there is an underlying drive to remove all emollients from the prescribing guidelines, which would leave patients and carers in a difficult position and potentially lead to more flare-ups and greater service use. It was agreed that we need to be clear in all communications that emollients should still be available and that this study suggests only that pouring them into the bath does not offer benefit. All agreed that using the term 'bath additives' rather than 'bath emollients' might avert some confusion.

Discussion and conclusions

Amanda Roberts was an integral member of the team from the first decision to respond to the call and was an enthusiastic, reliable and inspiring member of the team in terms of maintaining the focus of the study on providing answers for parents/carers on one of the key questions in eczema care. Her input was invaluable.

The following quotation illustrates her perspective on her involvement:

> *My take on what I contributed to the trial was this: everyone on the team was enthusiastic about bearing in mind the needs of the patients and carers – but they had other hats. I reminded people in telephone conferences things – like producing the newsletters etc. – that had been perhaps lost sight of in all the business of the trial.*
>
> *Reproduced with permission*

Input from the CEBD Patient Panel was useful at a number of points, but the other aspect of PPI input that was particularly valuable was obtaining feedback on results from a wide range of stakeholders, particularly PPI, at the end-of-study meeting for discussion of interpretation of findings. This prepared and briefed us for report writing, identifying early on how to communicate messages about trial findings and preparing wider materials for dissemination with trial participants, parents/carers of children with eczema and clinical and commissioning communities.

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Contributions of authors

Miriam Santer (Associate Professor in Primary Care Research) contributed to the conception and design of the study, trial oversight (as chief investigator) and interpretation of the data and drafted and critically reviewed the report.

Kate Rumsby (Clinical Trial Manager) contributed to the design of the study, managed the trial, contributed to interpretation of the data and drafted and critically reviewed the report.

Matthew J Ridd (Consultant Senior Lecturer in Primary Health Care) contributed to the conception and design of the study, was responsible for oversight of the trial at the Bristol centre (as principal investigator), contributed to interpretation of the data and critically reviewed the report.

Nick A Francis (Senior Clinical Research Fellow) contributed to the design of the study, was responsible for oversight of the trial at the Cardiff centre (as principal investigator), contributed to interpretation of the data and critically reviewed the report.

Beth Stuart (Senior Research Fellow and Medical Statistician) contributed to the conception and design of the study, was responsible for the statistical analysis plan, carried out the statistical analyses, contributed to interpretation of the data and drafted and critically reviewed the report.

Maria Chorozoglou (Senior Research Fellow and Health Economist) contributed to the design of the study, carried out the health economics analyses, contributed to interpretation of the data and drafted and critically reviewed the report.

Amanda Roberts (Patient Representative) contributed to the conception and design of the study and interpretation of the data and critically reviewed the report.

Lyn Liddiard (Clinical Studies Officer) contributed to the management of the study and to the collection of data and critically reviewed the report.

Claire Nollett (Clinical Studies Officer) contributed to the management of the study and to the collection of data and critically reviewed the report.

Julie Hooper (Trial Administrator) contributed to the management of the study and to the collection of data and critically reviewed the report.

Martina Prude (Clinical Studies Officer) contributed to the management of the study and to the collection of data and critically reviewed the report.

Wendy Wood (Research Adviser in NIHR Research Design Service and former Senior Trials Manager Southampton CTU) contributed to the conception and design of the study, was responsible for oversight of study setup and critically reviewed the report.

Emma Thomas-Jones (Senior Trial Manager) contributed to the design of the study, contributed to interpretation of the data and drafted and critically reviewed the report.

Taeko Becque (Research Fellow and Medical Statistician) carried out statistical analyses and critically reviewed the report.

Kim S Thomas (Professor of Applied Dermatology Research and Co-Director of the Centre of Evidence-Based Dermatology) contributed to the conception and design of the study and contributed to interpretation of the data, and drafted and critically reviewed the report.

Hywel C Williams (Professor of Dermato-Epidemiology and Co-Director of the Centre of Evidence-Based Dermatology) contributed to the conception and design of the study, contributed to interpretation of the data and drafted and critically reviewed the report.

Paul Little (Professor of Primary Care Research) contributed to the conception and design of the study, contributed to interpretation of the data and drafted and critically reviewed the report.

Publications

Santer M, Rumsby K, Ridd MJ, Francis NA, Stuart B, Chorozoglou M, *et al*. Bath additives for the treatment of childhood eczema (BATHE): protocol for multicentre parallel group randomised trial. *BMJ Open* 2015;**5**:e009575. https://doi.org/10.1136/bmjopen-2015-009575

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Stuart B, Rumsby K, Santer M, Ridd M, Francis N, Chorozoglou M, *et al*. 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* 2018; in press.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Summary patient information leaflet (from 12 July 2015)

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[redacted]

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www.southampton.ac.uk/bathe

BATHE Study

Summary Information Sheet

bathe

Bath Additives for the Treatment of cHildhood Eczema

NHS
National Institute for Health Research

www.southampton.ac.uk/bathe

Why are you doing this study?

Children with eczema are advised to regularly use emollients (moisturisers) directly on the skin to help improve eczema.

Some doctors also recommend using bath emollients (liquids that you add to the bath) but there's no evidence to show whether or not these help.

We are carrying out this study to find out whether adding emollients to the bath helps children with eczema or not.

What would I have to do?

If you tell us you would like to take part then we will contact you to arrange a convenient appointment at your GP surgery. We will explain the study in more detail and ask you to complete a questionnaire about your child's eczema. This is the only appointment you will need to attend.

If you agree to take part, your child will be allocated to one of two groups by chance, either:

1) usual care for eczema **with** bath emollient
2) usual care for eczema **without** bath emollient.

We would ask you to stick to this treatment group for one year.

We then would like you to complete a few questions about your child's eczema every week for 4 months, then once a month for the rest of the year. All these questions can be completed online or by post and only take a few minutes.

What will happen if my child's eczema gets worse while he/she is in the study?

Whichever group your child is randomised to, you will still be free to use any other medications and treatments and to see your GP as you normally would.

Do I have to take part?

It is up to you and your child whether you would like to take part in the study. Please read this information sheet to help you decide.

Will I be paid?

You will not be paid but can provide a small high street gift voucher (£10) for your expenses in attending the initial appointment.

What next?

If you would like to find out more then please read the detailed information leaflet in this pack. There is a short video for children at **www.southampton.ac.uk/bathe**

If you would like to take part then please complete the questionnaire in this pack and return it in the FREEPOST envelope.

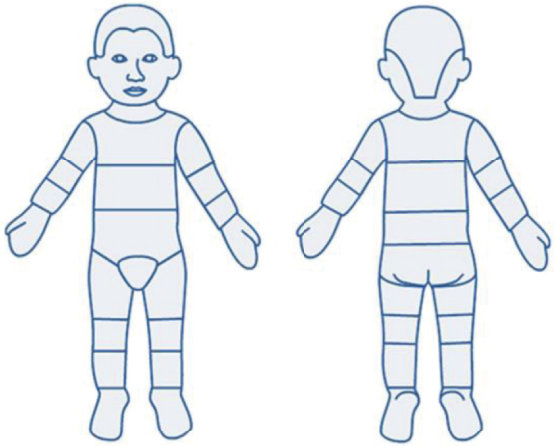
If you cannot or do not wish to take part in the study it would still be really helpful to us if you could fill in the reply slip and return it in the FREEPOST envelope.

Alternatively you can fill out the form online at **www.isurvey.soton.ac.uk/12983**

Thank you for taking the time to read this information

Appendix 2 Screening form/reply slip

7. Please put a cross on the diagrams to show how much of your child's body is affected by eczema **at the moment**. Mark each box on both the front and back of the diagram if eczema more than 2cm^2 is visible.



8. In the last month, have you put bath emollients in your child's bath (for instance, Oilatum, Balneum, Aveeno bath oil or similar liquid)?

Yes, every time	More than half the time	Less than half the time	Never
☐	☐	☐	☐

9. How effective do you think bath emollients are in treating eczema?

1	2	3	4	5	6	7	8	9
Not at all effective				Somewhat effective				Very effective

Please circle one of the numbers above – if you feel unable to answer then tick here:

I don't know ☐

10. How old is your child?

18 months or younger	Over 18 months but less than 4 years	4 years or older
☐	☐	☐

Please return this questionnaire in the pre-paid envelope

Thank you for your time

[redacted]

bathe

Bath Additives for the Treatment of cHildhood Eczema

NHS
National Institute for Health Research

REC: 14/NE/0098

WHAT DO I HAVE TO DO?

If you are interested in taking part in the study please fill out this form which asks questions about your child's eczema and then complete your details below so that we may contact you. Please then return this questionnaire to us in the pre-paid envelope enclosed.

The answers you give in this questionnaire will help us to find out if your child is able to take part in the study. We will try to contact you within 28 days.

This questionnaire can be completed online if you prefer: www.isurvey.soton.ac.uk/12983

Please read the information leaflet and tick one:

Yes, I would like to learn more about the BATHE study and I am happy to be contacted by a member of the study team ☐
Please complete the contact details below and return this questionnaire in the freepost envelope.

No, I cannot or do not wish to take part in the study ☐
If you have ticked this box and are willing to provide brief reasons for being unable or unwilling to take part, please do so below – this will help the researchers understand possible problems with the research. You do not need to fill in any contact details.

- My child's eczema is not a problem ☐
- I don't have a bath ☐
- I don't have time ☐
- Other _____ ☐

Your name: _____

Your address: _____

_____

_____ **Postcode:** _____

Phone number: _____

E-mail address: _____

I would prefer to be contacted by: ☐ **telephone** ☐ **e-mail**

The best time to phone me is: _____

PID: <<PatientIdentifier>> **Today's Date:** _____

1.	**In the last year, has your child had an itchy skin condition?** *By 'itchy' we mean scratching or rubbing the skin*	**Yes** ☐	**No** ☐

If your answer to Question 1 is "No" then we cannot include your child in this study. You do not need to complete the rest of this questionnaire but please do return it in the FREEPOST envelope. Your reply will remain anonymous and we will not see or store any information about you or your child. Thank you very much for your interest in the BATHE study.

If you ticked "Yes" please complete the rest of the questionnaire.

2.	Has this skin condition **ever** affected your child's skin creases in the past? *By 'skin creases' we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes*	**Yes** ☐	**No** ☐
3.	How old was your child when this skin condition began?	**Under 2 years** ☐	**2 years or older** ☐
4.	In the last year, has your child suffered from dry skin in general?	**Yes** ☐	**No** ☐

5. In the last 12 months has your child's skin condition been:

	Tick one
a) Present for less than 6 weeks in total?	☐
b) Present for between 6 weeks and less than 3 months in total?	☐
c) Present for between 3 months and less than 6 months in total?	☐
d) Present for between 6 months and less than 9 months in total?	☐
e) Present for more than 9 months in total?	☐

6. In the last 12 months, how often has your child's sleep usually been disturbed by itching or scratching due to their skin problem?

	Tick one
a) Sleep is not usually disturbed	☐
b) 1 night per week on average	☐
c) 2 or 3 nights per week on average	☐
d) 4 or 5 nights per week on average	☐
e) 6 or more nights per week on average	☐

PID: <<PatientIdentifier>>

Appendix 3 Patient invitation letter

PRACTICE HEADED PAPER

Parent or Guardian of «First_Name» «Surname»
«Address1»
«Address2»
«Address3»
«Address4»
«Postcode»

Dear Parent or Carer

Invitation to take part in a study about bath emollients for eczema

Our practice is helping researchers to find out whether bath emollients (moisturisers that are added to the bath) are an effective treatment for childhood eczema. We are writing to you because our records show that your child, «First_Name», has been brought to the practice with dry skin or a rash or eczema.

We would like to invite «First_Name» to take part in the study. We do not share your information with anyone outside of the practice, so if you wish to join the study you will need to contact the researchers directly.

Please read the information leaflet to find out more about the study. If you are interested in taking part in the study then complete and return the short questionnaire included in this information pack, using the **Freepost** envelope.

Alternatively, the short questionnaire can be completed online if you prefer at: **www.isurvey.soton.ac.uk/12983.** If you have any questions phone the study team using the contact details provided.

If your child no longer has a skin problem, or you do not want to take part in the study, it would still be helpful to the researchers if you could fill in the form. You do not need to fill in your contact details if you do not wish to.

If you have received more than one copy of this letter, please answer once only on behalf of the child with the worst skin problem.

Yours sincerely

«GPName»

BATHE | Invitation Letter v5 (1 May 2015) REC Ref: 14/NE/0098

Appendix 4 Patient information sheet

[redacted] [redacted] [redacted]

bathe

Bath Additives for the Treatment of cHildhood Eczema

Bath Additives for the Treatment of cHildhood Eczema (BATHE)

We would like to invite you to take part in our research study. This leaflet explains why the research is being done and what it would involve for you and your child.

What is the purpose of this research?

Children with eczema are advised to regularly use emollients (non-cosmetic moisturisers that you leave on the skin) and we know that applying emollients directly to the skin in this way helps to relieve eczema symptoms. Some doctors and nurses also recommend using bath emollients (moisturisers that you add to the bath) but there is no evidence to show whether or not this helps. We would like to find out whether adding emollients to the bath helps children with eczema or not.

Why have I been invited?

Your GP is helping us with our research by sending this information about the study to carers of children who have had dry skin or a rash or eczema.

Do I have to take part?

It is up to you and your child whether to take part in the study. Please read this information sheet to help you decide. You can phone us if anything is unclear or if you have any questions about the study at all. If you decide not to take part your child's care will not be affected in any way. If you do decide to take part your GP will be informed of your child's participation and which group s/he is allocated to. If you or your child change your mind about taking part then you are free to withdraw at any time, without giving a reason.

What will happen to me and my child if I take part?

If you would like to take part in this study then please complete the questionnaire included in this pack and return it directly to the study team in the enclosed FREEPOST envelope. A nurse will contact you to arrange a convenient appointment with you (and your child if you wish, although this is not essential) at your GP surgery. At this appointment the nurse will explain the study in greater detail and answer any questions that you may have. The nurse will also ask you to complete a questionnaire about your child's eczema. The appointment will take about 30 minutes.

Your child will be allocated to one of two treatment groups either (1) usual care for eczema **with** bath emollient, or (2) usual care for eczema **without** bath emollient. In order to make the study a fair test, your child will be placed into one of these two groups by chance, using a randomisation program:

- If your child is assigned to the bath emollient group then you will be given a repeat prescription for a bath emollient. You will need to bath your child using this bath emollient (or another brand if you prefer) at least once a week for a year.
- If your child is assigned to the usual care without bath emollient group we will ask you to commit to NOT adding any emollient to your child's bath for a year.

Whichever group your child is randomised to, you will still be free to use any other medications and treatments and to see your GP if necessary. All other aspects of your child's care will remain the same.

We would like you to fill in questionnaires about your child's eczema at regular intervals for the duration of the study so that we can find out whether using bath emollient makes any difference. We would ask you to answer a few short questions once a week for the first 4 months of the study and then once a month for the rest of the year. Ideally the questionnaires will be completed on-line, using a computer. However, you can answer the questions on paper or by e-mail if this is more convenient for you. If you decide to complete the questionnaire on paper we will include a pre-paid envelope for you to return it to the study team. When you have completed the study, your child's GP notes will be looked at by a member of the practice team or a researcher to see if

there have been any eczema-related consultations or prescriptions during that 12-month period. Your practice will not tell us any other information about you or your child.

We might ask if we can interview you to find out if there are any ways of making the study run more smoothly, but you don't need to do this to take part in the study.

What will happen if my child's eczema gets worse with the bath emollient?

An uncommon side effect of bath emollients is that they may cause skin to become red or irritated. If this happens to your child then please contact your GP and ask for a prescription for a different bath emollient. If the problem persists then please discuss with your GP or with the study team.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be kept strictly confidential. Personal details will be stored separately from any other information in a password-protected file and paper documents will be stored in a locked filing cabinet. These details will not be shared outside the study team and when the study is complete they will be archived in line with University procedures. No personally identifiable information such as names or address will ever be shared with any other organisations.

What will happen to the results of the research study?

We will use information from the study to write reports and journal articles but they will not include any information that makes it possible for you to be identified. At the end of the study we will send you a summary of the results of the study for your information.

Who is organising and funding the research?

This study is organised by researchers at the Universities of Southampton, Cardiff and Bristol. The study is funded by the National Institute for Health Research, which is part of the Department of Health.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee. This study has been reviewed and given a favourable opinion by the NRES Committee North East - Newcastle & North Tyneside 1 (Ref: 14/NE/0098).

What if there is a problem?

If you are concerned about the conduct of this study or any people involved in it then please contact either of the trial coordinating centres below. You may also contact Barbara Halliday, Director of Legal Services at the University of Southampton: email rgoinfo@soton.ac.uk or phone 02380 595058. If you remain unhappy and wish to complain formally you can do so through the NHS complaints procedure. Details are available from your own practice.

Should you feel that you suffer any negative consequences because of your involvement in this study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence you may have grounds for legal action against the University of Southampton.

What next?

If you would like to take part then please complete the questionnaire. Please fill in your contact details so that we are able to send you more information about how to join the study.
If you cannot or do not wish to take part in the study it would be helpful for us if you could fill in the reply slip and return it in the FREEPOST envelope.
If you would like to know more about the study or discuss anything in this information sheet please contact:

Kate Martinson
BATHE Study Manager
Department of Primary Medical Care
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tel: 023 8024 1087
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Appendix 5 Algorithm for calculating eligibility using Microsoft Access

APPENDIX : CALCULATING ELIGIBILITY FOR BATHE USING MS ACCESS

Variable	Screening Questionnaire *(corresponding question from validated measure)*	Coded Response
[PresentYear]	In the last 12 months has your child's skin condition been: (a) Present for less than 6 weeks in total? (b) Present for between 6 weeks and less than 3 months in total? (c) Present for between 3 months and less than 6 months in total? (d) Present for between 6 months and less than 9 months in total? (e) Present for more than 9 months in total? *(NESS Q1)*	(a) = 1 (b) = 2 (c) = 3 (d) = 4 (e) = 5
[SleepDisturb]	In the last 12 months, how often has your child's sleep usually been disturbed by itching or scratching due to their skin problem? (a) Sleep is not usually disturbed (b) 1 night per week on average (c) 2 or 3 nights per week on average (d) 4 or 5 nights per week on average (e) 6 or more nights per week on average. *(NESS Q2)*	(a) = 1 (b) = 2 (c) = 3 (d) = 4 (e) = 5
[Diagram]	Please put a cross on the diagrams to show how much of your child's body is affected by eczema at the moment. Mark each box on both the front and back of the diagram if eczema more than 2cm^2 (size of a 10 pence coin) is visible. *(NESS Q3)*	0 - 2 = 1 3 - 5 = 2 6 - 10 = 3 11 - 20 = 4 > 20 = 5
[NESS Score]	**NESS Score: Nz([PresentYear])+Nz([SleepDisturb])+Nz([Diagram])**	**(3 - 15)**
[Age]	How old is your child? (a) 18 months or younger (b) Over 18 months but less than 4 years (c) 4 years or older	(a) = 1 (b) = 2 (c) = 3
[ItchyYear]	In the last year, has your child had an itchy skin condition? *By 'itchy' we mean scratching or rubbing the skin. (UKDC Q0)*	No = 0; Yes = 1
[HowOld]	Child aged 4 and over: How old was your child when this skin condition began? *(UKDC Q1)*	2 years or older = 0; Under 2 = 1
[SkinCreases]	Has this skin condition ever affected your child's skin creases in the past? *By 'skin creases' we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes. (UKDC Q2)*	No = 0; Yes = 1
[DrySkinYear]	In the last year, has your child suffered from dry skin in general? *(UKDC Q3)*	No = 0; Yes = 1
[Creases]	Child aged 18m or younger: Face, neck, around eyes, creases or extensor surfaces are marked on diagram; Child aged older than 18m: Creases, neck or around eyes are marked on diagram. *(UKDC Q5)*	No = 0; Yes = 1
[UKDC Score]	**UKDC Score: Iif(([Screening.Age]=3),(Nz([SkinCreases],0)+Nz([DrySkinYear],0)+Nz([HowOld],0)+Nz([Creases],0)),(Nz([SkinCreases])+Nz([DrySkinYear])+Nz([Creases]))))**	**(0 – 4)**
[Eligible]	Iif([ItchyYear]=0,"NOT ELIGIBLE",Iif([NESS Score]<6,"NOT ELIGIBLE",Iif([UKDC Score]<2,"NOT ELIGIBLE",Iif([NESS Score]>5 And [ItchyYear]=1 And [UKDC Score]>2,"ELIGIBLE",Iif([NESS Score]>5 And [ItchyYear]=1 And [UKDC Score]=2 And [UKDC2]="","QUERY ELIGIBILITY",Iif([NESS Score]>5 And [ItchyYear]=1 And [UKDC Score]=2 And [UKDC2]="Yes","ELIGIBLE",Iif([NESS Score]>5 And [ItchyYear]=1 And [UKDC Score]=2 And [UKDC2]="No","NOT ELIGIBLE",""))))))))	"Eligible"; "Not Eligible"; "Query Eligibility"
NOT ELIGIBLE = thank you letter; ELIGIBLE = Recruit; QUERY ELIGIBLITY= telephone interview re Atopy:		
[ChildAtopy]	Child aged 4 or over: Iif(([NESS Score]>5 And [Screening.Age]=3 And [ItchyYear]=1 And [UKDC Score]="2"),"Does the child have a personal history of asthma or hay fever?","") *(UKDC Q4)*	""; "No"; "Yes"
[FamilyAtopy]	Child aged under 4: Iif(([NESS Score]>5 And [Screening.Age]<3 And [ItchyYear]=1 And [UKDC Score]=2),"Does the child or a first-degree relative have a history of asthma, eczema or hay fever?","") *(UKDC Q4)*	""; "No"; "Yes"
[UKDC2]	Iif([ItchyYear]=1 And [UKDC Score]+[FamilyAtopy]>2,"Yes", Iif([ItchyYear]=1 And [UKDC Score]+[ChildAtopy]>2,"Yes",Iif([ItchyYear]=1 And [UKDC Score]+[ChildAtopy]<3,"No",Iif([ItchyYear]=1 And [UKDC Score]+[FamilyAtopy]<3,"No","")))))	"No"; "Yes"

Appendix 6 Information leaflet for older children (aged ≥ 6 years)

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[redacted] [redacted] [redacted]

bathe

Bath Additives for the Treatment of cHildhood Eczema

The BATHE Study

REF Ref: 14/NE/0098 Information for children aged 6 or over – v1 11 November 2013

Sometimes your skin gets itchy and red. You may use cream to help your skin but sometimes this doesn't work.

Doctors, nurses and researchers are investigating ways to help with this. Some people think that using special bath oil will help but no-one really knows this for sure.

We are looking for 260 children like you to help in this investigation. Half of the children will be asked to use bath oils and the other half will be asked not to use any bath oil. A computer will decide which group you will be in.

To help the doctors and nurses to know if your skin is getting better, your parents will be asked to answer some questions. You can help them by telling them how you feel. Some of the information can be filled in on the computer and they may let you help them.

If we find out that the bath oils do help children like you, then we can give them to more children to make their skin better. If they don't really help then we can keep looking for ways to help everyone.

If you would like to chat about this or have any questions then please ask your mum or dad, or the nurse about this.

Thank you for reading this!

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Appendix 7 Information leaflet for younger children (aged ≤ 5 years)

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[redacted] [redacted] [redacted]

bathe

Bath Additives for the Treatment of cHildhood Eczema

The BATHE Study

REF Ref: 14/NE/0098 Information for children aged 5 or less – v1 11 November 2013

Sometimes you get itchy and your skin gets sore. Your mummy or daddy may use cream to help make your skin better but sometimes this doesn't work.

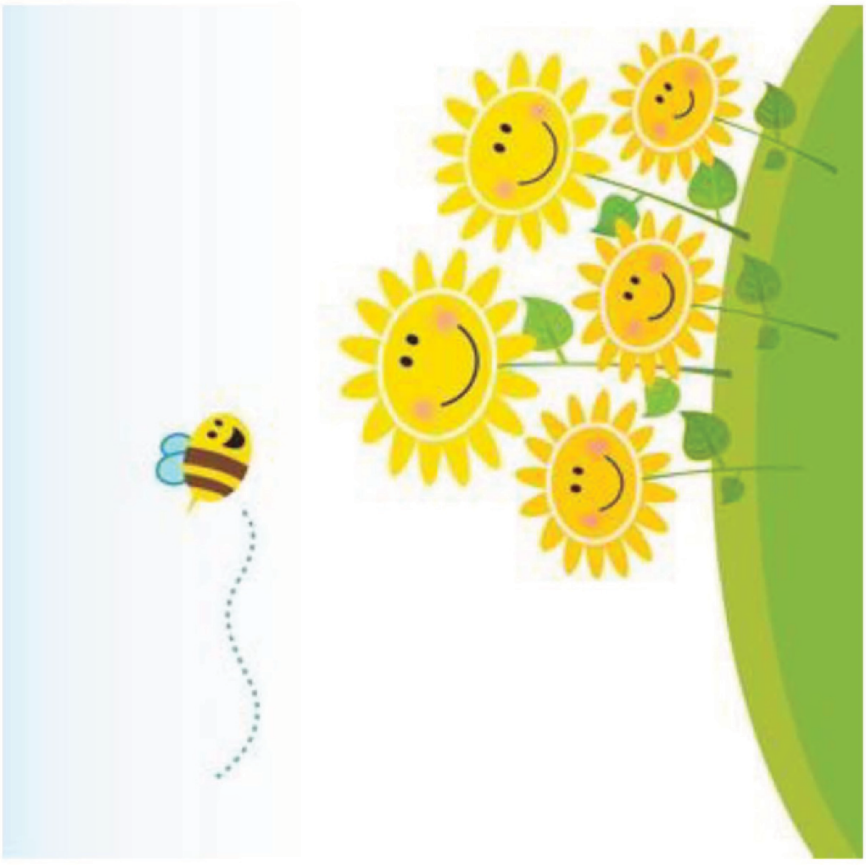
Doctors, nurses and researchers are trying to find ways to help with this. Some people think that adding special bath oil will help but no-one really knows this for sure.

To help the doctors and nurses to know if your skin is getting better, your mummy and daddy will be asked to answer some questions. You can help them by telling them how you feel.

If we find out that the bath oils do help children like you, then we can give them to more children to make their skin better. If they don't really help then we can keep looking for ways to help everyone.

You can chat more to your mummy or daddy or nurse about this.

[redacted]



REF Ref: 14/NE/0098 Information for children aged 5 or less – v1 11 November 2013

Appendix 8 List of bath additives permitted for use in Bath Additives for the Treatment of Eczema in cHildren

BATHE Study

Bath Emollient Information

The BATHE study is testing bath emollients without the addition of antimicrobials or anti-itch agents. There are many different products but the suggested mechanism of action is similar, i.e. oily substance creates a film over the skin surface to prevent dry skin.

The British National Formulary (BNF) lists many different bath additives, but in clinical practice a few of these are commonly prescribed. For this reason we will encourage participating practices to only issue the following:

- Oilatum Fragrance Free Junior
- Balneum Bath Oil
- Aveeno Bath Oil

These account for the majority of bath emollient prescriptions in the UK and appear in local prescribing formularies for participating centres. We also would prefer that participants in the intervention group who have previous experience of bath emollient are also only prescribed one of the above, but they can choose or if they don't have a preference, then the GP can choose.

If participants wish to change bath emollient during the trial then they will be encouraged to use one of these, but may choose others if their GP is happy to prescribe them. Some emollient products contain additional ingredients such as antipruritics and antiseptics (for instance, Dermol) and we would ask participants **NOT to use** the ones highlighted over leaf.

Pharmaceutical licensing

Oilatum Fragrance Free Junior and Balneum bath oil are licensed for pharmaceutical use in the EU and are being used within their licensed indication in this study. Aveeno Bath Oil does not have a EU pharmaceutical Marketing Authorisation but is approved by the ACBS (Advisory Committee on Borderline Substances) for the treatment of eczema. All three products have been used widely for many years with no safety concerns and are available to purchase over the counter without a prescription.

Prescribing arrangements

When a participant is randomised to the intervention the clinical studies officer / nurse will arrange for a bath emollient to be prescribed and recorded by their own GP. It will therefore be labelled by the community pharmacist in the usual way and products will be issued with information leaflets listing indications, contra-indications, possible adverse events, etc., in the usual way.

Adverse reactions

Known adverse reactions to bath emollients are recorded in the Summary of Product Characteristics for Oilatum Fragrance Free Junior and Balneum bath oil. These include: skin irritation, rash, erythema (redness), pruritus (itch). Accidental ingestion may cause gastrointestinal irritation with nausea, vomiting and diarrhoea. There is an increased risk of slipping due to the oil film on the skin and the oil film in the bath or shower. Aveeno Bath Oil does not have a Summary of Product Characteristics as it is not marketed as a pharmaceutical, but adverse reactions are likely to be the same.

V2 05.11.2014

Prescribing instructions

The GP can choose the directions and quantity of prescribing. Please issue as repeat prescriptions. Suggested regimens are:

Oilatum Junior Emollient bath additive
Direction: Add 1 – 3 capfuls to the bath
Quantity: 500ml

Balneum Bath Oil
Add 20 – 60ml to the bath
Quantity: 1 litre

Aveeno Bath Oil
Add 20 – 30ml to the bath
Quantity: 500ml (i.e. 2 * 250ml)

Emollient bath additives that CAN be prescribed to children in BATHE study

Product	Allowed in BATHE?	Comments
Aveeno Bath Oil	Yes	
Balneum Bath Oil	Yes	
Cetraben Bath Additive	Yes	
Dermalo Bath Emollient	Yes	
Diprobath Bath Additive	Yes	
Doublebase Bath Additive	Yes	
E45 Emollient Bath Oil	Yes	
Hydromol Bath and Shower Emollient	Yes	
Imuderm Bath Oil	Yes	
Oilatum Emollient Bath Additive	Yes	Oilatum 'Junior' is preferable (less fragrance)
Oilatum Junior Emollient Bath Additive	Yes	
QV Bath Oil	Yes	

Emollient bath additives that SHOULD BE AVOIDED in BATHE study

Product	Allowed in BATHE?	Comments
Aveeno Colloidal Bath Additive	No	Sachets, not liquid
Balneum Bath Oil Plus	No	Contains antipruritic
Dermol 600 Bath Emollient	No	Contains antimicrobial
Emulsiderm Liquid Emulsion	No	Contains antimicrobial
Oilatum Plus Bath Additive	No	Contains antimicrobial

V2 05.11.2014

Appendix 9 Washing leaflet (study version)

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ECZEMA AND BATHING

Eczema and bathing

Bathing and cleaning is an important part of looking after a child with eczema. There are lots of possible benefits: removing dirt, irritants and allergens from the skin surface, softening the skin by helping it to take up water, establishing a routine, giving play opportunities, providing a bonding activity between young children with eczema and their carers, and reducing stress through relaxing. But bathing can also dry out the skin and make it itch more if care is not given to applying plenty of emollients (moisturisers) to the skin after bathing. Skin does not have to feel dry and tight to be 'clean'.

Shower or bath?

There is no right or wrong answer to this question. It is much easier to bath a baby or toddler. Older children and adolescents tend to prefer showers. The important point is what you do to the skin when you get out of the bath or shower.

Temperature

Use warm rather than hot water. The hotter the water, the more damaging it is to the skin because very hot water takes away all the precious skin oils and also makes the skin more irritable and likely to itch. Equally, the water should be warm enough for the child to be comfortable. Some people have advocated lukewarm water, but lukewarm water is a miserable experience.

How long to soak

A child should not spend too long in the bath. But equally, the child can still have time to play and enjoy the experience. About 15 minutes is about right.

Soap substitute

Children with eczema should avoid soaps, bubble baths and shower gels because they dry out and can irritate the skin. Emollients (prescribed moisturisers) can be used instead.

Shampoo

National guidance advises not to use a shampoo for a child under one year of age. Up until this age, using an emollient as a shampoo substitute is advised. If this continues to suit the child, there is no need to change. If you feel you want to use a shampoo, find one that claims to be suitable for eczema. If you use a shampoo when showering, try not to let it run on to the body. Another way to avoid shampoo running onto the body is to lean over an empty bath and wash the hair using a shower head there so that all the suds run off into the bath rather than onto your skin.

Frequency of washing

This is one of those areas where different health care professionals will tell you different things. Generally the advice is that bathing should be no more than once daily but might be less than this. Go with whatever is comfortable for you and your child. And of course, exposure to dirt and irritants may vary from day to day, and this may change the bathing frequency too. Just as the time of year may affect bathing frequency, if a child gets sweatier in the summer for instance. Whilst bathing should not be more than once daily, cleaning a baby's face, hands and bottom may need to be more often!

Timing in the day

Some recommend that you perform your bathing and moisturizing at night just before going to bed. You are unlikely to further dry out or irritate your skin while sleeping, so the moisture can be more thoroughly absorbed into your skin.

After bathing or showering

This is the most important bit of advice regarding bathing. Whenever your child has bathed or showered or been in contact with water, the skin should be gently patted dry with a soft towel **followed by plentyof your child's chosen emollient applied directly to the skin.**

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Stinging

If your child has lots of broken skin, water can cause temporary stinging. This may be helped by applying moisturisers before the bath. If this doesn't work then seek advice from your doctor as your child may need stronger eczema treatment or antibiotics.

Water softeners

Although the hardness of mains water may affect the severity of eczema, a recent national study led from Nottingham study has shown that water softeners are not helpful for improving eczema.

Wet wipes

We do not recommend wet wipes as they often contain ingredients to which you can become allergic.

Other Advice

When using emollients in the bath or shower it is important that you clean the bath or shower afterwards. There are several reasons for this, the oils and grease can build up making the bath very slippery. We would recommend using washing up liquid, hot water and a soft cloth or brush to clean the area. Rinse well to remove all the detergent and dry with kitchen towel. Also it helps to clear the drains.

- Do not leave lids off pots of emollients as this could be another source of infection.
- Don't use flannels that have been left damp on the side of bath as these may be another source of infection.
- If using bath toys, grease may build up on them so wash in hot soapy water or dish washer.

More about Eczema

What is eczema?

Eczema is inflammation of the skin which gives it a red, dry and flaky appearance. Many children with eczema suffer from itching and poor sleep, but this should improve as you gain control over the eczema.

What causes eczema?

There is no single cause of eczema. We know that eczema can run in families, so a child with a family history of eczema, asthma or hay fever may be more at risk of developing eczema. A number of things in the environment can set off eczema in some children. These triggers are not always allergies. Irritation from soaps, wearing non-cotton clothing, overheating at night and contact with water are all important in eczema. Dry skin can be the first sign of eczema. Giving the skin extra help with emollient moisturisers at this stage can help prevent the skin from becoming red and itchy.

Can eczema be cured?

Unfortunately there is no cure for eczema at present. The good news is that 2 out of 3 children who have eczema will grow out of it by the age of 11. In the meantime, there is a lot you can do to manage eczema and control flare-ups so your child can enjoy life.

Caring for a child with eczema

There is no right or wrong way of managing eczema. Every skin responds to different things, and different emollient moisturisers and skin care routines will suit different people. **The important thing is finding something that works for you.** Finding the right emollient for you and your child is very important. It helps protect the skin and many children find it soothing.

What are emollient moisturisers?

Emollients are moisturisers that have been specifically designed for eczema. They are more natural than most cosmetic moisturisers as they contain less or no colours or perfumes. There are 3 main types:

1.	Leave-on emollients	Where emollients are applied to the skin and left to soak in
2.	Bath emollients	Oil and/or emulsifiers that disperse in the bath
3.	Soap substitutes	Where emollients are used instead of soap or other washing products

Skin experts agree that **using leave-on emollients regularly** is the most important part of daily care for eczema. In eczema the protective skin barrier is damaged, both in areas where you can see eczema and in areas where the skin looks clear. Emollients protect this top layer of skin by covering it with a protective coat. This forms a barrier against infection and helps control itching. Using emollients at least twice a day on all areas of the skin can dampen down the eczema process and also prevent future flare-ups.

There is much less certainty about whether adding emollients to the bath helps to protect the skin in the same way as applying them directly to the skin.

How can I find the right emollient for my child?

There is a huge variety of emollients available in the UK. They come as ointments, creams, lotions, gels and sprays. Ointments are usually greasy and see-through. They are generally better as they last longer on the skin and give better results on very dry skin. Creams and lotions are white and contain water so they are easier to rub in. Some people find these more pleasant to put on, but they don't last as long on the skin so need to be used more often than ointments.

It doesn't really matter which emollient your child uses as long as it is used regularly. You may need to try out different emollients until you find one that works for you and your child. You can discuss this with your GP, who can prescribe them for your child. You can also ask your pharmacist for advice.

Where can I find out more about eczema?

The Nottingham Support Group for Carers of Children with eczema – click on 'information' for high quality information on a wide range of topics:

http://www.nottinghameczema.org.uk

The National Eczema Society offers a telephone helpline and a list of local groups:

http://www.eczema.org/

This leaflet is based on information written by Professor Hywel Williams, Dr Ruth Murphy, Dr Jane Ravenscroft, Nurse Consultant Sandra Lawton and parents on behalf of the Nottingham Support Group for Carers of Children with Eczema

Website – www.nottinghameczema.org.uk
email – enquiry@nottinghameczema.org.uk

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Appendix 10 Baseline appointment standard operating procedure

BATHE

Baseline Appointment Checklist

1.	**Introduction** Ask the parent/carer (and child if present) if they have any questions before you start. Check they understand what is meant by 'bath emollient'; if not explain simply that: *"Bath emollients are liquids that can be added to bath water. Some people think they help with eczema but others think they don't and there is no research evidence either way. "*
2.	**Explain the purpose of the study** *"At the moment some GPs prescribe bath emollients to almost all children with eczema and some don't prescribe them at all. Also, dermatologists /skin specialists are not sure whether they help improve eczema or not. BATHE is a Fair Test or Randomised Trial of bath emollient, as this is the best way of finding out for definite whether they help children with eczema. What this means is that we ask the computer to randomly put half of the children who agree to take part in the 'bath emollient' group and half in the 'no bath emollient' group. And then we ask both groups to do their very best to stick to their groups for 12 months so that we can really answer that question confidently."*
3.	**Check the child's eligibility** i. Is the parent/carer aware that they could be randomised to either the 'bath emollient' or 'no bath emollient' group and that they will be asked to do their best to stick to this for 12 months? *"Would you be happy for your child to be allocated either of the groups: usual eczema care with bathe emollient or usual eczema care without bath emollient?"* ii. Is the child happy to take part in the study? iii. Is the child aged between 1 and 12 years – e.g. had their 1st birthday but not had their 12th birthday? iv. Does the child have a bath at least once a week?
4.	**Informed Consent** Ask the parent/carer if they have read the Information Sheet and if they have any questions. Ask the parent/carer to complete the Consent Form (and consider offering child assent form if appropriate and present).
5.	**Questionnaires** Ask the parent/carer if they are able to complete the questionnaires online *"We*

BATHE | SOP 11: Baseline Appointment Checklist v 2 (28 Nov 2014)

	are asking people to complete their questionnaires online in this study. Is that OK for you?" (if not offer paper questionnaire and make a note on the **RECRUITMENT LOG**) Emphasise the necessity to answer questions weekly due to the relapsing/remitting nature of the illness –*e.g. "We really value your time. It is very important for the study that you complete these weekly as that is really the best way to find out how your child's eczema is over the next 4 months, rather than at 1 or 2 time points"*. Emphasise to the parent/carer that here are only 8 questions and tell them we will send them either text, telephone* or e-mail reminders (each week for the first 4 months and then once a month after that until completion) – email for online users, text/telephone for paper users. ***NB Please ask when is the most convenient time of the day to phone them**
6.	**Log-In BATHE online questionnaires/LifeGuide** i. Log in to BATHE online site and ask the parent/carer to CREATE A PASSWORD in LifeGuide. ii. NB Stress to the parent/carer to either click on the link in their email or on the link on the BATHE website to access online questionnaires. (www.soton.ac.uk/bathe). If they use the web address stated on the card then type this into the navigation bar at the top of the screen and NOT using a search engine. Suggest they might wish to bookmark it as a 'favourite'. iii. Add their PID (provided on their screening questionnaire)* iv. Ask the parent/carer to fill in the baseline questionnaire in LIFEGUIDE. ***NB take a list of participant ID numbers to appointments**
7.	**Randomisation** i. Ensure they have completed randomisation and made a note of username (their email address) and the password on the card supplied. ii. The CSO should add their name and phone number to the card. iii. If allocated to the control group then stress to parent (and child if present) how important this group is in order to answer the study question. iv. If randomised to Emollient, ask if they have any preferences about which one they would like to use and inform them how they can obtain repeat prescriptions (previously agreed with surgery). v. NB If they already use one of the 3 'approved' Bath Emollients for the Study they can continue to use this and obtain their repeat prescriptions as usual. vi. Give them 'HOW TO WASH' leaflet and discuss principles: vii. *"What do you use to wash your child at the moment?" "One of the best things you can do for eczema is to avoid using soap."* Advise that they use the child's usual leave-on emollient as a soap substitute. If

	they don't have one then arrange for prescription at the end of the baseline appointment. Ask if they have any questions and see below for answers to frequently asked questions
8.	**Prescription** Seek prescription for bath emollient, if required – explain to carer how to obtain repeats. Explain that if they feel the BE is irritating their child's skin then they can request to change to a different one.
9.	**Flag/System Alert** Ask practice staff to place alert on system indicating that child is participating in BATHE and their group allocation. **NB the precise system to be used at each Practice should have been established at the 'sign up visit'.**
10.	**Thank You** Thank them for their participation and give them an appropriate gift for the child and their first voucher – add the Voucher Serial Number and PID information on the Voucher Log **ENSURE THE PARTICIPANT'S DETAILS ARE ON THE SCREENING LOG**
11.	**Frequently Asked Questions** WHEN SHOULD THEY CONTACT THEIR GP? If they have any issues about their eczema or its' treatment WHEN SHOULD THEY CONTACT THE RECRUITING CENTRE? If they have any issues with the study – problems with LifeGuide or the paper questionnaires, or they no longer wish to help with the study. Draw their attention to the following section in the Information Sheet: *'What do I do if I want to withdraw my child from the study?'* **What will happen if my child's eczema gets worse?** If your child is in either group and their eczema is getting worse then please discuss this with your GP as it might mean that they need to change one of their treatments. **Are there any Side Effects to Bath Emollients?** One possible side effect of bath emollients is that they may cause skin to become red or irritated. If this happens to your child after they bath then please contact your GP and ask for a prescription for a different bath emollient. If the problem persists then please discuss with your GP or with the study team. **If your child is really struggling (especially if in No Emollient Group) try to remain in study until first end point of 16 weeks. What if I don't have access to internet/an email address?** Ideally the questionnaires will be completed on-line, using a computer. However, if this is not convenient for you and you would rather complete it using the paper

BATHE | SOP 11: Baseline Appointment Checklist v 2 (28 Nov 2014)

	version then this can be sent to you by email or by post depending on which you prefer. If you decide to complete the questionnaire by post we will include a pre-paid envelope for you to return it to the study team. **What if I don't want my child's notes reviewed?** A year after the study, your child's GP notes will be looked at by a member of the practice team or a researcher if you agree to this. Re-enforce – *"this is only to see if your child has had any appointments or prescriptions for eczema and not to look at any other information about your child"*

Appendix 11 Notes review form

UNIVERSITY OF Southampton

Bath Additives for the Treatment of cHildhood Eczema

12 Months Notes Review Form

NHS
National Institute for Health Research

STUDY PARTICIPANT DETAILS:		
STUDY PID:	«Unique_PID»	
INITIALS:	«Initials»	
DATE OF BIRTH:	«DoB»	
PARTICIPATION:	From: «ParticipationFrom»	To: «ParticipationTo»

YOUR DETAILS:	
YOUR NAME:	
JOB TITLE:	
TODAY'S DATE:	

Please tick if patient has left this surgery: ☐ **Date of leaving (if known):**

COMMENTS:

1. Please record details of all oral or topical medicines LIKELY TO HAVE BEEN PRESCRIBED FOR ECZEMA during the study period. Include formulation (eg, cream, ointment) and strength of topical medications, if relevant. (Continue overleaf if necessary).

Date of prescription	Item prescribed *(eg, Doublebase gel, Hydrocortisone cream 1%)*	Amount prescribed *(eg, 550g, 100ml, 28 tablets)*	Was this prescription for eczema? Yes	Not sure
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
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/ /			☐	☐
/ /			☐	☐
/ /			☐	☐

Study PID: **«Unique_PID»** Study period: **«Participation»**

1. Prescriptions (continued)

Date of prescription	Item prescribed *(eg, Doublebase gel, Hydrocortisone cream 1%)*	Amount prescribed *(eg, 550g, 100ml, 28 tablets)*	Was this prescription for eczema? Yes	Not sure
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐
/ /			☐	☐

2. Please record ALL CONSULTATIONS during the study period (continue overleaf if necessary):

Date of consultation	Type of consultation (tick one box)									Is eczema or rash mentioned? (tick one box)			
	Did not attend booked appointment (DNA)	GP appointment at surgery	GP visit at home	GP telephone consultation	Practice Nurse/ Nurse Practitioner / Health Visitor	Out of Hours / Walk-In Centre	A&E attendance	Hospital Admission	If admitted to hospital, record number of nights (or NK)	Eczema flare or infection is mentioned, or there is prescription or advice to use topical steroids or antibiotics for eczema	Eczema mentioned but no clear indication that consultation was for an eczema flare or infection	Skin rash, itch or dryness mentioned but no mention of eczema	No mention of eczema or skin rash, itch or dryness
/ /										☐	☐	☐	☐
/ /										☐	☐	☐	☐
/ /										☐	☐	☐	☐
/ /										☐	☐	☐	☐
/ /										☐	☐	☐	☐
/ /										☐	☐	☐	☐
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/ /										☐	☐	☐	☐
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/ /										☐	☐	☐	☐

DOI: 10.3310/hta22570

HEALTH TECHNOLOGY ASSESSMENT 2018 VOL. 22 NO. 57

Study PID: **«Unique_PID»** Study period: **«Participation»**

2. Consultations (continued)

Date of consultation	Type of consultation (tick one box)									Is eczema or rash mentioned? (tick one box)			
	Did not attend booked appointment (DNA)	GP appointment at surgery	GP visit at home	GP telephone consultation	Practice Nurse/ Nurse Practitioner / Health Visitor	Out of Hours / Walk-In Centre	A&E attendance	Hospital Admission	If admitted to hospital, record **number of nights** (or NK)	Eczema flare or infection is mentioned, or there is prescription or advice to use topical steroids or antibiotics for eczema	Eczema mentioned but no clear indication that consultation was for an eczema flare or infection	Skin rash, itch or dryness mentioned but no mention of eczema	No mention of eczema or skin rash, itch or dryness
/ /										☐	☐	☐	☐
/ /										☐	☐	☐	☐
/ /										☐	☐	☐	☐
/ /										☐	☐	☐	☐
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/ /										☐	☐	☐	☐
/ /										☐	☐	☐	☐
/ /										☐	☐	☐	☐
/ /										☐	☐	☐	☐

3. Please record all letters related to HOSPITAL or CLINIC appointments during the study period:

Date of letter	From *(eg, GP Surgery, Allergy Clinic)*	To *(eg, Dermatology, Paediatrician)*	Brief Summary *(eg, new referral, follow-up, discharge)*	Was this appointment eczema-related? Yes	No	Not sure
/ /				☐	☐	☐
/ /				☐	☐	☐
/ /				☐	☐	☐
/ /				☐	☐	☐
/ /				☐	☐	☐
/ /				☐	☐	☐
/ /				☐	☐	☐
/ /				☐	☐	☐
/ /				☐	☐	☐
/ /				☐	☐	☐
/ /				☐	☐	☐
/ /				☐	☐	☐

Please return this form in the FREEPOST envelope supplied.

Thank you!

Appendix 12 Consent form

Patient ID number: 1 - [ ][ ] - [ ][ ][ ]

UNIVERSITY OF Southampton

CONSENT FORM FOR PARENTS/GUARDIANS

Bath Additives for the Treatment of cHildhood Eczema (BATHE)

Chief Investigator: Dr Miriam Santer

	Please **initial** each box
1. I confirm that I have read and understood the information sheet (Version 3 dated 31st July 2014) for the above study. I have had the opportunity to consider the information and to ask questions and have had these answered satisfactorily.	☐
2. I understand that my child's participation is voluntary and that I am free to withdraw my child at any time without giving any reason, without my or my child's medical care or legal rights being affected.	☐
3. If I withdraw my child from the study, I understand that any data which has already been collected may be retained and used for research purposes unless I inform the study team that I do not wish the information to be used.	☐
4. I give permission for my child's GP to be informed of their participation in this study.	☐
5. I understand that data collected during the study may be looked at by individuals from the study team, from the NHS Trust or from regulatory authorities.	☐
6. I understand that I may be contacted by text, telephone, e-mail or letter where this is necessary for the conduct of the study, and I may be offered an interview.	☐
7. I consent to my child's GP notes being reviewed by a member of the study team or practice staff for the purpose of this study.	☐
8. I agree to my child taking part in the above study.	☐

_____ on behalf of: _____

Name of parent *Name of child*

_____ _____

Parent's signature *Date*

_____ _____ _____

Name of person taking consent *Date* *Signature*

When completed: 1 (original) for study centre and scan onto child's notes, 1 for participant, 1 for site file

BATHE | Parental Consent Form v2 (31 July 2014) REC Ref: 14/NE/0098

Appendix 13 Assent form

Patient ID number: 1 - ☐☐ - ☐☐☐

UNIVERSITY OF Southampton

ASSENT FORM FOR CHILDREN

Bath **A**dditives for the **T**reatment of c**H**ildhood **E**czema **(BATHE)**

Chief Investigator: Dr Miriam Santer

Please write your **initials** in each box to show you agree

1. I have read the leaflet that explains the study. ☐
2. I have been able to ask questions about it. ☐
3. I understand what the study is all about. ☐
4. I understand that I do not have to take part if I do not want to. ☐
5. I can decide to change my mind and I do not have to say why. ☐
6. I agree to take part in the study. ☐

_____	_____	_____
Name of child	*Date*	*Signature*
_____	_____	_____
Name of person taking assent	*Date*	*Signature*

When completed: 1 (original) for study centre and scan onto child's notes, 1 for participant, 1 for site file

BATHE | Child Assent Form v2 (31 July 2014) REC Ref: 14/NE/0098

Appendix 14 Calculating eligibility for clinical studies officer/research nurses standard operating procedure

SOP 5
v1 1.12.2014

bathe
Bath Additives for the Treatment of cHildhood Eczema

CALCULATING ELIGIBILITY FOR THE BATHE STUDY

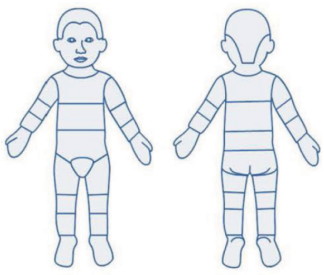
Patients must meet both the required severity on both the NESS (Nottingham Eczema Severity Score) and UKDC (UK Diagnostic Criteria for eczema) in order to be eligible to take part in BATHE.

NESS:

5. In the last 12 months has your child's skin condition been:	Tick one	Score
a) Present for less than 6 weeks in total?	☐	1
b) Present for between 6 weeks and less than 3 months in total?	☐	2
c) Present for between 3 months and less than 6 months in total?	☐	3
d) Present for between 6 months and less than 9 months in total?	☐	4
e) Present for more than 9 months in total?	☐	5

6. In the last 12 months, how often has your child's sleep usually been disturbed by itching or scratching due to their skin problem?	Tick one	Score
a) Sleep is not usually disturbed	☐	1
b) 1 night per week on average	☐	2
c) 2 or 3 nights per week on average	☐	3
d) 4 or 5 nights per week on average	☐	4
e) 6 or more nights per week on average	☐	5

7. Please put a cross on the diagrams to show how much of your child's body is affected by eczema **at the moment**. Mark each box on both the front and back of the diagram if eczema more than $2cm^2$ (size of a 10 pence coin) is visible.

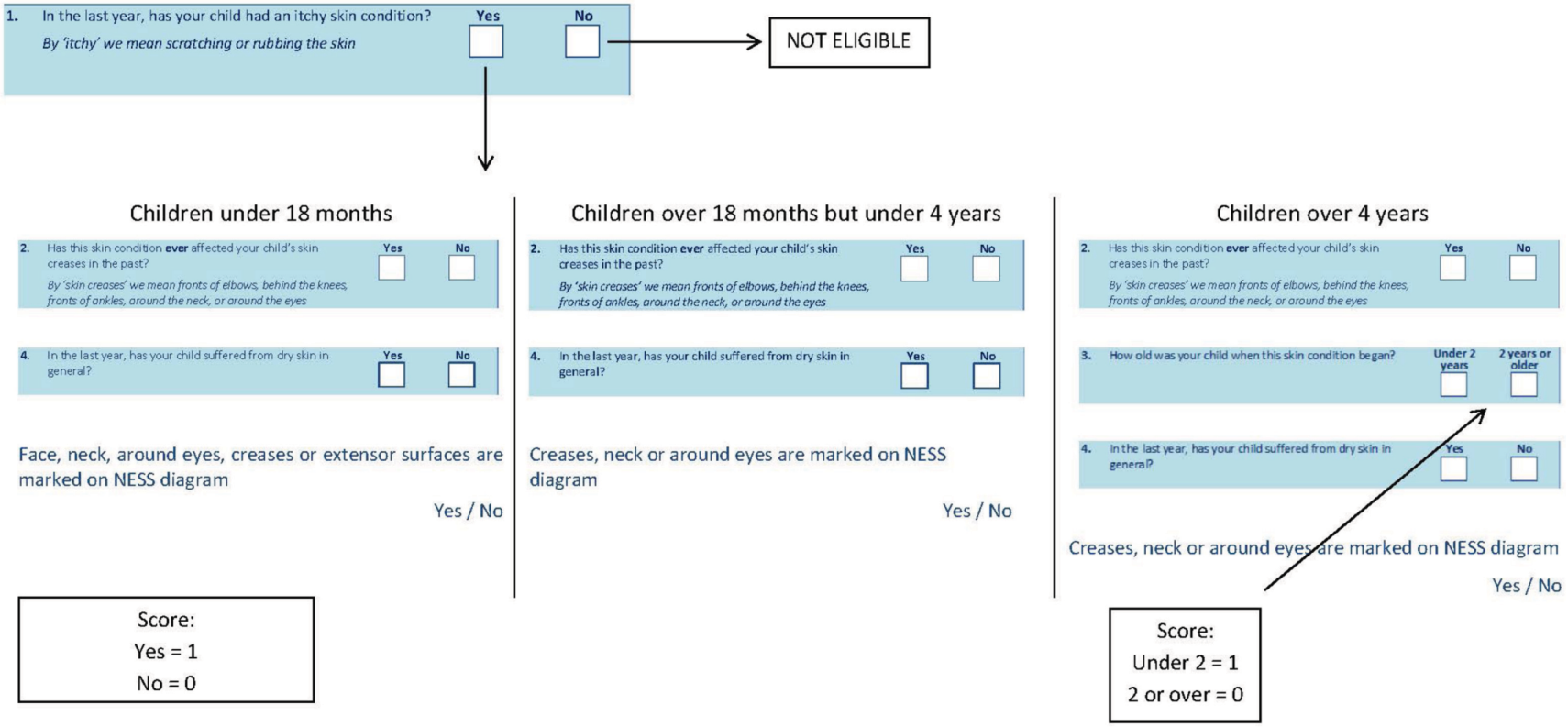


Number of ticks	Score
0 – 2	1
3 – 5	2
6 – 10	3
11 – 20	4
>20	5

TOTAL SCORE FROM 3 QUESTIONS: **0 – 5 = NOT ELIGIBLE**

6 – 15 = ELIGIBLE

UKDC:



If the total score from the questions in the column is **0 or 1** the child is NOT eligible.

If the total score is **3 or more** the child is ELIGIBLE.

If the score is **2**, ask supplementary question below (cf SOP 7):

Does the child or a first-degree relative (mother, father, brother or sister) have a history of eczema, asthma or hay fever?	Does the child or a first-degree relative (mother, father, brother or sister) have a history of eczema, asthma or hay fever?	Does the child have a personal history of asthma or hay fever?

Appendix 15 Additional information for future sample size calculations

Means and standard deviations of POEM for all weeks

	Bath additive Mean (s.d.)	No bath additive Mean (s.d)
Baseline	9.5 (5.7)	10.1 (5.8)
Week 1	8.3 (5.6)	9.1 (5.9)
Week 2	7.8 (5.5)	8.2 (5.9)
Week 3	7.4 (5.3)	8.5 (5.9)
Week 4	7.6 (6.0)	8.6 (6.1)
Week 5	7.6 (5.9)	8.3 (6.0)
Week 6	7.8 (6.3)	8.4 (5.7)
Week 7	7.5 (6.1)	8.8 (6.1)
Week 8	7.3 (6.2)	8.2 (5.8)
Week 9	7.2 (5.9)	8.1 (5.8)
Week 10	7.3 (5.8)	8.5 (5.8)
Week 11	7.6 (6.1)	8.2 (6.0)
Week 12	7.7 (6.2)	7.9 (5.9)
Week 13	7.1 (5.9)	8.3 (6.2)
Week 14	7.2 (6.3)	7.9 (6.3)
Week 15	7.0 (6.3)	8.4 (6.5)
Week 16	7.1 (6.1)	8.2 (6.3)
Week 20	6.9 (6.2)	8.7 (6.5)
Week 24	7.3 (6.5)	8.3 (6.7)
Week 28	7.4 (6.4)	8.8 (6.5)
Week 32	7.8 (6.7)	8.7 (7.0)
Week 36	7.2 (6.8)	8.8 (6.8)
Week 40	7.3 (6.4)	8.8 (6.7)
Week 44	6.9 (6.3)	8.2 (6.4)
Week 48	7.4 (6.6)	8.6 (6.9)
Week 52	7.1 (6.2)	8.0 (6.4)

Correlation between outcomes assessed weekly

	POEM0	POEM1	POEM2	POEM3	POEM4	POEM5	POEM6	POEM7	POEM8	POEM9	POEM10	POEM11	POEM12	POEM13	POEM14	POEM15	POEM16
POEM0	1.00																
POEM1	0.82	1.00															
POEM2	0.71	0.79	1.00														
POEM3	0.64	0.71	0.77	1.00													
POEM4	0.62	0.67	0.70	0.80	1.00												
POEM5	0.60	0.62	0.67	0.76	0.84	1.00											
POEM6	0.54	0.59	0.67	0.73	0.80	0.81	1.00										
POEM7	0.55	0.61	0.70	0.71	0.76	0.75	0.83	1.00									
POEM8	0.51	0.55	0.65	0.65	0.65	0.65	0.71	0.81	1.00								
POEM9	0.51	0.53	0.67	0.65	0.70	0.66	0.74	0.77	0.85	1.00							
POEM10	0.52	0.52	0.65	0.62	0.67	0.63	0.70	0.71	0.73	0.80	1.00						
POEM11	0.44	0.47	0.60	0.64	0.64	0.61	0.70	0.67	0.70	0.77	0.84	1.00					
POEM12	0.52	0.54	0.61	0.70	0.71	0.70	0.78	0.72	0.70	0.72	0.76	0.80	1.00				
POEM13	0.46	0.50	0.58	0.64	0.61	0.60	0.66	0.65	0.67	0.70	0.72	0.71	0.77	1.00			
POEM14	0.49	0.53	0.59	0.60	0.61	0.60	0.68	0.69	0.66	0.72	0.70	0.74	0.78	0.80	1.00		
POEM15	0.49	0.49	0.56	0.63	0.60	0.60	0.68	0.68	0.66	0.74	0.71	0.75	0.75	0.76	0.86	1.00	
POEM16	0.48	0.54	0.56	0.62	0.63	0.64	0.73	0.70	0.68	0.72	0.72	0.73	0.78	0.77	0.79	0.83	1.00

EME
HS&DR
HTA
PGfAR
PHR

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