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Emollients for preventing atopic eczema: Cost-effectiveness analysis of the BEEP trial

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Abstract

Background: Recent discoveries have led to the suggestion that enhancing skin barrier from birth might prevent eczema and food allergy.

Objective: To determine the cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children at 2 years from a health service perspective. We also considered a 5-year time horizon as a sensitivity analysis.

Methods: A within-trial economic evaluation using data on health resource use and quality of life captured as part of the BEEP trial alongside the trial data. Parents/carers of 1394 infants born to families at high risk of atopic disease were randomised 1:1 to the emollient group, which were advised to apply emollient (Doublebase Gel or Diprobase Cream) to their child at least once daily to the whole body during the

Trial Registration: The trial is registered with ISRCTN, number ISRCTN21528841. <https://www.nottingham.ac.uk/research/groups/cebcd/projects/1eczema/beep-maintrial.aspx>.

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first year of life or usual care. Both groups received advice on general skin care. The main economic outcomes were incremental cost-effectiveness ratio (ICER), defined as incremental cost per percentage decrease in risk of eczema in the primary cost-effectiveness analysis. Secondary analysis, undertaken as a cost-utility analysis, reports incremental cost per Quality-Adjusted Life Year (QALY) where child utility was elicited using the proxy CHU-9D at 2 years.

Results: At 2 years, the adjusted incremental cost was £87.45 (95% CI -54.31, 229.27) per participant, whilst the adjusted proportion without eczema was 0.0164 (95% CI -0.0329, 0.0656). The ICER was £5337 per percentage decrease in risk of eczema. Adjusted incremental QALYs were very slightly improved in the emollient group, 0.0010 (95% CI -0.0069, 0.0089). At 5 years, adjusted incremental costs were lower for the emollient group, -£106.89 (95% CI -354.66, 140.88) and the proportion without eczema was -0.0329 (95% CI -0.0659, 0.0002). The 5-year ICER was £3201 per percentage decrease in risk of eczema. However, when inpatient costs due to wheezing were excluded, incremental costs were lower and incremental effects greater in the usual care group.

Conclusions: In line with effectiveness endpoints, advice given in the BEEP trial to apply daily emollient during infancy for eczema prevention in high-risk children does not appear cost-effective.

KEYWORDS

atopic eczema, cost-effectiveness, economic evaluation, emollients, prevention

1 | INTRODUCTION

The Barrier Enhancement for Eczema Prevention (BEEP) randomised controlled trial sought to determine whether advising parents to apply emollients to their child's skin during the first year of life in addition to standard infant skin care advice prevented the onset of eczema (syn, with atopic eczema or atopic dermatitis in this study) in high-risk children. Taking a pragmatic, randomised, controlled, parallel group, multicentre assessor-blind design, parents were asked to follow the skin care advice for their child at home with minimal clinical contact. 1394 newborns at high risk of developing eczema were randomised to the intervention or control group. All parents received standard infant skin care advice and the intervention group were also advised to apply emollient daily to the child's entire body surface area for the first year of their life. There were two choices of emollients (Doublebase Gel® and Diprobace Cream®). The primary outcome was a diagnosis of eczema between 12 and 24 months of age (defined as meeting the United Kingdom (UK) Working Party Diagnostic criteria). The main trial analysis showed no evidence of a preventive effect for eczema, asthma, food allergy and hay fever at 24 and 60 months.^{1,2}

Alongside the trial, data on health resource use and quality of life were captured to undertake a within-trial economic evaluation. The intervention was preventive in nature, and when designing the

Key messages

- The Barrier Enhancement for Eczema Prevention (BEEP) trial assessed daily emollient for preventing eczema.
- We undertook an economic evaluation of the 1394 infants randomised in the BEEP trial
- We found daily emollient during the first year was not cost-effective for preventing atopic eczema

study, we considered the possibility of it not being found clinically effective yet estimated to be cost-effective.³ This is because the intervention is relatively cheap, and thus, even a small insignificant improvement across lots of people could potentially be deemed cost-effective. Xu et al published a decision tree model estimating the cost-effectiveness of seven candidate moisturisers used in the first 6 months of life to prevent eczema in high-risk individuals.⁴ Assuming a very large 50% reduction of atopic eczema incidence based on a small pilot study,⁵ they concluded that daily moisturisation is a cost-effective preventive strategy that can reduce eczema burden. It is therefore important to report the economic evaluation based on individual level data collected alongside the definitive trial to add to the evidence base around whether this preventive strategy is cost-effective or not.

2 | METHODS

2.1 | Resource use and costs

The analysis used health service perspective in keeping with the National Institute for Health and Care Excellence (NICE) reference case.⁶ Disease-specific (eczema, wheezing and rhinitis) resource use was collected. Personal Social Service (PSS) resource use was not captured, as it was anticipated that these types of services would not be accessed for the diseases of interest. The trial had only one face-to-face contact at 24 months, which was not included in costs as it was undertaken for research purposes. The economic evaluation base case captured the intervention costs to the National Health Service (NHS) and the participant's wider disease-specific resource use and did not collect any costs incurred by the family or wider society to ensure the respondent burden was low.

The intervention cost was estimated using data collected by the clinical trials unit (CTU) and costed using published unit costs for Doublebase Gel® and Diprobase Cream® in the prescription cost analysis (PCA).⁷ We assumed that the cost of distribution of the emollients would not be incurred in the same way in practice, it is unlikely the NHS would send out emollients, and rather people would collect these via repeat prescription from their GP surgery/ pharmacy. As such, postage costs incurred in the trial were not captured in the economic evaluation. It was assumed that advice about skin care would be given during routine appointments, so no clinic visit was included.

Wider NHS disease-specific resource use was recorded by participants in online or postal paper questionnaires at 3, 6, 12, 18 and 24 months in line with other trial questionnaire timepoints. Resource use relevant to the NHS perspective was valued using UK unit costs (£ Sterling) from the most current price year available at the time of the analysis (2019/20). Unit costs were identified from published sources, such as Unit Costs of Health and Social Care,⁸ PCA⁷ and NHS Reference Costs.⁹

All reported resource use costs were calculated for each participant to estimate a mean cost per participant for each intervention group.

2.2 | Outcome measures

The primary economic outcome measure was incremental cost per percentage decrease in risk of eczema. That is, those without a diagnosis of eczema over the past year (where a diagnosis of eczema was defined by the UK working party refinement of the Hanifin and Rajka diagnostic criteria for eczema and assessed by research nurses masked to treatment allocation) at age 2 years were used. We chose to frame the analysis in this way so that a positive number indicated a good outcome (i.e. less eczema) to aid interpretability of the incremental cost-effectiveness ratio. Secondary analysis reported a cost-utility analysis (CUA) using Quality-Adjusted Life Years

(QALYs) estimated using utility scores obtained from the parental proxy CHU-9D at 24 months. CHU-9D, a generic preference-based measure of health-related quality of life (HR-QoL), asks how a child is today on nine questions (worries, sad, pain, tired, annoyed, school-work/ homework, sleep, daily routine and activities) each with five response levels (ranging from no difficulty through to a lot or cannot do). We provided the additional guidance for parents of pre-school age children supplied by the developer of the CHU-9D to help parents answer the questions.

In the CUA, the responses received on the quality-of-life instruments were converted to utility scores. For the CHU-9D, we used published valuation set,¹⁰ where utility scores range from 0.33 (worst HR-QoL) through to 1 (best HR-QoL). Utility values were then used to calculate the number of QALYs generated over 24 months, using both linear interpolation and area under the curve analysis with and without baseline adjustment.¹¹ Child utility at baseline was assumed to be 1, perfect health, at birth, for all participants. This is because it is inappropriate to use the CHU-9D for babies at birth. Moreover, babies were not eligible for the study if they had a serious health issue or severe widespread skin condition.

2.3 | Economic analysis

A cost-effectiveness analysis (CEA) was undertaken as the economic base-case analysis and included all randomised participants with complete cost and outcome data available. Using a time horizon of 24 months, costs and benefits in months 13 to 24 were discounted using recommended rates, 3.5%.⁶

The main base-case analysis was a CEA, where decision-makers have to make a value judgement about how much society is willing to pay per percentage decrease in risk of eczema. For the secondary analysis, the estimated mean costs and QALYs per participant associated with each intervention were estimated and combined using a 24-month time horizon. The economic analysis used a cost-effectiveness threshold (λ) of £20,000 (£30,000) per QALY.⁶

Mean (standard deviation, SD) resource use and mean (SD) cost per participant were estimated for each randomised group. Mean difference (95% CI) in cost per participant between groups was estimated unadjusted and adjusted (for centre and number of immediate family members with atopic disease [1, 2 or more than 2]). Mean (SD) utility and mean (SD) QALYs per participant per randomised group are presented, and mean difference (95% CI) QALYs between groups were estimated unadjusted and adjusted.

The unadjusted cost-effectiveness analysis was analysed using the 'heabs' command¹² in STATA (for which explanatory variables cannot be added to the regression command). The adjusted CEA was analysed using a generalised linear model (GLM) for binary and continuous outcomes and presented as unadjusted and adjusted. The Gaussian distribution was used for the cost GLM model and the binomial for the outcome GLM model. The identity option was used as the link function on both GLM models. The CUA analysis used seemingly unrelated regression equations.¹³

Non-parametric bootstrapping was employed to determine the level of sampling uncertainty surrounding the mean incremental cost-effectiveness ratios (ICERs) by generating 10,000 estimates of incremental costs and benefits. Cost-effectiveness acceptability curves (CEACs) were also produced, which show the probability that the intervention is cost-effective at different values of willingness to pay. No sub-group analysis was undertaken as FLG mutation was not shown to be important in terms of the clinical effect.¹ Stata MP version 17 was used to conduct the analysis.

A sensitivity analysis using the 5-year data (which was collected annually post 24 months) was conducted to assess whether the findings at 2 years still held or whether the economic outcomes were different using a longer timeframe. Since missing data was a much larger issue by 5 years we used multiple imputation in the cost-utility analyses, assuming data were missing at random¹⁴ and using chained equations to evaluate the impact of missing data on the cost-utility estimates (Appendix S1).

This economic evaluation is reported following the CHEERS guidance¹⁵ (see Figure S1) and the health economic analysis plan that was finalised before the database was locked.¹⁶

3 | RESULTS

The full trial papers^{1,2} provide a detailed description of the final sample size and characteristics at 24 months. Of the 1394 babies randomly assigned to the emollient or control group at the start of the study, 186 infants did not have sufficient data for the economic analyses at 24 months. This resulting sample consisted of 1208 infants at 24 months for the CEA base-case analysis, 598 allocated the emollient intervention alongside standard skin care advice and 610 allocated standard skin care advice only. There were no missing data for the number of cases with and without eczema. The percentage

of missing data for the secondary outcome measures was roughly similar for the two groups.

3.1 | Resource use and costs

Unit costs and their sources are presented in Table S1. Resource use between the emollient and control groups was not significantly different (Table 1). Table 2 reports the mean discounted costs per infant for both groups disaggregated. The mean unadjusted total cost per infant was slightly higher for the emollient group £349.32 (SD 1314.29) than for the control, £301.94 (SD 1083.61) with an unadjusted mean difference of £47.37 per participant (95% CI -82.84 to 177.59). The largest component of the cost was overnight hospital stays, particularly for those infants with admitted.

3.2 | Outcome measures

Table 3 presents the outcomes for both groups unadjusted. Over the 24-month period, the percentage without eczema according to the UKWP-AD definition for the emollient group was 76.76% and 75.49% for the control, representing a difference of 1.27% (95% CI -3.55% to 6.08%). The proxy CHU-9D utility measured was marginally higher for the emollient group but not statistically significant.

3.3 | Primary economic analysis

Table 4 presents the adjusted results of the CEA in terms of the number of eczema cases diagnosed to provide the ICERs and CEAC estimates. The incremental difference in cost for the

| | Emollient group | Usual care group (n = 701) | Mean difference |
|--|-------------------|-------------------------------|------------------------|
| | Mean ± SD (n) | Mean ± SD (n) | (95% CI) |
| Intervention | 4.21 ± 2.20 (693) | 0.00 ± 0.00 (637) | 4.21 (4.04 to 4.38) |
| Doublebase Gel® | 2.52 ± 2.05 (693) | 0.00 ± 0.00 (637) | 2.52 (2.36 to 2.68) |
| Diprobace Cream® | 1.70 ± 1.54 (693) | 0.00 ± 0.00 (637) | 1.70 (1.58 to 1.81) |
| Wider NHS resource use (number of visits/episodes/mediation items) | | | |
| GP | 1.73 ± 3.31 (693) | 1.73 ± 2.81 (637) | 0.0003 (-0.33 to 0.33) |
| Practice nurse | 0.12 ± 0.53 (693) | 0.17 ± 0.80 (637) | -0.06 (-0.13 to 0.02) |
| Hospital doctor | 0.35 ± 1.27 (693) | 0.38 ± 1.48 (637) | -0.03 (-0.18 to 0.12) |
| Hospital nurse | 0.02 ± 0.18 (693) | 0.03 ± 0.27 (637) | -0.01 (-0.03 to 0.02) |
| Other health professional | 0.14 ± 0.68 (693) | 0.18 ± 0.75 (637) | -0.04 (-0.12 to 0.03) |
| Hospital episode | 0.17 ± 1.50 (693) | 0.19 ± 1.81 (637) | -0.02 (-0.19 to 0.16) |
| Medication | 3.74 ± 9.84 (693) | 3.50 ± 7.71 (637) | 0.24 (-0.72 to 1.20) |

TABLE 1 Mean (standard deviation) total NHS resource by treatment group over 2 years.

Note: Data shown are mean NHS costs per infant for eczema, rhinitis and wheezing at age 2 years.

Abbreviation: NHS, UK National Health Service.

TABLE 2 Mean (standard deviation) total cost by treatment group over 2 years.

| | Emollient group (n = 693) | | Usual care group (n = 701) | | Mean difference |
|------------------------------------|---------------------------|---------|----------------------------|---------|--------------------------|
| | Mean ± SD (n) | Missing | Mean ± SD (n) | Missing | (95% CI) |
| Total Intervention | 28.00 ± 14.65 (693) | | 0.00 ± 0.00 (637) | | 28.00 (26.86 to 29.14) |
| Doublebase Gel® | 16.69 ± 13.59 (693) | | 0.00 ± 0.00 (637) | | 16.69 (15.63 to 17.74) |
| Diprobace Cream® | 11.32 ± 10.25 (693) | | 0.00 ± 0.00 (637) | | 11.32 (10.52 to 12.11) |
| Wider NHS cost | | | | | |
| GP | 67.33 ± 129.01 (693) | | 67.30 ± 109.54 (637) | | 0.03 (-12.90 to 12.96) |
| Practice nurse | 2.40 ± 10.89 (693) | | 3.59 ± 16.77 (637) | | -1.19 (-2.70 to 0.32) |
| Hospital doctor | 50.14 ± 207.69 (693) | | 51.17 ± 226.93 (637) | | -1.03 (-24.40 to 22.35) |
| Hospital nurse | 0.40 ± 3.31 (693) | | 0.56 ± 5.18 (637) | | -0.16 (-0.63 to 0.30) |
| Other health professional (eczema) | 6.67 ± 32.99 (693) | | 10.46 ± 47.42 (637) | | -3.79 (-8.15 to 0.58) |
| Hospital episode | 170.32 ± 1106.85 (693) | | 145.29 ± 950.98 (637) | | 25.03 (-86.43 to 136.50) |
| Medication | 24.06 ± 83.95 (693) | | 23.58 ± 79.39 (637) | | 0.48 (-8.33 to 9.28) |
| Mean total cost (Int + NHS) | 349.32 ± 1314.29 (693) | | 301.94 ± 1083.61 (637) | | 47.37 (-82.84 to 177.59) |

Note: Data shown are mean NHS costs per infant for eczema, rhinitis and wheezing at age 2 years, shown in UK£ sterling. Data are unadjusted, available case for age 2 years of assessment.

Abbreviation: NHS, UK National Health Service.

TABLE 3 Mean eczema and quality-of-life outcomes by treatment group.

| | Intervention (n = 693) | | Usual care (n = 701) | | Mean difference |
|---|------------------------|---------|-----------------------|---------|--------------------------|
| | Mean ± SD (n) | Missing | Mean ± SD (n) | Missing | (95% CI) |
| Proportion without eczema at 24 months (based on UKWP-AD) | 0.7676 ± 0.4227 (598) | 99 | 0.7549 ± 0.4305 (612) | 89 | 0.0127 (-0.0355, 0.0608) |
| CHU-9D 24 months | 0.9349 ± 0.0690 (524) | 169 | 0.9338 ± 0.0685 (541) | 160 | 0.0010 (-0.0071, 0.0091) |
| QALYs at 24 months | 1.9030 ± 0.0672 (524) | 169 | 1.9020 ± 0.0642 (541) | 160 | 0.0010 (-0.0069, 0.0089) |

Note: Data shown are unadjusted, available case for age 2 years of assessment.

emollient group (n = 598) compared to the control (n = 610) was £87.45 (95% CI -£54.31, 229.27) (unadjusted £86.07 [95% CI -£57.77, 229.90]). The adjusted incremental difference in proportion without eczema for the emollient group compared with the control was 0.0164 (95% CI -0.0329, 0.0656) (unadjusted 0.0120 [95% CI -0.0359, 0.0600]), meaning that the emollient group had less cases (by a 1.64% margin) of eczema at 24 months. The ICER was £5337 (unadjusted £7281) per percentage decrease in risk of eczema. The amount decision-makers would be willing to pay per percentage decrease in risk of eczema is unknown. Figure 1 shows the estimated probability of the emollient intervention being cost-effective at different willingness-to-pay levels for a percentage decrease in risk of eczema.

3.4 | Secondary economic analysis

3.4.1 | CHU-9D

The adjusted mean QALYs for children were very slightly more in the emollient group, mean difference of 0.0010 (95% CI -0.0069,

0.0089), see Table 4. The adjusted incremental difference in cost for the emollient group (n = 524) compared to the control (n = 541) was £81.47 (95% CI -77.90, 240.83) meant that the emollient group was more expensive and slightly more effective than the control group. The adjusted ICER was £82,580 per QALY. The probability of the intervention being cost-effective was estimated as 29% (36%) at a willingness-to-pay threshold of £20,000 (£30,000) per QALY [6] (Figure S2), which suggests the intervention is unlikely to be viewed as cost-effective.

3.5 | Sensitivity analyses

In the 5-year analysis results (Tables S2 and S3), Table S2 shows that the proportion of cases without a parent report of a clinical diagnosis of eczema in the previous year was lower for the emollient group than the control group (89.39% vs. 93.15%, respectively, representing a mean difference of -3.75% [95% CI -7.32% to 0.19%]). The mean (SD) of QALYs from the CHU-9D for the emollient group was 4.424 (0.1820) and 4.4053 (0.1740) for controls, with a mean difference of 0.0181 (95% CI: -0.0126, 0.0488).

TABLE 4 Cost-effectiveness and cost-utility analysis results over 2 years.

| Analysis (N e, N c) | Incremental cost (UK£) (95% CI) | Incremental effect (95% CI) | ICER | % Cost-effective at £20 k (£30K) |
|--|---------------------------------|-----------------------------|---|---|
| CEA base case (CCA, unadjusted) (598, 610) | 86.07 (-57.77, 229.90) | 0.012 (-0.0359, 0.0600) | £7281 per percentage decrease in risk of eczema | Willingness-to-pay threshold per percentage decrease in risk of eczema unknown. |
| CEA base case (CCA, adjusted) (598, 610) | 87.45 (-54.31, 229.27) | 0.0164 (-0.0329, 0.0656) | £5337 per percentage decrease in risk of eczema | |
| CUA (CCA, CHU-9D, unadjusted) (524, 542) | 81.47 (-80.21, 243.14) | 0.0010 (-0.0069, 0.0089) | £82,250 per QALY | 30% (36%) |
| CUA (CCA, CHU-9D, adjusted) (524, 542) | 84.28 (-78.36, 246.93) | 0.0010 (-0.0068, 0.0089) | £82,580 per QALY | 29% (36%) |

Abbreviations: CCA, complete case analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; N c, sample size control group; N e, sample size emollient group.

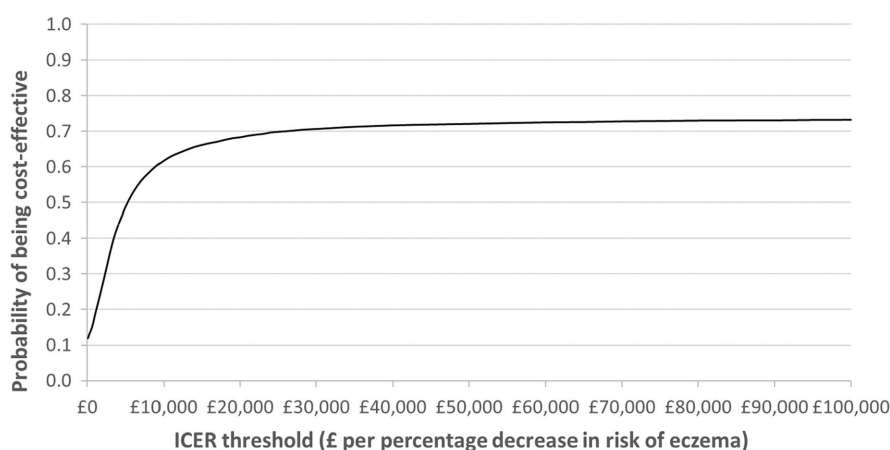


FIGURE 1 Cost effectiveness acceptability curve (CEAC) for the complete case adjusted CEA analysis (UKWP-AD) at 2 years. This cost-effectiveness acceptability curve (CEAC) figure summarizes the uncertainty in estimates of cost-effectiveness derived from the joint distribution of costs and effects for complete cases in adjusted cost effectiveness analysis at 2 years. The CEAC illustrates the probability that emollient intervention is cost-effective compared to usual care over different willingness to pay levels for a percentage decrease in risk of eczema in the BEEP trial. CEA denoted cost-effectiveness analysis, UKWP-AD means United Kingdom Working Party's in Atopic Dermatitis, ICER denotes incremental cost-effectiveness ratio. The abscissa is the ICER threshold measured as £ per percentage decrease in the risk of eczema and the ordinates as the probability of being cost-effective.

Table S3 presents the adjusted results of the CEA in terms of the number of eczema cases diagnosed to provide the ICERs and CEAC estimates at 5 years. The incremental difference in cost for the emollient ($n=383$) compared to the control ($n=411$) group was $-\text{£}106.89$ (95% CI $-\text{£}354.66, 140.88$) (unadjusted difference $-\text{£}123.74$ [95% CI $-\text{£}382.55, 127.08$]), meaning the emollient use was cost saving. The adjusted incremental difference in effect in proportion without eczema was -0.0329 (95% CI $-0.0659, 0.0002$) (unadjusted 0.0386 [95% CI $-0.0776, 0.0004$]), meaning there were more cases of eczema in the emollient group. The ICER was $\text{£}3201$ per percentage decrease in risk of eczema. Of note is the small number of participants with high inpatient costs due to wheezing, particularly in the usual care group. The 5-year CEA without the inpatient wheezing costs showed an adjusted incremental cost difference of $\text{£}100.34$ (95% CI $-\text{£}30.09$ to 230.83). Thus, without wheezing inpatient costs,

the intervention was dominated (the emollient group had higher costs and worse outcomes than the usual care group). The results of the CUA are contradictory to that of the CEA analysis, since despite more cases of eczema in the emollient group, they also had slightly higher mean QALYs, though as in the 2-year analysis, these values were small and not significant.

4 | DISCUSSION

4.1 | Main primary analysis

In our economic analysis of this multicentre, pragmatic randomised controlled trial of high-risk infants, we found no evidence that regular emollient use for the first year of life is cost-effective at 2 years

of age, using a two-year time horizon. This result is in keeping with the findings of the effectiveness study.^{1,2} We find that the intervention is more expensive, prevents only marginally more cases of eczema and generates very slightly more QALYs as measured using the CHU-9D by proxy. When the results were adjusted for covariates, the same conclusion held for the primary and secondary outcome measures and results confirmed after robustness tests of bootstrapping and sensitivity analysis.

4.2 | Sensitivity analysis

Analysis at 5 years undertaken as sensitivity analysis had around 44% missing sample cost data. The complete case CEA estimated the intervention was cost saving if inpatient costs related to wheezing were included but more costly if these were excluded. This finding was also associated with poorer outcomes, because the control group had a greater proportion without eczema at 5 years than the emollient group. In the 5-year CUA (complete case or using multiple imputation), the intervention was found to dominate, indicating the intervention was cost saving with higher incremental effect in the emollient group. Given the intervention was not clinically effective, the plausibility of these results needs to be questioned. In part, the cost savings found in the 5-year analyses were driven by differences in number of inpatient hospital stays associated with wheezing between study groups in years 3–5, in whom less than 4% of the sample incurred inpatient stays due to wheezing but were associated with high cost. When these were removed as part of sensitivity analysis, the incremental cost was positive indicating higher mean cost per participant in the intervention arm in the cost-utility analysis. Incremental QALYs were also very small and not too different from zero. Given there is no evidence that the intervention was clinically effective at preventing eczema, it seems unlikely that wheezing resource use was associated with use of the intervention such that the 5-year CUA results including wheezing costs are likely to be spurious. That we find this seemingly “paradoxical”³ finding at 5 years (particularly in the CUA) is symptomatic of there being no statistically significant small incremental costs and effects.

These results alongside the trial's clinical outcomes have important implications for the existing evidence on whether to apply emollients to the skin of healthy infants as a preventive measure. In contrast, Xu et al⁴ concluded that daily moisturisation is a cost-effective preventive strategy that can reduce the burden of atopic eczema. Their study was a secondary analysis based on pilot evidence, of small sample size, about the effectiveness of emollients from the UK⁵ and Japan¹⁷ where relative risk reduction was estimated as 50% and 25%, respectively. Using these estimates along with assumptions over the amount of emollient that would be used, the decision tree was reportedly analysed using a CUA approach for a 6-month time horizon. Our findings, using data from a larger, definitive study, suggest that use of our study emollients and those reported in a recent individual patient data meta-analysis¹⁸ as a

preventive measure early in life for high-risk infants is probably not effective or cost-effective.

4.3 | Strengths and limitations

The current level of economic evidence available for interventions aimed at preventing and treating eczema is limited.^{19,20} This study adds to the evidence base and in particular to understanding about the scope and size of resource use, costs and quality of life of infants at high risk of atopic disease with and without the use of emollients in early life. Our results can help inform future studies including economic modelling.

There are three potential limitations. Firstly, resource use related to allergy was not collected in this study due to this aspect of the study being incorporated after the start. Secondly, the recall period for resource use questions varied throughout the study. Recall period was 3 months in the first 6 months of the study, increasing to 6 months between 6 months and 24 months, before switching to 12 month recall periods until 5 years. This was in line with other trial questionnaires, but we acknowledge that longer recall periods may reduce the reliability of data provided by patient report. Participants would have learnt during the course of the study what they were going to be asked as question format was kept similar over time. In addition, only disease-specific resource use was collected rather than all resource use, which would have necessitated a higher respondent burden. Thirdly, capturing utility for infants and young children is difficult in economic evaluations. In this study, we used the CHU-9D by parental proxy for infants at ages 2, 3, 4 and 5 years, using the additional guidance notes supplied to us by the instrument developers for use with parents of pre-school children. The CHU-9D is currently validated for children 7 years and upwards [9] and for children aged 5–7 years by parental proxy.²¹ We are unaware of other studies using CHU-9D in children ≤5 years.²² Using data from this study, we plan to undertake further research to explore the validity of the CHU-9D for children and infants aged ≤5 years. This will add to the growing academic discussion on appropriate HR-QoL measures for young children and infants and associated issues such as using parental proxies.²³

5 | CONCLUSIONS

The daily use of all-over-body emollient during the first year of life as delivered in the BEEP trial was not estimated to be a cost-effective intervention in preventing atopic eczema in high-risk children under 2 years of age. This study provides robust new evidence and comes to a different conclusion to that of a previously published illustrative economic study.⁴

AUTHOR CONTRIBUTIONS

THS was the lead health economist with responsibility for the design, analysis and reporting of the economic evaluation undertaken alongside the BEEP trial. STL and CD conducted the health economic

analyses and contributed to the writing of the paper. HCW conceived the BEEP trial and was the chief investigator. HCW, JRC, RJB, RHH, LEB, AAM, KST, SJB, MJR, MJC, THS, CF, EJM, SD-J, NJ and MRP all contributed to the conception or design of the trial and the acquisition, analysis or interpretation of the data. JRC, RHH, EJM and KST supported the design and conduct of the trial. RS and ST contributed to the conduct of the trial (data collection and management). RJB led the food allergy assessments aided by NJ, MK and MRP. AAM and LEB were responsible for the statistical analysis. MJC provided expertise in emollients and the skin barrier. SJB was responsible for the genetic analysis. KST, MJR, SJB, SL, SD-J and CF all contributed clinical experience of eczema or eczema trials, or both. The manuscript was drafted by THS, STL and CD; all other authors critically reviewed and revised the manuscript. All authors have approved the final version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

Funding for the trial was obtained from the National Institute for Health and Care Research (NIHR) Health Technology Assessment funding stream (reference 12/67/12). Additional funding for the food allergy and sensitisation tests was obtained from Goldman Sachs Gives and the Sheffield Children's Hospital Research Fund (reference CA15008). Research nurse support was provided by the NIHR Clinical Research Networks. The trial was developed with and supported by the UK Dermatology Clinical Trials Network (UK DCTN). THS is a steering committee member of the UK Dermatology Clinical Trials Network and Chair of the NIHR Research for Patient Benefit Regional Advisory Panel for the East of England. SJB holds a Wellcome Trust Senior Research

Fellowship in Clinical Science (reference 106865/Z/15/Z). CF held an NIHR Career Development Fellowship (CDF-2014-07-037) during the trial and is supported by the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. MK holds an NIHR Transitional Research Fellowship (TRF-2017-10-003). MJR held a Post-Doctoral Research Fellowship from NIHR (PDF-2014-07-013). THS held a NIHR Career Development Fellowship (CDF-2014-07-006) during part of this study. The views expressed here are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. CF received a grant from the EU IMI grant scheme (Horizon 2020). His department has received investigator-led funding for microbiome research. Both are outside of the submitted work. CF leads the European Dermatology Forum treatment guidelines for eczema. MJC received grants and personal fees from Sanofi-Genzyme/Regeneron, Pfizer, Leo Phgroupa, L'Oreal/LaRoche Possay, Johnson & Johnson, Perrigo/ACO Nordic and grants from Galapagos, outside of the submitted work. HCW was the director of the NIHR Health Technology Assessment Programme 2015 to 2020. THS was a member of NIHR HTA Efficient Study Designs-2, HTA Efficient Study Designs Board, HTA End of Life Care and Add-on-Studies, HTA Primary Care Themed Call Board and the HTA Commissioning Board between 2013 and Dec 2019. She is a steering committee member of the UK Dermatology Clinical Trials Network and Chair of the NIHR Research for Patient Benefit Regional Advisory Panel for the East of England. HCW and THS had no part in the decision-making for funding this study. All other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Access to the data will be subject to review of a data sharing and use request (available from ctu@nottingham.ac.uk) by a committee including the CI and sponsor and will only be granted upon receipt of a data sharing and use agreement. Any data shared will be pseudo-anonymised, which may impact on the reproducibility of published analyses. The study protocol, statistical analysis plan and health economics analysis plan are available on the trial website: <https://www.nottingham.ac.uk/research/groups/cebd/projects/1eczema/beep-maintrial.aspx>.

ETHICS STATEMENT

This study was conducted in compliance with the ethical principles of the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice guidelines. The study protocol was reviewed and approved by the Institutional Review board and/or Independent Ethics Committee at each participating centre. All participants provided written informed consent. Ethical approval for the trial was given by West Midlands Ethics Committee, UK (14/WM/0162).

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REFERENCES

- Chalmers JR, Haines RH, Bradshaw LE, et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. *Lancet*. 2020;395(10228):962-972.
- Bradshaw LE, Wyatt LA, Brown SJ, et al. Emollients for prevention of atopic dermatitis: 5-year findings from the BEEP randomized trial. *Allergy*. 2022;78:995-1006. doi:10.1111/all.15555
- Raftery J, Williams HC, Clarke A, et al. 'Not clinically effective but cost-effective'—paradoxical conclusions in randomised controlled trials with 'doubly null' results: a cross-sectional study. *BMJ Open*. 2020;10(1):e029596.
- Xu S, Immaneni S, Hazen GB, Silverberg JI, Paller AS, Lio PA. Cost-effectiveness of prophylactic Moisturization for atopic dermatitis. *JAMA Pediatr*. 2017;171(2):e163909.
- Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134(4):818-823.
- National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal*. National Institute for Health and Care Excellence; 2013.
- Health and Social Care Information Centre, Prescription Cost Analysis. 2020. Accessed December 16, 2022. <https://www.nhs.uk/statistical-collections/prescription-cost-analysis-england/prescription-cost-analysis-england-2019>
- Curtis L, Burns A. Personal Social Services Research Unit, in Unit Costs of Health and Social Care 2020. Accessed December 16, 2022. <https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/>
- Department of Health. NHS Schedule of Reference Costs, 2019/20. Accessed December 16, 2022. <https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/>
- Stevens K. Valuation of the child health utility 9D index. *Pharmacoeconomics*. 2012;30(8):729-747.
- Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ*. 2005;14(5):487-496.
- Gallacher D. HEABS: Stata module to calculate the ICER and Net Benefit for up to two datasets. Accessed September 2, 2022. <https://EconPapers.repec.org/RePEc:boc:bocode:s458438>
- Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ*. 2004;13(5):461-475.
- Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics*. 2014;32(12):1157-1170.
- Husereau D, Drummond M, Augustovski F, et al. Consolidated health economic evaluation reporting standards 2022 (CHEERS 2022) Statement: updated reporting guidance for health economic evaluations. *BMJ*. 2022;376:e067975.
- Sach T. Health Economic Analysis plan for the BEEP trial. Accessed December 21, 2022. <https://www.nottingham.ac.uk/research/groups/cebd/documents/researchdocs/beep-health-economics-analysis-plan-final-1.0-26th-sept-2018.pdf>
- Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):824-830.e6.
- Kelleher MM, Phillips R, Brown SJ, et al. Skin care interventions in infants for preventing eczema and food allergy. *Cochrane Database Syst Rev*. 2022;11(11):CD013534. doi:10.1002/14651858.CD013534.pub3
- Sach TH, McManus E, Levell NJ. Economic evidence for the prevention and treatment of atopic eczema. *Br J Dermatol*. 2019;181(4):e95.
- McManus E, Sach T, Levell N. The use of decision-analytic models in atopic eczema: a systematic review and critical appraisal. *Pharmacoeconomics*. 2018;36(1):51-66.
- Canaway AG, Frew EJ. Measuring preference-based quality of life in children aged 6-7 years: a comparison of the performance of the CHU-9D and EQ-5D-Y--the WAVES pilot study. *Qual Life Res*. 2013;22(1):173-183.
- Sheffield Clinical Trials Research Unit, Study Protocol. *The MAGIC trial (Melatonin for Anxiety prior to General anaesthesia in Children): A Multicentre, Parallel Randomised Controlled Trial of Melatonin Versus Midazolam in the Premedication of Anxious Children Attending for Elective Surgery Under General Anaesthesia*. National Institute for Health Research, Version 4.1; 2020.
- Bray N, Noyes J, Harris N, Edwards RT. Measuring the health-related quality of life of children with impaired mobility: examining correlation and agreement between children and parent proxies. *BMC Res Notes*. 2017;10(1):377.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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