Effectiveness and safety of lotion, cream, gel, and ointment emollients for childhood eczema: a pragmatic, randomised, phase 4, superiority trial

Matthew J Ridd, Miriam Santer, Stephanie J MacNeill, Emily Sanderson, Sian Wells, Douglas Webb, Jonathan Banks, Eileen Sutton, Amanda Roberts, Lyn Liddiard, Zoe Wilkins, Julie Clayton, Kirsty Garfield, Tiffany J Barrett, J Athene Lane, Helen Baxter, Laura Howells, Jodi Taylor, Alastair D Hay, Hywel C Williams, Kim S Thomas

Summary

Background To our knowledge, there are no trials comparing emollients commonly used for childhood eczema. We aimed to compare the clinical effectiveness and safety of the four main emollient types: lotions, creams, gels, and ointments.

Methods We did a pragmatic, individually randomised, parallel group, phase 4 superiority trial in 77 general practice surgeries in England. Children aged between 6 months and 12 years with eczema (Patient Orientated Eczema Measure [POEM] score >2) were randomly assigned (1:1:1:1; stratified by centre and minimised by baseline POEM score and age, using a web-based system) to lotions, creams, gels, or ointments. Clinicians and parents were unmasked. The initial emollient prescription was for 500 g or 500 mL, to be applied twice daily and as required. Subsequent prescriptions were determined by the family. The primary outcome was parent-reported eczema severity over 16 weeks (weekly POEM), with analysis as randomly assigned regardless of adherence, adjusting for baseline and stratification variables. Safety was assessed in all randomly assigned participants. This trial was registered with the ISRCTN registry, ISRCTN84540529.

Findings Between Jan 19, 2018, and Oct 31, 2019, 12 417 children were assessed for eligibility, 550 of whom were randomly assigned to a treatment group (137 to lotion, 140 to cream, 135 to gel, and 138 to ointment). The numbers of participants who contributed at least two POEM scores and were included in the primary analysis were 131 in the lotion group, 137 in the cream group, 130 in the gel group, and 126 in the ointment group. Baseline median age was 4 years (IQR 2–8); 255 (46%) participants were girls, 295 (54%) were boys; 473 (86%) participants were White; and the mean POEM score was 9·3 (SD 5·5). There was no difference in eczema severity between emollient types over 16 weeks (global p value=0·77), with adjusted POEM pairwise differences of: cream versus lotion 0·42 (95% CI –0·48 to 1·32), gel versus lotion 0·17 (–0·75 to 1·09), ointment versus lotion –0·01 (–0·93 to 0·91), gel versus cream –0·25 (–1·15 to 0·65), ointment versus cream –0·43 (–1·34 to 0·48), and ointment versus gel –0·18 (–1·11 to 0·75). This result remained unchanged following multiple imputation, sensitivity, and subgroup analyses. The total number of adverse events did not significantly differ between the treatment groups (lotions 49 [36%], creams 54 [39%], gels 54 [40%], and ointments 48 [35%]; p=0·79), although stinging was less common with ointments (12 [9%] of 138 participants) than lotions (28 [20%] of 137), creams (24 [17%] of 140), or gels (25 [19%] of 135).

Interpretation We found no difference in effectiveness between the four main types of emollients for childhood eczema. Users need to be able to choose from a range of emollients to find one that they are more likely to use effectively.

Funding National Institute for Health and Care Research.

Lancet Child Adolesc Health 2022

Published Online May 24, 2022 https://doi.org/10.1016/S2352-4642(22)00146-8

Population Health Sciences (Prof M J Ridd PhD, S Wells MSc, D Webb MSc, E Sutton PhD, L Liddiard BSc, J Clayton PhD, H Baxter PhD, Z Wilkins, Prof A D Hay MD) **and Bristol Trials Centre** (S J MacNeill PhD, E Sanderson MSc, K Garfield PhD, Prof J A Lane PhD, J Taylor PhD), **University of Bristol, Bristol, UK; National Institute for Health Research Applied Research Collaboration West** (J Banks PhD) **and South West Medicines Information and Training** (T J Barrett MSc), **University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK; Centre of Evidence-Based Dermatology, University of Nottingham, Nottingham, UK** (L Howells PhD, Prof H C Williams PhD, Prof K S Thomas PhD)**; Primary Care Research Centre, University of Southampton, Southampton, UK** (Prof M Santer PhD)**; Nottingham Support Group for Carers of Children with Eczema, Nottingham, UK** (A Roberts BSc)

Correspondence to: Prof Matthew J Ridd, Population Health Sciences, University of Bristol, Bristol BS8 2PS, UK **m.ridd@bristol.ac.uk**

Introduction

Eczema (also known as atopic eczema or atopic dermatitis) affects around 20% of children. It is characterised by dry and inflamed, itchy skin. The impairment in health-related quality of life is similar to that of many other long-term conditions in children, including diabetes and asthma.[1] Daily use of emollients as a leave-on treatment is recommended, alongside topical anti-inflammatory agents such as corticosteroids to treat or prevent flares.[2]

Emollients treat symptoms of dry skin, act as a barrier to irritants, and might have mild anti-inflammatory properties. Internationally, the availability of specific emollients varies but the four main types are lotions, creams, gels, and ointments, which vary in their consistency from watery and thin through to solid and

Research in context

Evidence before this study

Research directly comparing the effectiveness and acceptability of emollients as a leave-on treatment for atopic eczema or dermatitis (eczema) is scarce. There are multiple emollients, the majority of which are classed as lotions, creams, gels, or ointments. A trial and error approach to prescribing is common, which can lead to underuse, waste, and frustration for families. A Cochrane review published in 2017 summarised evidence from 77 trials on the effectiveness of emollients in eczema. It concluded that emollients prolong time to eczema flare, and reduce the number of flares and the need for topical corticosteroids. However, because of an absence of good quality, head-to-head comparisons, the review was unable to say whether some emollients or their ingredients were better than others. In addition, reporting of adverse events was limited. We have not identified any subsequent reviews, so we searched Ovid MEDLINE, Embase, Cochrane Central and WHO International Clinical Trials Registry Platform (with no language restrictions, using "emollient(s)" and "moisturiser(s)"/"moisturizer(s)") between 2017 and November, 2021, for published studies or on-going trials comparing different types of emollients as a leave-on treatment for children with eczema. We only identified our own feasibility study of 197 children with eczema aged 1 month to younger than 5 years, who were randomly assigned to lotion, cream, gel, or ointment for 12 weeks. Data were reported on a range of outcomes, including eczema symptoms and signs, but as a feasibility trial it was not powered to detect any differences.

Added value of this study

To our knowledge, the Best Emollients for Eczema study is the first pragmatic trial of its kind and collected data in key domains that are important to patients. We found no difference between lotions, creams, gels, and ointments for childhood eczema in terms of symptoms (primary outcome), eczema signs, quality of life, or impact on the family (secondary outcomes). Usage of allocated and non-allocated emollients, and topical corticosteroids, were similar across all groups. Adverse reactions were frequent (occurring in 37% of participants), most commonly localised skin reactions (worsening of eczema, itching, inflammation, dryness, and stinging). Participants' previous experience of, and opinions regarding, the four main types of emollient were variable.

Implications of all the available evidence

Contrary to popular belief that some emollient types are better than others, we found no difference in effectiveness between the four main type of emollients for childhood eczema. However, their acceptability varies for different users, so parents and older children need to be aware of the characteristics of, and be able to choose from, the four emollient types. Future research is needed to compare novel emollients or ones that contain humectants such as urea.

greasy. However, prescribers can choose from more than 100 different products. With weak evidence that any one specific emollient or type is more effective or acceptable than another,[3] the consensus has favoured greasier emollients as more effective but less acceptable. "Which emollients are the most effective and safe in treating eczema?" emerged as one of the top four uncertainties in a James Lind Alliance eczema research-priority setting exercise.[4]

We therefore aimed to compare the effectiveness and safety of lotions, creams, gels, and ointments for children with eczema in primary care.

Methods

Study design

The Best Emollients for Eczema study was a pragmatic, individually randomised, parallel group, phase 4, superiority trial of four types of emollient (lotions, creams, gels, and ointments), which recruited participants via 77 general practice surgeries in three centres (National Institute for Health and Care Research Clinical Research Networks West of England, Wessex, and East Midlands) in England. Ethics approval was granted by the National Health Service (NHS) Research Ethics Committee (South West–Central Bristol Research Ethics Committee 17/SW/0089). A protocol summary was previously published.[5]

Participants

Parents or carers (hereafter parents) of potentially eligible children were approached by post and opportunistically. Children with an eczema diagnosis and recent relevant prescription were identified by means of an electronic medical records search, the results of which were screened for appropriateness by the general practitioner before sending an invitation letter. Parents who expressed an interest attended a baseline visit, where eligibility was confirmed, written informed consent received, and baseline data collected. For children aged approximately 7 years and older, written assent was sought.

To be eligible, children had to be aged 6 months to less than 12 years; have eczema diagnosed by a health-care professional; have mild eczema or worse (as determined by a parent-completed Patient Orientated Eczema Measure [POEM] score of >2 within previous 28 days);[6] and the family had to be willing to use the randomly allocated emollient type as the only leave-on emollient for 16 weeks. Children were ineligible if they had known sensitivity to study emollients or their constituents; or the parent was unable to give informed consent or had insufficient written English to complete outcome measures.

In recognition of participants' time and to encourage questionnaire completion, parents were offered a £10 voucher at the baseline and 16-week visits, and at

around 52 weeks. We also offered the child a bee soft toy or rubber ball and ruler, of about £5 in value.

Randomisation and masking

Participants were randomly assigned (1:1:1:1) to receive lotions, creams, gel, or ointment. Randomisation was stratified by centre and minimised by baseline POEM score (mild *vs* moderate or severe)[7] and participant age (younger than 2 years *vs* 2 years and older) using a web-based randomisation system, where allocation cannot be changed. It was not possible to mask participants and their clinicians. The trial administrator and coordinator (ESu and ZW), who randomly assigned participants and notified general practitioners and parents of allocation, and the clinical trials unit staff who maintained the randomisation database, were unmasked.

Trial managers were fully masked until version 1.0 of the statistical analysis plan was written. Thereafter, they were unmasked on an individual participant basis when required to undertake randomisations and deal with potential serious adverse events. Members of the trial management group, including the chief investigator, were masked to allocation, with the exception of JB, who supervised the nested qualitative study.

The researchers undertaking the skin assessments were fully masked. This was achieved by asking participants to not reveal which emollient they had been allocated and by asking the researchers at 16 weeks which type of emollient they thought the participant was using (including "don't know"). Using these data, we calculated the Bang blinding index,[8] which takes a value between –1 and 1: 1 indicates complete absence of masking, 0 is consistent with perfect masking and –1 indicates opposite guessing, which might be related to unmasking.

Procedures

An emollient of the allocated type was prescribed by the participant's general practitioner, according to which study-approved emollient was on their local NHS formulary. If more than one study-approved emollient of the allocated type was available, the prescribing general practitioner decided which to issue. All study-approved emollients were paraffin-based and none contained antimicrobials or urea: lotions contained glycerol; creams had no humectant or lanolin; gels did not contain povidine; and ointments had no additives. General practitioner were asked to initially prescribe 500 g or 500 mL with the directions to "Apply twice daily and as required". The total amount of emollient prescribed during the study was determined by the family, with repeat prescriptions obtained from their general practitioner.

In the event of problems with the study emollient, the general practitioner was encouraged to prescribe and the parent use another emollient of the same type, thus respecting the random assignment. If this was not possible, we asked that general practitioners prescribe and parents use a study-approved emollient of another type. After 16 weeks, participants could continue to use their allocated emollient or change. Parents were encouraged to use their allocated emollient as a soap substitute but use of other emollients as wash products was permitted.

We did not try to promote emollient use. At the baseline visit, the researcher gave participants simple verbal advice and a one-page emollient information leaflet (created by the research team on the basis of advice in the public domain), which included a link to a generic 2-min video on how to apply emollients. Usual care was otherwise unchanged, with parents and clinicians free to make appointments and referrals and to continue to use or change other treatments as normal.

Parents were contacted by the research team within 1 week of random assignment to check that they had collected and started using their study emollient. Thereafter, with the exception of the 16-week skin assessment visit, follow-up was remote by means of parent-completed questionnaires, weekly for the first 16 weeks and every 4 weeks until 52 weeks.

Outcomes

The primary outcome was parent-reported eczema symptoms, as captured by POEM, measured weekly for 16 weeks. POEM is a seven-item questionnaire of eczema symptoms over the previous week.[6] POEM scores have a range from 0 (no symptoms) to 28 (very severe symptoms).

The following secondary outcomes were collected. Eczema signs (Eczema Area Severity Index [EASI]) were collected by a masked researcher at 16 weeks with scores ranging from 0 (no disease) to 72 (very severe disease).[9] Eczema symptoms by POEM were measured every 4 weeks for 52 weeks. The effect of the participant's eczema on the family (Dermatitis Family Impact questionnaire [DFI]) in the past week[10] was measured at 16 and 52 weeks, with total DFI score ranging from 0 to 30 and a higher score indicating greater impairment in family quality of life. Participant quality of life (disease-specific Atopic Dermatitis Quality of Life [ADQoL][11] and generic Child Health Utility-9 Dimension [CHU-9D][12,13]) was measured as a secondary outcome at 6, 16, and 52 weeks. Parent-reported use of emollients and topical corticosteroids and parent-reported adverse events were measured throughout the study. Adverse events were assessed in all randomly assigned participants. Parent overall satisfaction with study emollient and intentions regarding continued use of study emollient were assessed at 16 weeks and the acceptability of the study processes (including following directions on study emollient use) was assessed at 52 weeks. The final secondary outcome was the proportion of well controlled weeks between weeks 1 to 16, derived from POEM. Each week was classified as well controlled (POEM score ≤2) or not (POEM score >2), with the proportion of weeks with well controlled symptoms

calculated as the number of well controlled weeks divided by the number of weeks with non-missing POEM scores.

We collected data using the core outcome measures recommended by Harmonising Outcome Measures in Eczema (HOME) in the domains of symptoms (POEM) and signs (EASI).[14]

Statistical analysis

The sample size was calculated to detect a difference between any two emollient types of 3·0 in POEM scores (the minimum clinically important difference in POEM for this age group).[15–17] Assuming an SD of 5·5, 20% loss to follow-up, and a significance level of 0·05, after adjustment for multiple pairwise comparisons we sought to recruit 520 patients.

The primary statistical analyses between the randomly assigned groups were done on a modified intention-to-treat basis, defined as analysing participants as randomly assigned without imputation for missing data. For the primary outcome, linear mixed models (weekly observations, level 1; nested within participants, level 2) were used to explore whether there were differences in mean POEM scores between treatment groups after adjusting for baseline scores and all stratification and minimisation variables used in the randomisation. Pairwise comparisons were done to identify which intervention groups differed, and were presented as mean differences with 95% CIs and p values. To account for multiple testing, we used a modified α of 0·0083 (0·05/6 pairwise comparisons equivalent) as a threshold when interpreting p values.

To assess the robustness of the primary analysis to model selection and data collection, the following prespecified sensitivity analyses for the primary outcome were done: adjusting for variables found to be imbalanced at baseline; excluding randomly assigned participants later found to be ineligible; use of researcher-collected POEM at 16 weeks where parent self-reported POEM was missing; and imputing missing data. Three separate approaches were taken to imputing missing POEM data: multiple imputation by chained equations; using a best-case scenario; and using a worst-case scenario. Under the best-case scenario, it was assumed that when POEM scores were missing, it was because POEM scores were low (ie, mild symptoms), so missing POEM scores were replaced by the mean minus 1 SD for that treatment group. Under the worst-case scenario, it was assumed that when POEM scores were missing, it was because scores were high (ie, worse symptoms), so missing POEM scores were replaced by the mean plus 1 SD for that treatment group.

Prespecified subgroup analyses investigated whether treatment effectiveness (POEM) was modified by factors measured at randomisation (parent expectation of the effectiveness of the emollient, age, disease severity, and whether or not the child met the UK diagnostic criteria for eczema). These analyses were carried out by introducing appropriate interaction terms in the regression models and likelihood ratio tests were used to compare the model with the interaction term with the model without.

A per-protocol analysis was planned in the event of substantial contamination, which was not defined in the statistical analysis plan. When we inspected the data, use of non-allocated emollients (contamination) during the primary outcome period was low. Therefore, we decided to repeat the primary analysis restricted to participants who reported using their allocated emollient at least 1 in every 4 weeks (that is, in weeks 1–4, 5–8, 9–12, and 13–16) and for at least 60% of days in a reported week.

Analyses of secondary outcomes were done on a modified intention-to-treat basis, according to the data type and frequency of recording. Continuous outcomes measured at multiple timepoints (POEM over 52 weeks, ADQoL, DFI, and CHU-9D) were analysed similarly to the primary outcome as described above. EASI and DFI scores at follow-up were found to be highly skewed and contained values of 0; therefore, scores were transformed by taking the natural logarithm of the score plus 1. The results of these analyses are shown as the ratio of the geometric means of the two groups being compared. The proportion of weeks with well controlled symptoms was analysed using a linear regression model adjusting for stratification and minimisation variables.

Participants were asked to record study emollient, other emollient, and topical corticosteroid use on a daily basis (any or none) during the primary outcome period. We described self-reported use of these topical treatments as the proportion of the total number of days for which non-missing data were available. Analyses tested whether there were differences between treatment groups in the number of treatment-adherent days per week, the use of non-study emollients, and topical corticosteroid use. A mixed-effect Poisson model adjusting for randomisation variables was used for the number of adherent days. Mixed-effect negative binomial models adjusting for randomisation variables were used for non-study emollient use and topical corticosteroid use. For each of these models, the p value for the likelihood ratio test comparing the model with and without treatment group is shown.

We explored the possible impact of UK public health guidance introduced in March, 2020, in response to the SARS-CoV-2 (COVID-19) pandemic. A linear mixed model (weekly observations [level 1] nested within participants [level 2]) including a binary interaction term (classifying participant's follow-up as being before or after public health advice) was used to explore whether the differences in mean POEM scores between treatment groups differed. The model also adjusted for baseline POEM scores and variables used in the randomisation.

There was an independent Trial Steering Committee (TSC) and Data Monitoring Committee. The statistician on the TSC approved the statistical analysis plan.

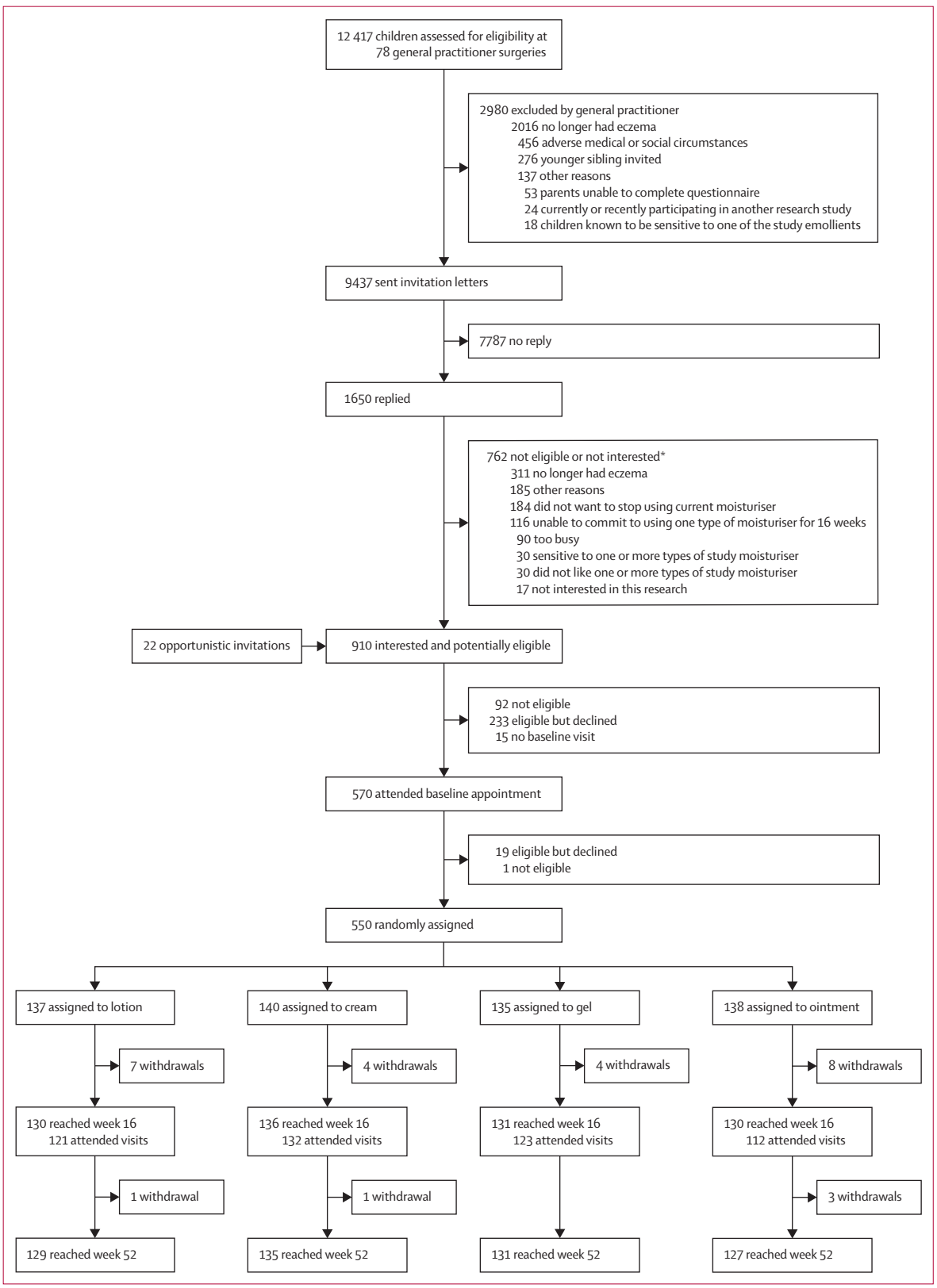

Figure 1: **Trial profile**
*Reasons for declining invitation provided by the parents are not mutually exclusive; therefore, the number of exclusion reasons do not total the number excluded

Stata (version 16) was used for all statistical analyses. This trial is registered with the ISRCTN registry, ISRCTN84540529.

See Online for appendix

	Number of participants (%)
Lotions	
QV lotion (5% white soft paraffin, pump)	77 (56%)
Cetraben lotion (white soft paraffin 5%, light liquid paraffin 4%, pump)	37 (27%)
Diprobase lotion (white soft paraffin, pump)	15 (11%)
Non-lotion*	2 (2%)
Unknown	6 (4%)
Total	137 (100%)
Creams	
Epimax cream (liquid paraffin 6%, white soft paraffin 15%, bottle)	72 (51%)
Zerobase cream (liquid paraffin 11%, pump)	40 (29%)
Diprobase cream (liquid paraffin 6%, white soft paraffin 15%, cetomacrogol 2·25%, pump)	10 (7%)
Aquamax cream (white soft paraffin 20%, liquid paraffin 8%, tub)	8 (6%)
Non-study cream†	2 (1%)
Unknown	8 (6%)
Total	140 (100%)
Gels	
Epimax Isomol gel (isopropyl myristate 15%, liquid paraffin 15%, bottle)	96 (71%)
Zerodouble gel (isopropyl myristate 15%, liquid paraffin 15%, pump)	21 (16%)
Doublebase gel (isopropyl myristate 15%, liquid paraffin 15%, pump)	9 (7%)
AproDerm gel (isopropyl myristate 15%, liquid paraffin 15%, pump)	1 (1%)
Non-gel‡	2 (2%)
Unknown	6 (4%)
Total	135 (100%)
Ointments	
White soft and liquid paraffin 50:50 ointment (white soft paraffin 50% liquid paraffin 50%, tub)	88 (64%)
Emulsifying ointment BP (emulsifying wax 30%, liquid paraffin 20%, white soft paraffin 50%, tub)	29 (21%)
Diprobase ointment (white soft paraffin 50% liquid paraffin 50%, tub)	9 (7%)
Non-ointment	3 (2%)
Unknown§	9 (7%)
Total	138 (100%)

The manufacturer details for the emollients listed by their proprietary names are as follows: QV lotion (QC Skincare, Melbourne, VIC, Australia); Cetraben lotion (Thornton & Ross, Huddersfield, UK); Diprobase lotion (Bayer, Reading, UK); Epimax cream (Aspire Pharma, Petersfield, UK); Zerobase cream (Thornton & Ross); Diprobase cream (Bayer); Aquamax cream (Intrapharm Laboratories, Maidenhead, UK); Epimax Isomol gel (Aspire Pharma); Zerodouble gel (Thornton & Ross); Doublebase gel (Diomed Developments, Hitchin, UK); AproDerm gel (Fontus Health, Walsall, UK); and Diprobase ointment (Bayer). *Two participants prescribed Cetraben cream. †Two participants prescribed Zerocream. ‡One participant prescribed Zeroderm ointment and one participant prescribed Diprobase cream; §Two participants prescribed Diprobase cream and one participant prescribed Zeroveen cream.

Table 1: **Study-approved emollients by type issued at baseline**

Role of the funding source

The funder of the study was involved in refining the trial design through the funding peer review process, but had no role in data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 19, 2018, and Oct 31, 2019, 12 417 children were assessed for eligibility, 550 of whom were randomly assigned to a treatment group (137 to lotion, 140 to cream, 135 to gel, and 138 to ointment; figure 1). The numbers of participants who contributed at least two POEM scores (one baseline and another between weeks 1 and 16) and were included in the primary analysis were 131 in the lotion group, 137 in the cream group, 130 in the gel group, and 126 in the ointment group. The number of participants prescribed specific emollients are listed in table 1. There was a median 4 days (IQR 3–7) between random assignment and self-reported first use of emollient, with 430 (80%) reporting first use within 7 days of random assignment. At least one week of parent-reported data on emollient use was provided by 455 (83%) participants (appendix p 4).

Of the 762 parents who declined to participate, 129 completed a screening POEM and their children were eligible in terms of age and POEM. 130 parents completed the POEM and their children were not eligible on the basis of age or POEM. 503 did not complete the screening POEM. The age and sex of potentially eligible children excluded by their general practitioner (appendix p 3), who did not attend a baseline visit or give consent were similar to those who were included, did attend, and did give consent (appendix p 3). Respondents who were screened for participation were slightly younger than those who did not respond to their invitation or declined (appendix p 3) and mean POEM scores were lower among those who attended at baseline visit but did not give consent (appendix p 3). Baseline characteristics were balanced across treatment groups (table 2, appendix p 5), except for sex where there were more girls in the cream group than the gel group (77 [55%] *vs* 54 [40%]). Median age of participants was 4 years (IQR 2–8) and 94 (17%) were younger than 2 years. Most participants were White (473 [86%]), met the UK diagnostic criteria for atopic dermatitis (447 [81%]), and had mild–moderate eczema (451 [82%]; table 2 and appendix p 6). There was substantial variation in reported previous experience of different emollient types, which was reflected in opinions on effectiveness and acceptability of emollients (appendix p 5): 519 (95%) had used a cream (47 [9%] put "Don't know" for effectiveness and 42 [8%] put "Don't know" for acceptability), 365 (67%) had used an ointment (189 [35%] put "Don't know" for effectiveness and 130 [24%] put "Don't know" for acceptability), 345 (63%) had used a lotion (208 [38%] put "Don't know" for effectiveness and 149 [27%] put "Don't know" for acceptability), and 136 (25%) had used a gel

(407 [75%] put "Don't know" for effectiveness and 308 [56%] put "Don't know" for acceptability).

During the primary outcome period, the median number of days per week of allocated (p=0·48) and non-allocated emollient use (p=0·11) did not differ between treatment groups. 29 (5%) participants withdrew (appendix p 4). All participants had completed their primary outcome period before public health measures were introduced in the UK in response to the COVID-19 pandemic. There was no difference between the treatment groups in the primary outcome (repeated measures analysis of POEM over 16 weeks) overall (figure 2 and table 3; appendix p 7) or in any of the pairwise comparisons (table 3). Adjusted pairwise differences were: cream versus lotion 0·42 (95% CI –0·48 to 1·32), gel versus lotion 0·17 (–0·75 to 1·09), ointment versus lotion –0·01 (–0·93 to 0·91), gel versus cream –0·25 (–1·15 to 0·65), ointment versus cream –0·43 (–1·34 to 0·48), and ointment versus gel –0·18 (–1·11 to 0·75). Estimates of pairwise differences between treatment groups in the primary outcome were not altered by adjustment for sex imbalance at baseline (appendix p 8), after imputing for missing parent-reported with researcher-collected POEM scores at 16 weeks (appendix p 8), or after excluding the three participants with a POEM score of 2 or less before baseline (appendix p 9).

There was no difference in objective EASI scores, assessed by masked researchers, between the treatment groups at 16 weeks (table 3; appendix p 13). Researcher masking was maintained for 485 (99%) of the participants assessed for EASI. For all groups, the Bang blinding index did not differ from 0, indicating excellent masking (appendix p 6). There was no difference between the treatment groups for quality of life (eczema-specific ADQoL [appendix p 14] and generic CHU-9D [appendix p 15]) or DFI [appendix p 16]). The proportion of weeks with well controlled symptoms during the first 16 weeks did not differ between treatment groups (appendix p 17). There was no difference in mean POEM scores between the treatment groups over 52 weeks (figure 2 and appendix p 18). The majority of POEM scores (9628 [92%] of 10 518) were collected before public health measures were introduced in the UK in response to the COVID-19 pandemic, and there was no difference in POEM scores before and after this timepoint (p=0·18; appendix p 12). There were no differences between treatment groups in reported use of topical corticosteroids in the primary outcome period (appendix p 4). Overall satisfaction at 16 weeks was highest with lotions (72 [67%] of 107 were very or mostly satisfied) and gels (69 [64%] of 107 were very or mostly satisfied), and was lowest with creams (38 [34%] of 111 were dissatisfied or very dissatisfied) and ointments (36 [40%] of 89 were dissatisfied or very dissatisfied; p=0·0020, appendix p 19). Parents in the lotion and gel groups were more likely to report intention to continue using the study emollient after 16 weeks than those allocated cream or ointment (appendix p 19). Almost half of parents reported persisting with their allocated emollient during the primary outcome period for a longer than they would normally (appendix p 20).

Parents were asked about the acceptability of study processes at 52 weeks: 138 (39%) of 355 parents said it was "not at all" difficult to follow the recommendation of applying their study emollient at least twice every day; 191 (54%) 354 said it was "not at all" difficult to only use their assigned study emollient for the first 16 weeks of the study; and 164 (47%) 352 said they used their assigned study emollient for a longer period of time than they would normally.

There were no serious adverse events. Adverse events were common, with 205 (37%) of 550 participants reporting at least one adverse event (table 4), but there was no evidence that the proportion of children reporting

	Lotion (n=137)	Cream (n=140)	Gel (n=135)	Ointment (n=138)	Total (n=550)
Sex					
Female	64 (47%)	77 (55%)	54 (40%)	60 (44%)	255 (46%)
Male	73 (53%)	63 (45%)	81 (60%)	78 (57%)	295 (54%)
Ethnic group					
White	119 (87%)	126 (90%)	112 (83%)	116 (84%)	473 (86%)
African, Caribbean, or Black British	1 (1%)	4 (3%)	4 (3%)	9 (7%)	18 (3%)
Asian or Asian British	3 (2%)	4 (3%)	7 (5%)	2 (2%)	16 (3%)
Mixed	14 (10%)	6 (4%)	12 (9%)	11 (8%)	43 (8%)
Meet UK diagnostic criteria for atopic dermatitis	113 (83%)	108 (77%)	109 (81%)	117 (85%)	447 (81%)
Self-reported food allergy*					
No	103 (76%)	109 (78%)	111 (83%)	112 (82%)	435 (80%)
Yes	26 (19%)	20 (14%)	15 (11%)	17 (13%)	78 (14%)
Unsure or not diagnosed	6 (4%)	11 (8%)	8 (6%)	7 (5%)	32 (6%)
POEM baseline score†	8·7 (5·2)	9·3 (5·3)	9·8 (5·4)	9·5 (6·0)	9·3 (5·5)
Age, years	4 (2–7)	5 (2–8)	4 (2–8)	4 (2–7)	4 (2–8)
Index of multiple deprivation‡§	13·7 (7·6–20·2)	11·7 (5·8–21·1)	13·2 (6·4–20·6)	11·8 (5·9–20·8)	12·5 (6·3–20·6)
EASI¶	3·3 (2·0–7·2)	3·1 (2·0–6·3)	4·0 (2·5–8·0)	3·3 (1·6–6·5)	3·5 (1·9–6·9)
DFI‖	3 (1–6)	3 (1–6)	3 (1–8)	2 (0–6)	3 (1–6)
ADQoL**	0·36 (0·36–0·50)	0·36 (0·36–0·50)	0·36 (0·36–0·56)	0·36 (0·36–0·50)	0·36 (0·36–0·50)
CHU-9D score††	0·90 (0·80–0·97)	0·91 (0·78–0·97)	0·90 (0·78–0·97)	0·89 (0·70–0·97)	0·90 (0·78–0·97)

Data are n(%), mean (SD), or median (IQR). ADQoL=Atopic Dermatitis Quality of Life. CHU-9D=Child Health Utility-9 Dimension. DFI=Dermatitis Family Impact. EASI=Eczema Area Severity Index. POEM=Patient Orientated Eczema Measure. *N=545 (lotion=135, cream=140, gel=134, ointment=136). †N=549 (lotion=137, cream=140, gel=134, ointment=138). ‡Based on home postcode. §N=503 (lotion=130, cream=128, gel=126, ointment=119). ¶N=543 (lotion=135, cream=139, gel=133, ointment=136). ||N=543 (lotion=135, cream=137, gel=135, ointment=136). **N=540 (lotion=136, cream=137, gel=134, ointment=133). ††N=533 (lotion=134, cream=137, gel=128, ointment=134).

Table 2: **Baseline characteristics**

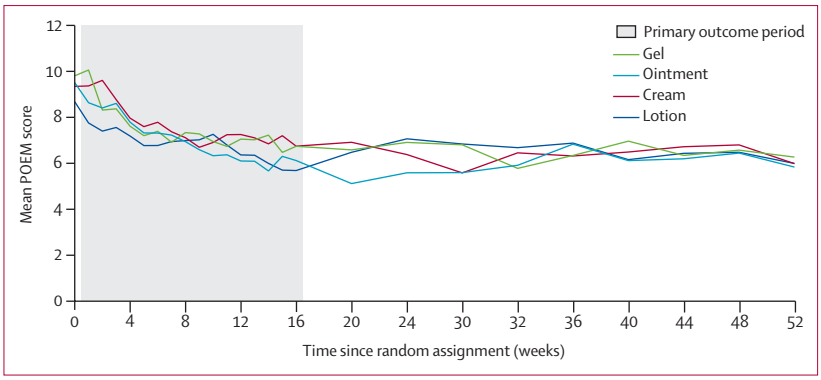

Figure 2: **Mean POEM scores over weeks 1–52 by treatment group**
POEM=Patient Orientated Eczema Measure.

	Lotion (n=137)	Cream (n=140)	Gel (n=135)	Ointment (n=138)	p value*
POEM					
Number analysed	131 (96%)	137 (98%)	130 (96%)	126 (91%)	..
Baseline	8·7 (5·2)	9·3 (5·3)	9·8 (5·4)	9·5 (6·0)	..
Over 16 weeks	6·8 (5·1)	7·6 (5·4)	7·5 (5·8)	7·0 (6·1)	0·77
EASI					
Number analysed	121 (88%)	132 (94%)	123 (95%)	112 (81%)	..
Baseline	3·3 (2·0–7·2)	3·2 (2·0–6·3)	4·0 (2·4–8·0)	3·3 (1·6–6·5)	..
16 weeks	2·2 (0·6–3·6)	2·3 (0·9–5·2)	2·25 (0·9–5·15)	2·2 (0·8–4·8)	0·42

Data are n (%), mean (SD), or median (IQR). EASI=Eczema Area Severity Index. POEM=Patient Orientated Eczema Measure. *Linear mixed models comparing mean POEM scores between treatment groups after adjusting for baseline scores and all stratification and minimisation variables used in the randomisation.

Table 3: **POEM and EASI scores at baseline and 16 weeks, by allocated emollient**

adverse reactions in the first 16 weeks differed by treatment group (lotion 49 [36%] patients reported adverse events, cream 54 [39%], gel 54 [40%], ointment 48 [35%]; p=0·79). Most reported adverse reactions were application site reactions: worsening of eczema (131 [24%] participants), itching (124 [23%]), redness or inflammation (112 [20%]), dryness (89 [16%]), and stinging (89 [16%]). Stinging was less common with ointments (12 [9%] of 138 participants) than lotions (28 [20%] of 137), creams (24 [17%] of 140), or gels (25 [19%] of 135). Skin infections were more common with gels and ointments and slips or falls were more common with creams and ointments (table 4), but the total number of events (12 skin infections in 12 participants; 12 slips or falls in nine participants) was small.

Regarding the primary outcome, there was no evidence that the pairwise differences differed from the null using multiple imputation (multiple imputation by chained equations p=0·70; appendix p 8) or worst-case scenario imputation (p=0·35; appendix p 8). In best-case scenario imputation, there was evidence of a difference (global p=0·0021; appendix p 8), where there was a greater reduction in POEM scores in the cream group than the ointment group (–1·71 [95% CI –2·59 to –0·84]; p=0·0001). In four prespecified subgroup analyses, treatment group differences were not modified by parental expectation of effectiveness, participant age, or meeting the UK diagnostic criteria for atopic dermatitis at baseline (appendix p 10). There was weak evidence of a difference between children with mild versus moderate or worse disease severity (POEM p=0·042, EASI p=0·057; appendix p 10). Regarding the per-protocol analysis, 152 (28%) participants (lotion 43 [31%], cream 47 [34%], gel 35 [26%], and ointment 27 [20%]) reported using their allocated emollient at least 1 week in every 4 for at least 60% of days in a reported week. The POEM scores did not differ between treatment groups (p=0·24; appendix p 11). Pairwise differences between groups were generally greater than in the primary analysis with wider CIs.

Discussion

There was no difference in eczema symptoms between lotions, creams, gels, or ointments over 16 weeks. This finding was robust to sensitivity analyses, in which 95% CIs also excluded the prespecified minimum clinically important difference. Secondary outcome measures, including an objective measure of eczema severity collected by a masked researcher, also showed no difference between emollient types. More than a third of participants reported at least one adverse reaction (most commonly a localised skin reaction), the proportion being similar across the treatment groups. At 16 weeks, overall satisfaction and intention to continue treatment was highest for lotions and gels. In addition, our findings suggest different emollient types might not need to be applied more or less frequently than another for the same benefit.

To our knowledge, this is the first pragmatic trial of its kind, conducted in primary care. Although a study design specifying one emollient per type has the advantage of meaning any effect was attributable to that specific emollient, it would have limited the generalisability of the findings to similar emollients of the same type. We allowed multiple similar emollients of each type because it met the needs of commissioners, medicine management teams, and patients, who want recommendations by type. It also reduced the influence of branding on participant perception, avoided any perceived conflicts of interest or commercial promotion of one product, and mitigated the risk of one or more emollients being withdrawn during or after the study (as Diprobase cream subsequently has been). We present unique data on effectiveness and the frequency and nature of adverse reactions. In accordance with guidance from the HOME group,[14] we collected data in the key domains (using recommended outcome measures) of symptoms (POEM), clinical signs (EASI), quality of life, and long-term control. We chose parent-reported POEM as our primary outcome because it

captures symptoms of importance to parents and patients over the previous week;[6] and it has good validity, repeatability, and responsiveness to change.[16] We chose repeated measures because eczema is a relapsing and remitting long-term condition and this approach captures effectiveness of treatments better than comparing outcomes at a single timepoint. This also meant that incomplete cases (ie, participants who did not complete all of their weekly scores) still contributed to the analysis.

Children in our study, who were mostly White (86%) with mild-to-moderate disease severity (82%), are similar to the typical population seen in primary care in the UK.[18] The emollients we compared are in everyday use in the UK, and comparison of emollients by type (rather than specific named products) strengthens the generalisability of the findings. However, some research suggests that emollients that are ostensibly identical in their major constituents can still be experienced as different by the user.[19–21] Also, it cannot be assumed that the findings apply to non-study emollients. Missing electronic medical record data and the pragmatic nature of our design, in which the prescription was issued via the participant's general practitioner and usual pharmacy, meant that we were unable to confirm for some participants (29 [5%]) which emollients they initially received, and that nine (2%) participants received an emollient of the correct type but that was not study approved. We sought to compare the effectiveness of different emollient types, not enhance their use. Despite apparently low adherence to the direction to apply twice daily and when required (between 3 and 6 days per week), POEM scores improved in all emollient groups during the primary outcome period (figure 2). This finding might reflect a behavioural change (increased frequency, improved application of emollients from baseline, or both) but because there was no non-emollient (control) group, we are unable to attribute this to emollient use. Although there is some evidence for the effectiveness of emollients over no emollients,[3] what was observed might also be regression to the mean. Clinicians and parents were not masked to participants' allocation because emollient types differ so much in their appearance and consistency, and (in keeping with the pragmatic nature of the trial) were issued via the participants' general practitioner. Masking is not essential, possible, or appropriate for all clinical trials, and can discourage participation.[22] Yet, the primary outcome might have been influenced by beliefs and knowledge of the allocated treatment. We sought to minimise the potential for performance bias by ensuring that, at the point of consent, parents were willing to use any of the four emollients for the first 16 weeks, and in a subgroup analysis did not find any evidence that reported effectiveness was linked to high or low expectations. The use of an objective measure of eczema severity (EASI) by a masked researcher as a secondary outcome allowed us to objectively compare effectiveness in relation to eczema signs. Overall parent satisfaction with their study emollient was assessed by a single, unvalidated five-point scale (from very dissatisfied to very satisfied).

	Lotion (n=137)	Cream (n=140)	Gel (n=135)	Ointment (n=138)	Overall (n=550)
Worsening of eczema	28 (20%)	35 (25%)	36 (27%)	32 (23%)	131 (24%)
Itching	24 (18%)	33 (24%)	38 (28%)	29 (21%)	124 (23%)
Redness or inflammation	25 (18%)	28 (20%)	32 (24%)	27 (20%)	112 (20%)
Dryness	19 (14%)	22 (16%)	27 (20%)	21 (15%)	89 (16%)
Stinging	28 (20%)	24 (17%)	25 (19%)	12 (9%)	89 (16%)
Burning sensation	12 (9%)	14 (10%)	9 (7%)	5 (4%)	40 (7%)
Pain	6 (4%)	10 (7%)	14 (10%)	10 (7%)	40 (7%)
Peeling of the skin	6 (4%)	6 (4%)	8 (6%)	6 (4%)	26 (5%)
Tingling	7 (5%)	7 (5%)	2 (1%)	2 (1%)	18 (3%)
Swelling	1 (1%)	4 (3%)	4 (3%)	6 (4%)	15 (3%)
Other: rash	2 (1%)	1 (1%)	1 (1%)	4 (3%)	8 (1%)
Skin infection	3 (2%)	1 (1%)	4 (3%)	4 (3%)	12 (2%)
Slip or fall	1 (1%)	4 (3%)	0	4 (3%)	9 (2%)
Other: grease	2 (1%)	1 (1%)	1 (1%)	8 (6%)	12 (2%)
Other: disliked emollient	2 (1%)	0	2 (1%)	3 (2%)	7 (1%)
Other: allergic reaction	0	1 (1%)	0	0	1 (<1%)
Total	49 (36%)	54 (39%)	54 (40%)	48 (35%)	205 (37%)

Data show the number of participants reporting at least one adverse event as a proportion of all participants in the safety analysis.

Table 4: **Number of participants with adverse reactions during weeks 1–16 by treatment group**

Our findings challenge the previous consensus that ointments are more effective, require less frequent application, and have fewer adverse effects than other emollient types, especially for more severe eczema. The closest comparable study is by Hlela and colleagues,[23] in which 80 children aged 1–12 years with mild-to-moderate eczema were randomly assigned to emulsifying ointment, cetomacrogol cream, white petroleum jelly, or glycerine or petroleum. Hlela and colleagues' study did not specify a primary outcome but the authors reported no difference in parent-reported symptoms, objective signs, or quality of life. Previous research suggests that emollients improve eczema signs, reduce the number of disease flares, and reduce the need for topical corticosteroids.[3] All participants received an emollient, so we cannot say from our study that emollients improve eczema symptoms. We did not find any difference in well controlled weeks between the four emollient types but it is possible that differences might have been seen with alternative definitions of disease flare.[24] Reducing topical corticosteroid use might be desirable in terms of simplifying treatment burden and minimising the risk of adverse effects, but should not distract from the appropriate use of topical corticosteroids to treat inflamed skin.[25]

The findings from a nested qualitative study emphasised how the acceptability of the same product varies between users.[26] These findings are consistent with previous qualitative research, which identifies trade-offs between effectiveness and acceptability when choosing an

emollient.[27,28] In short, a one size fits all approach is not appropriate and users need to be able to choose from a range of emollient types to suit their needs and preferences.

Interpretation of our findings will be strengthened by a planned formal health economic analysis. Although our study supports the safety of emollients, recent evidence has highlighted associated risks of burns,[29] slippages,[30] and skin infections,[30] and further work is needed to elucidate a possible association with food allergy.[30] Ointments that contain emulsifying agents deserve evaluation, as they might be more acceptable than the simple ointments we compared, as do emollients that contain urea or antimicrobials, because these might be more effective in people with more severe eczema. In addition, there are multiple products marketed as being natural, and other novel emollients being developed, that claim to have superior skin barrier enhancement properties or to favourably change the skin microbiome. Research comparing the effectiveness and acceptability of different emollient types for adolescents and adults, to whom our findings might not apply, is also required.

Based on the available evidence, patients should be able to choose emollients from a range of lotions, creams, gels, and ointments. Therefore, all emollient formularies must include at least one of each type. Decision making should be shared. Prescribers can help parents and older children choose what to try when, by eliciting preferences and sharing the key differences between the different emollient types. It might be appropriate to prescribe different types of emollient for different body sites (eg, lotion for face and gel for trunk) or situations (eg, ointment at home and cream for school). Children with all but the mildest disease will need flare control cream (usually a topical corticosteroid) for inflamed skin, with advice that their use might reduce the incidence of localised skin reactions that are common with all types of emollients. Better informed and involved patients should mean that they find a suitable emollient more easily and quickly, thereby improving treatment use and disease control.

Contributors

MJR conceived the trial and was chief investigator. MJR, HCW, KST, MS, SJM, AR, JB, ADH, KG, TJB, JAL, LH, and HB contributed to the design of the study and the acquisition, analysis, or interpretation of the data. SW, DW, LL, ESu, ZW, JT, JC, HB, and LH operationalised the study. Axovided patient representation. ESa and SJM were responsible for the statistical analysis. The manuscript report was drafted by MJR, ESa, and SJM with all authors revising it critically for important intellectual content. All authors have had full access to all the data in the study and had final responsibility for the decision to submit for publication. ESa and SJM have accessed and verified the data.

Declaration of interests

LH currently acts as a consultant for the University of Oxford on an educational grant funded by Pfizer, unrelated to the submitted work. All other authors declare no competing interests.

Data sharing

No later than 3 years after the completion of the study, we will deposit a de-identified individual participant data set in an appropriate data archive. The study protocol and statistical analysis plan are available on the trial website (www.Bristol.ad.uk/bee-study) and the National Institute for Health and Care Research (NIHR) journals library (https://fundingawards.nihr.ac.uk/award/15/130/07).

Acknowledgments

The study was funded by the NIHR Health Technology Assessment programme (reference 15/130/07). MJR was funded by an NIHR post-doctoral research fellowship (PDF-2014-07-013). ADH is supported by an NIHR senior investigator award (NIHR 200151). JB was supported by the National NIHR Applied Research Collaboration West at University Hospital Bristol NHS Foundation Trust. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. The Best Emollients in Eczema study was hosted by Bristol, North Somerset and South Gloucestershire (BNSSG) Clinical Commissioning Group and developed with support from UK Dermatology Clinical Trials Network (UK DCTN). The UK DCTN is grateful to the British Association of Dermatologists and the University of Nottingham for financial support of the Network. This study was designed and delivered in collaboration with the Bristol Randomised Trials Collaboration, a UK Clinical Research Collaboration registered clinical trials unit which, as part of the Bristol Trials Centre, is in receipt of National Institute for Health Research Clinical Trials Unit support funding, and is supported by NIHR Clinical Research Networks West of England, Wessex, and East Midlands. Thank you to all the children, parents, and general practitioner surgeries who took part in the study. We are also grateful to the trial steering committee members (Richard McManus, Ben Carter, Joanne Protheroe, Sariqa Wagley, and Andrew Moore) and data monitoring committee members (John Ingram, Catriona Keerie, and Chin Whybrew).

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