BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012021
Article Type:	Research
Date Submitted by the Author:	24-Mar-2016
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Primary Subject Heading:	Dermatology
Secondary Subject Heading:	General practice / Family practice
Keywords:	Eczema < DERMATOLOGY, PRIMARY CARE, Paediatric dermatology < DERMATOLOGY

Title page

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Choice of Moisturiser for Eczema Treatment (COMET): feasibility study of randomised controlled parallel group trial in children recruited from primary care

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Word count

3928/4000

Abstract

Objectives: To determine the feasibility of a randomised controlled trial of "leave on" emollients for children with eczema.

Design: Single centre, pragmatic, four arm, researcher masked, parallel, randomised feasibility trial.

Setting: General Practices in the UK

Participants: Children with eczema aged one month to less than five years.

Outcome measures: Primary outcome – proportion of children approached who were randomised to a study emollient and used it for the duration of follow-up (3 months). Other feasibility outcomes – optimal recruitment pathway, participant retention and adherence to intervention, data completeness, resource use, and masking of researchers to allocation.

Interventions: Aveeno® lotion, Diprobase® cream, Doublebase® gel or Hydromol® ointment

Results: 197 participants were recruited – 107 by self-referral (mainly via practice mail-outs) and 90 by in-consultation (clinician consenting and randomising) pathways. Participants recruited in-consultation were younger, had more severe Patient Orientated Eczema Measure (POEM) scores and were more likely to withdraw than self-referrals. 20 (10%) of all randomised participants reported using their allocated emollient daily for 84 days. Use of other non-study emollients was common. Completeness of data collected by parent-held daily diaries and at monthly researcher visits was good. Daily diaries were liked (81%) but mainly done in paper rather than electronic ("app") form. Major costs drivers were GP consultations and eczema-related prescriptions. Researcher unmasking was infrequent, and occurred at the baseline or first follow-up visit through accidental disclosure. There was one serious adverse event (hospitalisation with infected eczema).

Conclusions: It is feasible in a primary care setting to recruit and randomise young children with eczema to emollients, conduct follow up, and collect relevant trial data, while keeping researchers masked to their allocation. Self-referral was the more "efficient" recruitment pathway, with the caveat that participants recruited via this route were younger and had less severe parent-reported eczema.

Trial registration: ISRCTN21828118 (01.05.2014)/EudraCT2013-003001-26 (23.12.2013)

Funding: National Institute for Health Research for Patient Benefit Programme (PB-PG-0712-28056)

Word count: 293/300

Strengths and limitations of this study

- This pragmatic study demonstrates that it is feasible to recruit children with eczema from primary care, randomise them to a "leave on" emollient, and follow them up for three months with good retention and researcher masking.
- Participant retention was better in participants who referred themselves into the study compared with those who were recruited during consultations with their General Practitioner or Practice Nurse, although they also differed in respect of their age and parent-reported eczema severity.
- While it was possible to collect daily, weekly and monthly outcome data, missing data in parent-completed diaries has made interpretation of adherence to allocation challenging.
- There were practical and technical limitations with the "app" version of the parent-completed diary.

Introduction

Eczema (also referred to as atopic dermatitis or atopic eczema) affects around 20% of children in the UK. Incidence peaks in the first two years of life and decreases thereafter.[1] It is characterised by dry and itchy skin, and it can have a significant impact on the quality of a child's life and their family.[2]

In countries with strong systems of primary care, such as the UK, the majority of children with eczema are both diagnosed and managed by their family physician or General Practitioner (GP) with emollients and topical corticosteroids. Emollients are recommended for all and they are primarily used as a "leave on" treatment to improve skin comfort. Applied directly to the skin, emollients reduce water loss by occlusion and/or directly adding water to the dry outer layers of the skin. However, there are many products and formulations available (lotions, creams, gels and ointments) that vary in their consistency from "light" to "heavy". Despite claims from the manufacturers, evidence that any one is better than another is weak.

Two systematic reviews have highlighted a paucity of research to help guide clinicians and patients in their choices.[3 4] In summary, the field is characterised by a lack of good quality, randomised controlled trials (RCTs) directly comparing commonly used emollients, with medium to long term data on clinically relevant outcomes. While undertaking this research represents unique challenges, such as the range of possible emollients to compare and the inability to mask users to emollients of very different consistencies (e.g. lotion versus ointment), patients and clinicians have highlighted it as an important issue. In the recent James Lind Alliance eczema treatment research priority setting partnership, "Which emollients are the most effective and safe in treating eczema?" emerged as one of the highest ranked uncertainties for further research.[5]

In order to address this uncertainty, we want to undertake an RCT of commonly prescribed emollients for the treatment of childhood eczema in primary care. However, the feasibility of being able to conduct such a trial was questionable, because of key issues such as whether parents/carers would be willing to both be assigned and then use a randomly allocated emollient for several months, and uncertainty about optimal methods of recruitment and data collection. Therefore, we conducted a trial to determine the feasibility of recruiting, retaining and collecting outcome data on young children with eczema in a primary care setting, and to inform the design of a full trial.

Methods

Design, participants and interventions

Full details can be found in the protocol paper.[6] In brief, COMET was a feasibility study of a pragmatic, researcher masked, RCT to compare the clinical and cost-effectiveness of "leave on" emollients in the treatment of children with eczema. Throughout this paper we will use the term "parent" to denote all carers/guardians.

Between July 2014 and April 2015 (10 month planned recruitment period), participants were recruited in primary care (general practice) via two pathways: "self-referral" (usually in response to a letter sent by their practice inviting them to take part) or "in-consultation" (approached during a surgery visit by General Practitioner (GP)/Practice Nurse (PN), who also received consent and undertook randomisation).

To be eligible, children had to have eczema, be aged one month to under five years and not be known to be sensitive or allergic to any of the study emollients or their constituents. Participants were randomly allocated by a web based system (1:1:1:1 ratio) to one of four emollients (Aveeno® lotion 400ml, Diprobase® cream 500g, Doublebase® gel 500g, Hydromol® ointment 500g) to use as

their primary leave-on emollient with the directions to "Use twice daily and when required". All other care (appointments, prescriptions, referrals) was as per usual care. Researchers undertaking the baseline and follow-up visits (but not clinicians or parents) were masked to emollient allocation.

Three key changes to the original protocol were implemented in the final four months of recruitment. First, the diagnostic criterion was relaxed from "doctor diagnosis of eczema" to "diagnosed by a doctor or an appropriately qualified health care professional with oversight from a medically qualified doctor". Second, the upper age limit was raised from under three years to under five years of age. Third, the number of practices was increased from 16 to 22. These additional practices were only asked to do the mail-out, not recruit in-consultation as well.

Outcomes

Participants were followed-up for three months (84 days). During this time researcher visits were scheduled to take place 28, 56 and 84 days after baseline and parents were asked to complete a daily diary (paper and electronic "app" versions were offered). In addition, the primary care electronic medical record (EMR) were reviewed for the three months participants were in the study.

Data were collected on:

- Use of study emollient and other eczema treatments (daily parent reported)
- Eczema severity: weekly parent reported (Patient Orientated Eczema Measure, POEM[7]; parent global assessment) and monthly researcher completed (Eczema Area Severity Index, EASI;[8] Six Area, Six Sign Atopic Dermatitis, SASSAD;[9] Three Item Severity, TIS[10]) assessments.
- Quality of life: Atopic Dermatitis Quality of Life (ADQoL)[11] and Dermatitis Family Impact (DFI)[12] (both monthly parent reported)
- Skin hydration using a corneometer (see below) (monthly researcher collected)
- Eczema-related prescriptions and healthcare resource use (weekly parent reported and EMR review)
- Eczema-related personal costs, parent time off work and child time away from school/day care (weekly parent reported)

Parents who withdrew from the study at any point were asked to complete a withdrawal questionnaire. At the end of the study, parents were asked to complete an exit questionnaire which included questions about their experience of taking part in the study.

Corneometry

Skin hydration was measured at two sites on the body (antecubital fossa and forearm) using a corneometer (Corneometer® CM825, Courage & Khazaka electronic GmbH, Cologne, Germany), in arbitrary units of 0 to 100, with a higher measurement representing greater hydration. Presented measurements were adjusted for ambient temperature and humidity, to give the prediction of what each measurement would have been had it been taken in the average conditions seen in the study; 22 degrees centigrade temperature and 48.6 units humidity. This adjustment was based on an equation estimated by regressing the corneometry measurements taken in the study on the corresponding temperature and humidity readings (see appendix).

Sample size

Because this was a feasibility study a formal sample size calculation was not required. We aimed for a target sample size of 160 participants. With this number, a true consent rate of 50% (160 children

participating having invited 320 potentially eligible children) would be estimated with 95% confidence interval of the order 44% to 56%.

Analysis

We conducted linear, logistic or ordered logistic regression (as appropriate) to compare the characteristics of participants recruited via the two recruitment pathways and those who withdrew/stayed in the study. Researcher masking was assessed using the Bang Blinding Index,[14] which takes a value between -1 and +1: +1 indicates complete lack of masking and 0 is consistent with perfect masking. Negative values indicate the respondent is wrong more often than would be expected by chance, which can arise, for example, if all participants are said to be on one particular treatment irrespective of what they receive.

Health care resource use and prescribed medications were costed using relevant unit costs[13-16] valued in pound sterling and at 2014 prices. The cost of the intervention emollients were estimated using three alternative methods; firstly via the Prescription Cost Analysis (PCA),[14] secondly using the British National Formulary (BNF),[17] and thirdly using the Drug Tariff (DT)[18] and Dictionary of Medicines and Devices (DMD).[19] The final method aimed to estimate the true cost to the NHS of prescribed medications by estimating the amount community pharmacists are reimbursed for dispensing prescriptions. This method incorporates a deduction for any discount the pharmacy may have received, dispensing fees and payments for containers, consumables or other associated costs.

Health state utility values were estimated at each time point using scores from the ADQoL.[11] QALYs were derived using the area under the curve approach[20] and by multiplying to an annual equivalent.

Ethics

The study was approved by Central Bristol Research Ethics Committee (REC reference: 13/SW/0297), Clinical Trial Authorisation given by the Medicines and Healthcare products Regulatory Agency (MHRA reference: 03299/0017/001-003) and research governance approvals obtained across all areas prior to the start of recruitment. All participants gave written informed consent.

Results

Recruitment of practices and participants

Between July 2014 and May 2015, 197 children were recruited via 22 practices. The flow of the participants through the trial is shown in the CONSORT diagram (figure 1), which distinguishes between the two recruitment pathways.

Recruitment by self-referral pathway: 2026 potentially eligible children were screened and GPs excluded 9% (177/2026), the most common reason being “no longer has eczema” (37%, 66/177). Of the 1849 invitation letters sent, responses were received from 20% (374/1849) with 13% (246/1849) declining to take part. Again, the most common reason for not taking part was the child having either no or only mild eczema (62%, 152/246). A further four children were recruited by word-of-mouth or after being given a study flyer, giving a total of 132 potentially eligible participants who were screened by the research team. Of these, 19% (25/132) were not recruited, mainly because the carer could not be contacted (12/25, 48%).

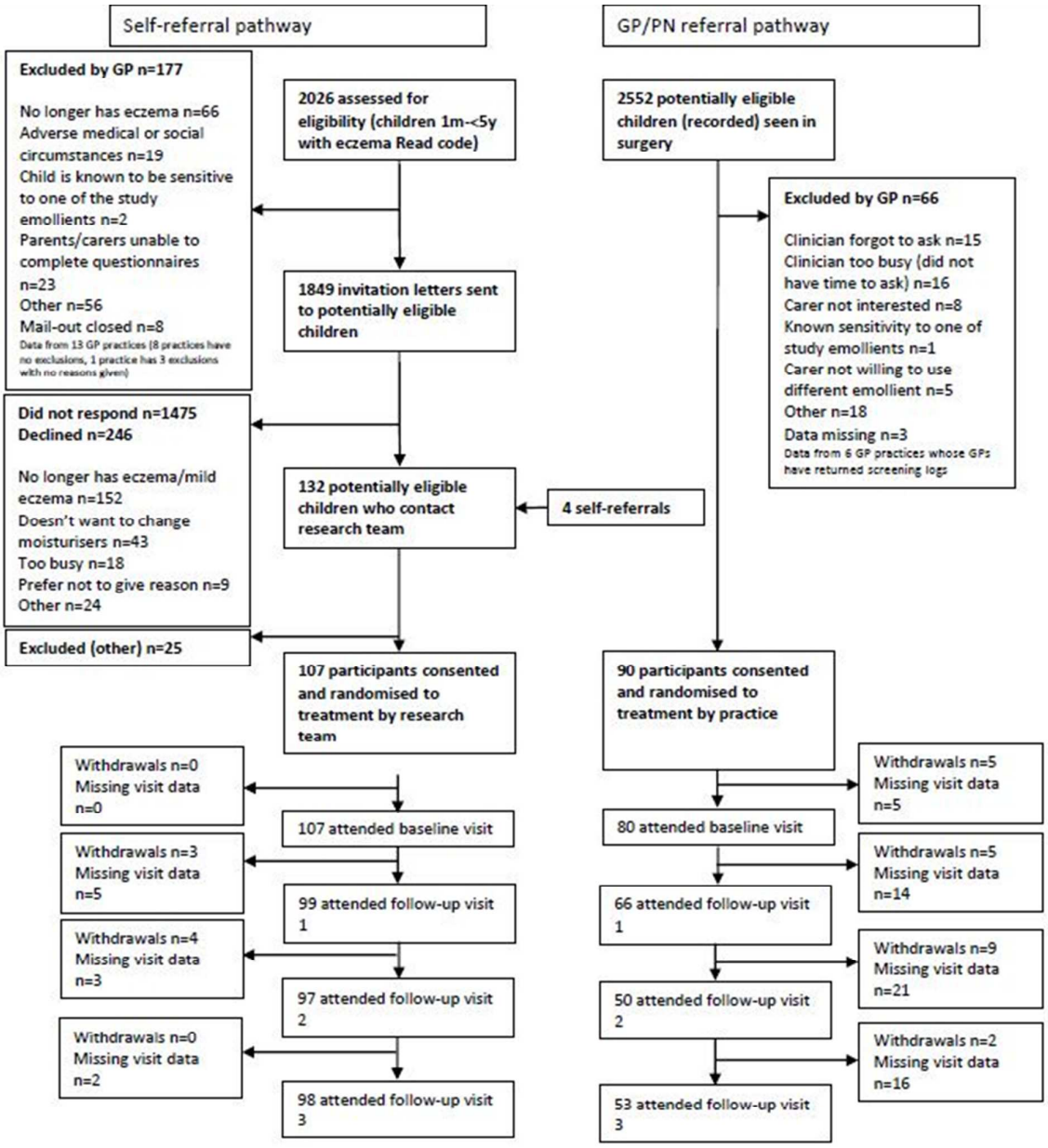

Figure 1: CONSORT diagram – recruitment by referral pathway

Recruitment by in-consultation pathway: Clinicians were asked to record all approaches to recruiting potentially eligible participants. However, "recruitment logs" were returned by only six practices, detailing 66 encounters. The most common reasons given for not recruiting were that clinicians either forgot to ask or were too busy (47%, 31/66). At the end of the study, practices ran searches of their appointments database and identified 2552 potentially eligible children who had had at least one appointment with the practice during the recruitment period.

The majority of participants (62%, 54/87) recruited during the first six months came via the self-referral pathway (figure S1). However, during the final four months of recruitment, the number of in-consultation referrals increased so that by the end of the study 90 (46%) of the total 197 participants came via this route. Practices 1 to 16 sent reminder letters to people who did not

respond to the initial invitation and still met the eligibility criteria, which resulted in four additional participants.

Characteristics of participants

The baseline characteristics of participants were balanced across the different arms of the study. The mean age (SD) of participants at baseline was 21.7 months (12.8), with 85 (43%) female, 155 (85%) white and a mean IMD score (SD) of 21.8 (14.2). Mean (SD) eczema severity scores were as follows: POEM 8.8 (5.9), EASI 2.9 (3.8), SASSAD 8.8 (8.4) and TIS 2.0 (1.7). Mean (SD) DFI and ADQoL were 3.6 (4.8) and 0.787 (0.084) respectively.

However, as can be seen from table 1, participants recruited in-consultation were younger (mean age in months 17.0 versus 25.7, p<0.031), and had higher mean POEM (10.3 vs 7.6, p=0.012) scores than those who were recruited via self-referral.

	Self-referral (N=107)		In-consultation (N=90)		P-value
		n		n	
Mean age in months (SD)	25.7 (11.6)	107	17.0 (12.6)	90	0.031[a]
Number female (%)	46 (43%)	107	39 (43%)	90	0.868[b]
Number white (%)	98 (93%)	108	57 (74%)	77	0.088[b]
Mean IMD score (SD)	15.7 (10.5)	104	25.4 (13.8)	88	0.201[a]
Mean eczema severity scores (SD)					
- POEM [min 0, max 28, high = worse]	7.6 (5.7)	107	10.3 (5.8)	89	0.012[a]
- EASI [min 0, max 72, high = worse]	2.8 (4.1)	105	3.1 (3.4)	79	0.841[a]
- SASSAD [min 0, max 108, high = worse]	9.0 (8.7)	107	8.5 (7.9)	79	0.918[a]
- TIS [min 0, max 9, high = worse]	2.1 (1.9)	107	2.0 (1.5)	79	0.571[a]
Skin hydration[#] [high = better]					
- Forearm	31.3 (11.8)	98	32.9 (10.1)	70	0.719[a]
- Antecubital fossa	36.5 (14.8)	98	39.5 (12.6)	71	0.325[a]
Mean DFI score (SD) [min 0, max 30, high = worse]	2.9 (4.0)	107	4.6 (5.6)	79	0.224[a]
Mean ADQoL (SD) [min 0.356, max 0.841, high = better]	0.799 (0.065)	105	0.770 (0.103)	75	0. 239[a]

[a] Linear regression model adjusting for GP practice; [b] Logistic regression model adjusting for GP practice; [c] Ordered Logistic regression model adjusting for GP practice

[#]Measurements adjusted to average study conditions of temperature (22 degrees centigrade) and humidity (48.6 units) (model described in methods/appendix). Data presented in arbitrary units ([min 0, max 100, high = more hydrated).

Table 1: Characteristics of participants at baseline by referral pathway

Participant retention

28 (14%) participants withdrew from the study and 151 (77%) attended the final follow-up visit. Most participants who withdrew were recruited in-consultation (21/90, 23%, compared to 7/107, 7%, of self-referrals), including five children who did not attend their baseline visit. All bar one participant recruited in-consultation returned a withdrawal questionnaire, and the most commonly cited reason for withdrawing was lack of time (table 2).

Reasons for withdrawal†	Self-referral (n=7)	In-consultation (n=20)
Study emollient not working/effective	0	2
Adverse reaction to study emollient	2	0
Disliked emollient given	0	2
Just simply changed my mind	0	2
Don't have enough time	4	10
My child's skin has improved – no longer need emollient	0	4
Other	2	7

†More than one reason could be cited.

Table 2: Reasons for participant withdrawal

Collection of outcome data

22/185 (12%) of parents started using the app version of the daily diary but only 11 people used it for the duration of the study. Technical problems meant that it was not promoted after the first three months of recruitment. Of 150 people completing an exit questionnaire, 121 (81%) said they liked the daily diary, 22 (15%) said they weren't sure and 7 (5%) disliked it.

Table 3 shows that completeness of daily, weekly and monthly data collected via the participant diary was good. Completion rates for individual sections varied from 70% to 95% among those who returned the diaries and from 57% to 78% of all participants. Collectively, completion rates were satisfactory too, with the proportion (number) of participants providing complete data on daily study emollient use, weekly POEM and monthly DFI ranging from 53% (105/197) for diary 1, through 60% (119/197) for diary 2 and 62% (122/197) for diary 3. Due to the cumulative nature of health care costs, complete costing of health care resources was possible for only 62% (122/197) of participants despite the relevant section of each diary having been completed by at least 70% (138/197).

		Diary 1 (days 1-28)			Diary 2 (days 29-56)			Diary 3 (days 57-84)		
Frequency of question item completion	Question items	n	% of returners (n=162)	% of participants (n=197)	n	% of returners (n=151)	% of participants (n=197)	n	% of returners (n=150)	% of participants (n=197)
Daily	Eczema treatments	113	70	57	129	85	65	128	85	65
Weekly	POEM	145	90	74	139	92	71	139	93	71
	HCP contacts	141	87	72	138	91	70	138	92	70
	Time off school & work	130	80	66	114	75	58	124	83	63
Monthly	ADQoL	150	93	76	135	89	69	140	93	71
	DFI	153	94	78	141	93	72	143	95	73

POEM: Patient Orientated Eczema Measure; HCP: Health Care Professional; ADQoL: Atopic Dermatitis Quality of Life; DFI: Dermatitis Family Impact

Table 3: Completeness of data collected by parent-completed daily diary

Completeness of data collected by the researchers was also good, with the median number (IQR) of visits with complete data (maximum 4) for EASI, TIS and SASSSAD all being 4.0 (3.0 to 4.0). The completeness for corneometry were lower and differed by site (forearm 3.0 (2.0 to 4.0), antecubital fossa 4.0 (2.0 to 4.0)), mainly reflecting the fact that it was not always possible to use the one corneometer across multiple follow-up visits. A greater proportion of researcher visits occurred ±10 days than ±5 days of the scheduled date, and baseline visits were more likely to be timely for participants who self-referred (table S1).

The Bang-Blinding Indices for researcher unmasking to the different emollients are shown in table 4 (researcher guess and treatment assignment for each assessment, by which this index was calculated, are show in tables S2 to S5). Researchers reported not knowing which study emollient the participants were using at most visits. They correctly identified the study emollient in eight participants at the baseline and eight participants at first follow-up visit. The most common reasons given for unmasking was the parent/carer telling them (6/8 baseline and 6/8 visit 1) or the researcher seeing the study emollient during the visit (2/8 baseline and 1/8 visit 1).

	Visit			
Study emollient	Baseline	1	2	3
Aveeno® lotion	0.2 (0.0, 0.4)	0.0 (0.0, 0.1)	CE	CE
Hydromol® ointment	0.1 (-0.1, 0.2)	0.0 (-0.1, 0.1)	CE	CE
Diprobase® cream	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	CE	CE
Doublebase® gel	0.1 (0.0, 0.2)	0.0 (-0.1, 0.0)	CE	CE

CE: cannot be estimated due to lack of data (see supplementary Tables S2-S5)

Table 4: Bang blinding index with 95% two sided Confidence Interval (comparing correct treatment response with incorrect treatment or don't know response)

Adherence to intervention

Of the 197 participants, 20 (10%) reported using their allocated emollient daily for 84 days. However, 38 (19%) did not give any data on study emollient use. Therefore of the 159 participants who completed this question at least once, 49 (31%) said they used the study emollient on each occasion that they completed the question.

The majority (156/162, 96%) of participants reported some use of a non-study emollient: 25% (41/162) reported use every day (that data were provided) and 51% (82/162) reported using an "other" emollient on up to 50% of days. Use of another emollient *instead* of the study emollient occurred less frequently: 53% (85/159) of participants reported using an "other" emollient at least once. Of these 85 participants, 86% (73/85) used an "other" emollient rather than the study emollient half of the time.

Analysis of the EMRs revealed that during the follow-up period while the mean (SD) number of intervention emollient prescriptions was 1.44 (0.78), the number of eczema-related prescriptions for non-intervention emollients was 1.28 (2.13). This included a mean (SD) number of 0.48 (0.99) non-study leave on emollient, 0.43 (0.93) topical corticosteroid and 0.31 (0.69) bath/shower product prescriptions.

Economic Evaluation

The main cost driver as recorded in the EMRs was GP appointments with a mean cost of £11.77 over the follow-up period (Table S6). On average the cost of eczema-related prescribed medications excluding trial emollients equated to £6.97. Health care and intervention emollient costs did not appear to differ considerably between treatment arms (Table 5). The mean (SD) cost to the NHS of each of the trial emollients using the DT and DMD was £11 (£5), £9 (£5), £9 (£5) and £8 (£5), for Aveeno® lotion, Diprobase® cream, Doublebase® gel and Hydromol® ointment, respectively. Emollient costs were slightly higher using this method in comparison to the PCA or BNF (Table 5). Complete ADQoL data for 119 participants allowed estimation of mean (SD) annual QALYs of 0.799 (0.061).

	Aveeno® lotion (N=51)			Diprobase® cream (N=53)			Doublebase® gel (N=46)			Hydromol® ointment (N=47)		
	n	Mean cost	(SD)	n	Mean cost	(SD)	n	Mean cost	(SD)	n	Mean cost	(SD)
Total health care cost - EMR only	51	23	(50)	53	28	(50)	46	32	(85)	47	62	(258)
Total health care cost – EMR plus diary	30	25	(97)	32	32	(54)	33	35	(93)	27	16	(21)
Intervention emollient cost (PCA)	51	8	(4)	53	9	(5)	46	9	(5)	47	7	(4)
Intervention emollient cost (BNF)	51	8	(4)	53	9	(5)	46	8	(4)	47	7	(4)
Intervention emollient cost (DT & DMD)	51	11	(5)	53	9	(5)	46	9	(5)	47	8	(5)
Total cost (EMR, diary and DT & DMD emollient)	30	38	(98)	32	42	(57)	33	43	(94)	27	24	(23)
Annual QALYS	32	0.798	(0.061)	29	0.812	(0.055)	33	0.790	(0.061)	25	0.800	(0.070)

Table 5: Total healthcare cost (£) and QALYs, by treatment allocation

Parents reported additional expenditure due to their child's eczema on items including: eczema treatments (n=25), clothes (n=14), household items (n=12), toiletries (n=11) and food and drink (n=9). Time off paid employment or school/day care was reported infrequently: over the entire follow-up period only 3 days off paid employment and 2 days off school/day care were reported across all participants.

Adverse events

Participants experienced 297 adverse events (any untoward medical occurrence in a clinical trial participant). Most were common childhood viral illnesses: upper respiratory tract infections (114, 38%), vomiting and/or diarrhoea (36, 12%) and fever (28, 9%). There were 10 reports of infected eczema, including one serious adverse event, when a participant was hospitalised for two days and given intravenous antibiotics.

Discussion

This is the first study to show that it is feasible in a primary care setting to recruit and randomise young children with eczema to "leave-on" emollients and follow them up, keeping researchers masked to their allocation. We exceeded our recruitment target, although in the final four months we enlisted the help of six more practices than originally planned and relaxed the age and diagnostic eligibility criteria. While similar numbers of children were recruited by self-referral and in-consultation, participants entering via these two routes differed in their baseline characteristics and withdrawal rates. The most common reason for participant withdrawal was lack of time to participate in the research.

We conducted a well-executed, pragmatic trial overcoming many practical and logistical challenges, meeting regulatory requirements of a Controlled Trial of an Investigational Medicinal Product (CTIMP). More detail on trial conduct can be found in the published trial protocol[6] and we report the findings in accordance with CONSORT.[21] A strength of this study is its exploration of the two possible recruitment pathways and their feasibility in a main trial. By asking most practices to try and recruit via the two routes, we now have a strong understanding of the number (and characteristics) of children likely to be recruited in a definitive trial, and the proportion likely to withdraw (and reasons why). With respect to the mail-out invitation, the high number of children identified with mild or no eczema reflects the fact that for many their diagnosis will be historical and for others, erroneous. One way to improve this may be to limit invitations to children with a recent relevant prescription (suggesting "active" disease), as per the BATHE study.[22] The rise in the rate of children recruited in-consultation may reflect both the staggered nature in which the practices came into the study but also a learning and confidence effect among recruiting clinicians. Although all practices were members of the Clinical Research Network, they had variable levels of experience in recruiting to studies of this type and each study has its unique processes that have to be followed.

In addition to investigating recruitment and retention, we have also collected important adherence, outcome (including corneometry) and health economic data. We found that it is feasible to both collect and cost the data required to perform an economic evaluation in this setting. EMR records provided a rich source of complete healthcare resource use data, indicating that in further studies healthcare resource use collected from diaries could be reduced. Given that time away from paid employment and school were very rarely reported, capturing these data in future would not be important. Our assessment of additional items bought due to eczema has highlighted a list of important categories to include in future studies. At inception, no generic measure of health-related quality of life that was psychometrically and conceptually robust enough for young children under the age of three was available. For this reason we used the ADQoL from which we were able to

estimate QALYs. However, given that this is a condition-specific preference-based measure, the results may not be comparable across conditions.

While researcher unmasking was low, it is possible that they under-reported knowledge of allocation. However, we were able to minimise its impact because when unmasking was reported, the majority of participants were followed-up thereafter by another (still masked) researcher. Parental completion of the daily diary was generally good, but questions on the use of eczema treatments (including study emollient) were the most poorly completed. This may be because parents left an item blank when a treatment was not used, rather than recording "None" or "0", meaning it was classed as "missing". For example, if missing data on "other" emollient use is treated as "no use" on those days for which complete data are available on use of the study emollient, then only 6% (10/162) (compared with 25%) of participants used a non-study emollient every day and 71% of participants (115/162) (compared with 51%) reported using another emollient on up to 50% of days. Another limitation in the data on emollient use is that we are unable to distinguish between use as leave-on therapy (in the same way as the study emollients) and use as soap substitute.

Related to this, a key limitation of the study was the "app" version of the diary. Collecting data via study apps is attractive to researchers for a number of reasons, including improved user experience and monitoring of data entry – participants can be automatically reminded to complete them and validation rules put in place to minimise errors. Although initial interest among parents in using our "app" was high, its development and incorporation in this study was challenging because: a) regulatory requirements for CTIMPs meant, additional and time consuming testing to ensure that data were transmitted securely; and b) the cost required to develop a fully functional app for the most common smart phone and tablet platforms (iOS and Android). Therefore, while we cannot conclude that studies similar to ours should not consider data collection via bespoke apps, we would certainly caution against under-estimating the time, cost and technical implications of doing this. In our opinion, automatic email prompts to participants to complete online questionnaires are probably a safer and more cost effective alternative.

This study has implications for future trials of emollients and other treatments for children with eczema, but also for trials of treatments of other long-term conditions in primary care with medium-term follow-up. For the latter, we have shown that it is feasible to recruit children both by self-referral and in-consultation. While having the two pathways into the study helped the trial meet its recruitment target, researchers need to be mindful that the characteristics of participants, and perhaps their commitment to staying in the trial, are likely to differ for participants recruited via these two routes. Similarly, as it is unrealistic to expect parents of young children to adhere to strict follow-up schedules, study protocols should provide realistic "windows" (e.g. ±10 days if permissible) within which to expect data collection. The importance of clear instructions to parents around diary completion and where it is desirable to keep the researcher masked, avoiding accidental disclosure, are important learning points too.

For trials of emollients specifically, researchers should be encouraged that participants who consent to taking part generally stay in the trial, although this may differ of course if the interventions are very different to the emollients used in COMET. However, researchers also need to be aware that co-use of emollients appears to be common, and the extent to which this matters will depend on where future studies sit on the efficacy-effectiveness spectrum. Whatever the design, this study provides the foundations for future definitive studies to answer the prioritised research question "Which emollient is the most effective and safe in treating eczema?"[5]

Acknowledgements

We would like to thank all the children, parents and surgeries who took part in the study and the joint Trial Steering/Data Monitoring Committee (TS/DM-C) and Dr Stephanie MacNeill for her assistance in analysing the adherence data. This study has been designed and delivered in collaboration with the Bristol Randomised Trials Collaboration (a UKCRC Registered Clinical Trials Unit in receipt of National Institute for Health Research CTU support funding) and the sponsor, University of Bristol.

Declarations

Authors contribution

MJR proposed the original study idea its design, and NB, NMR, SH, SP, RG and LS helped develop this idea and obtain funding for the project. Specific input provided by authors included: NB and LS on the choice and use of emollients in eczema and assessment of eczema severity; RG on collection and interpretation of skin hydration data; DMG and CM on analysis, development of skin hydration model and reporting of main feasibility findings; SH and KG on analysis and reporting health economic data; KP and VW assisted with collation, cleaning and reporting of findings; NMR and SP input on study design and delivery; CM on trial methodology and conduct. MJR wrote the first draft and led on all subsequent revisions; NMR, KG, VW, SH, SP, KP, CM, DMG, NB, LS and RG all commented on and contributed to revised versions of the manuscript. All authors have read and approved the final manuscript.

Competing interests statement

All authors have completed the ICMJE uniform disclosure form atwww.icmje.org/coi_disclosure.pdf. NB has been an employee of Galderma (UK) Ltd since May 2015; all other authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

The COMET study independent research funded by the National Institute for Health Research (Research for Patient Benefit Programme, PB-PG-0712-28056). The views expressed in the publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Data sharing statement

The research team will consider reasonable requests for sharing of patient level data. Requests should be made to MJR. Consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low.

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Choice of Moisturiser for Eczema Treatment (COMET): feasibility study of randomised controlled parallel group trial in children recruited from primary care

Supplementary figure & tables

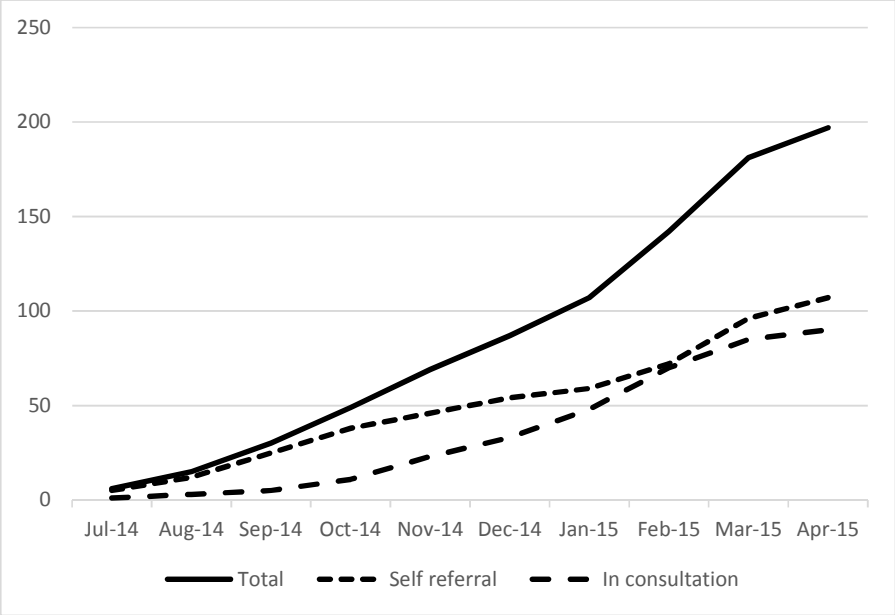

Figure S1: Cumulative participant recruitment: total and by referral pathway

	n/N (%)				
Appointment window	±5 days		±10 days		Number of assessments with complete date data‡
Recruitment pathway	Self-referral	In-consultation	Self-referral	In-consultation	
Baseline†	102/107 (95)	26/80 (33)	104/107 (97)	64/80 (80)	187
Visit 1	72/99 (73)	55/68 (81)	99/99 (100)	68/68 (100)	167
Visit 2	75/97 (77)	41/51 (80)	94/97 (97)	49/51 (96)	148
Visit 3	67/97 (69)	39/49 (80)	90/97 (93)	49/49 (100)	146

† Baseline visit fell within +/- 5/10 days of referral date

‡ Missing date of assessment or referral date possible

Table S1: Number (proportion) of researcher baseline and follow-up visits taking place within ±5 and ±10 days of planned scheduled dates by recruitment pathway

	Researcher guess					
Assignment	Aveeno® cream	Hydromol® ointment	Diprobase® cream	Doublebase® gel	Don't know	Total
Aveeno® cream	3	0	0	0	14	17
Diprobase® cream	0	0	2	0	20	22
Doublebase® gel	0	0	0	2	18	20
Hydromol® ointment	0	1	0	0	16	17
Total	3	1	2	2	68	76

The 109 participants who self-referred were prescribed their study emollient after the baseline visit; and 1 participant was recorded as an "other" response.

Table S2: Number of subjects by treatment assignment and guess at baseline visit

	Researcher guess					
Assignment	Aveeno® cream	Hydromol® ointment	Diprobase® cream	Doublebase® gel	Don't know	Total
Aveeno® cream	1	0	0	0	37	38
Diprobase® cream	0	0	3	1	39	43
Doublebase® gel	0	0	1	0	37	38
Hydromol® ointment	0	1	0	1	33	35
Total	1	1	4	2	146	154

CSOs recorded 5 participants as "other" response.

Table S3: Number of subjects by treatment assignment and guess at visit 1

	Researcher guess					
Assignment	Aveeno® cream	Hydromol® ointment	Diprobase® cream	Doublebase® gel	Don't know	Total
Aveeno® cream	1	0	0	0	36	37
Diprobase® cream	0	0	0	0	39	39
Doublebase® gel	0	0	0	0	36	36
Hydromol® ointment	0	1	0	0	30	31
Total	1	1	0	0	141	143

CSOs recorded 3 participants as other responses.

Table S4: Number of subjects by treatment assignment and guess at visit 2

	Researcher guess					
Assignment	Aveeno® cream	Hydromol® ointment	Diprobase® cream	Doublebase® gel	Don't know	Total
Aveeno® cream	0	0	0	0	39	39
Diprobase® cream	0	0	0	0	38	38
Doublebase® gel	0	0	0	0	38	38
Hydromol® ointment	0	0	0	0	32	32
Total	0	0	0	0	147	147

CSOs recorded 2 participants as other responses.

Table S5: Number of subjects by treatment assignment and guess at visit 2

EMR resource use for all participants (N=197)				
	Mean no contacts	(SD)	Mean cost	(SD)
GP face-to-face	0.31	(0.71)	11.77	(27.16)
GP telephone	0.10	(0.36)	2.22	(8.24)
GP out of hours	0.02	(0.12)	1.04	(8.39)
Nurse face-to-face	0.08	(0.27)	0.92	(3.11)
Nurse telephone	0.02	(0.17)	0.11	(0.91)
Other/unknown	0.04	(0.21)	10.63	(116.20)
Outpatient appointments	0.02	(0.12)	2.29	(20.06)
Prescribed medications	-		6.97	(12.05)

Table S6 Mean health care contacts and costs (£) from electronic medical records

Choice of Moisturiser for Eczema Treatment (COMET): feasibility study of randomised controlled parallel group trial in children recruited from primary care

Appendix: Skin hydration multivariable model

Skin hydration is affected by room temperature and humidity and all measurements were undertaken in participant's homes, in non-standardised conditions. We did not identify any published guidance on an analysis method to account for these environmental influences on the readings, so we constructed a multivariable linear regression model to adjust for the variation in temperature and humidity. Coefficients for this model were estimated by regressing the mean of the three measurements at baseline in each of the two sites (antecubital fossa and forearm) as the outcome on the temperature and humidity of the room. This model (calculation A below) predicted an average skin hydration measurement of 34.875 for the study average conditions of temperature (22 degrees centigrade) and humidity (48.6 units). The difference between the observed level of hydration, and the average level of hydration predicted for the temperature and humidity in which measurements were taken (the residual, calculation B) was added to the constant of 34.875 (calculation C) giving the skin hydration measure adjusted to average conditions of temperature and humidity. These calculations were done for each visit and for each site (antecubital fossa and forearm):

A: Predicted outcome model: Predicted average skin hydration= 2.452 + 1.177* temperature + 0.135* humidity

B: Residual = Actual measurements taken-Predicted average skin hydration

C: Adjusted measure of skin hydration (corneomtry outcome) = 34.875 + Residual

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1 & 2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4 & 5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4 & 5 (see protocol also)
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	7 & 9
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8 (in text) & table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Not applicable (feasibility study)
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	6-12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3 & 12-13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-13
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Choice of Moisturiser for Eczema Treatment (COMET): feasibility study of a randomised controlled parallel group trial in children recruited from primary care

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012021.R1
Article Type:	Research
Date Submitted by the Author:	12-Jul-2016
Complete List of Authors:	Ridd, Matthew; University of Bristol, Centre for Academic Primary Care, Social & Community Medicine Garfield, Kirsty; University of Bristol, Bristol Randomised Trials Collaboration, School of Social and Community Medicine Gaunt, Daisy; University of Bristol Faculty of Medicine and Dentistry, Bristol Randomised Trials Collaboration, School of Social and Community Medicine Hollinghurst, Sandra; University of Bristol, Centre for Academic Primary Care, Social & Community Medicine Redmond, Niamh; University of Bristol, Centre for Academic Primary Care, Social & Community Medicine Powell, Kingsley; University of Bristol, Centre for Academic Primary Care, Social & Community Medicine Wilson, Victoria; University of Bristol, Centre for Academic Primary Care, Social & Community Medicine Guy, Richard; University of Bath, Department of Pharmacy & Pharmacology Ball, Nicola; University of Bristol, Centre for Academic Primary Care, Social & Community Medicine Shaw, Lindsay; University Hospitals Bristol NHS Foundation Trust, Department of Dermatology Purdy, Sarah; University of Bristol, Centre for Academic Primary Care, Social & Community Medicine Metcalfe, Chris; University of Bristol, Bristol Randomised Trials Collaboration, School of Social and Community Medicine
Primary Subject Heading:	Dermatology
Secondary Subject Heading:	General practice / Family practice
Keywords:	Eczema < DERMATOLOGY, PRIMARY CARE, Paediatric dermatology < DERMATOLOGY

Title page

Title

Choice of Moisturiser for Eczema Treatment (COMET): feasibility study of a randomised controlled parallel group trial in children recruited from primary care

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Word count

3911/4000

Abstract

Objectives: To determine the feasibility of a randomised controlled trial of 'leave on' emollients for children with eczema.

Design: Single centre, pragmatic, four arm, observer masked, parallel, randomised feasibility trial.

Setting: General Practices in the UK

Participants: Children with eczema aged one month to less than five years.

Outcome measures: Primary outcome – proportion of parents who reported use of the allocated study emollient every day for the duration of follow-up (12 weeks). Other feasibility outcomes – participant recruitment and retention, data collection and completeness and masking of observers to allocation.

Interventions: Aveeno® lotion, Diprobase® cream, Doublebase® gel, Hydromol® ointment

Results: 197 children were recruited – 107 by self-referral (mainly via practice mail-outs) and 90 by in-consultation (clinician consenting and randomising) pathways. Participants recruited in-consultation were younger, had more severe Patient Orientated Eczema Measure (POEM) scores and were more likely to withdraw than self-referrals. Parents of 20 (10%) of all the randomised participants reported using the allocated emollient daily for 84 days. Use of other non-study emollients was common. Completeness of data collected by parent-held daily diaries and at monthly study visits was good. Daily diaries were liked (81%) but mainly completed on paper rather than via electronic ('app') form. Major costs drivers were GP consultations and eczema-related prescriptions. Observer unmasking was infrequent, and occurred at the baseline or first follow-up visit through accidental disclosure.

Conclusions: It is feasible in a primary care setting to recruit and randomise young children with eczema to emollients, follow them up, and collect relevant trial data, while keeping observers masked to their allocation. However, reported use of emollients (study and others) has design implications for future trials.

Trial registration: ISRCTN21828118 (01.05.2014)/EudraCT2013-003001-26 (23.12.2013)

Funding: National Institute for Health Research for Patient Benefit Programme (PB-PG-0712-28056)

Word count: 286/300

Strengths and limitations of this study

- This pragmatic study demonstrates that it is feasible to recruit children with eczema from primary care, randomise them to a 'leave on' emollient, and follow them up for 12 weeks with good observer masking.
- Participant retention was better in participants who referred themselves into the study compared with those who were recruited during consultations with their General Practitioner or Practice Nurse, although they also differed in respect of their age and parent-reported eczema severity.
- While it was possible to collect daily, weekly and monthly outcome data, missing data in parent-completed diaries has made interpretation of adherence to allocation challenging.
- There were practical and technical limitations with the 'app' version of the parent-completed diary.

Introduction

Eczema (also referred to as atopic dermatitis or atopic eczema) affects around 20% of children in the UK. Incidence peaks in the first two years of life and decreases thereafter.[1] It is characterised by dry and itchy skin, and it can have a significant impact on the quality of a child's life and their family.[2]

In countries with strong systems of primary care, such as the UK, the majority of children with eczema are both diagnosed and managed by their family physician or General Practitioner (GP) with emollients and topical corticosteroids. Emollients are recommended for the majority of patients and they are primarily used as a 'leave on' treatment to reduce eczema symptoms. Applied directly to the skin, emollients reduce water loss by occlusion and/or directly adding water to the dry outer layers of the skin. However, there are many products and formulations available (lotions, creams, gels and ointments) that vary in their consistency from 'light' to 'heavy'. Despite claims from the manufacturers, evidence that any one is better than another is weak.

Two recent systematic reviews have highlighted a paucity of research to help guide clinicians and patients in their choice.[3 4] In summary, the field is characterised by a lack of good quality, randomised controlled trials (RCTs) directly comparing commonly used emollients, with medium to long term data on clinically relevant outcomes. While undertaking this research represents unique challenges, such as the range of possible emollients to compare and the inability to mask users to emollients of very different consistencies (e.g. lotion versus ointment), patients and clinicians have highlighted it as an important issue. In the recent James Lind Alliance eczema treatment research priority setting partnership, "Which emollients are the most effective and safe in treating eczema?" emerged as one of the highest ranked uncertainties for further research.[5]

In order to address this uncertainty, we wanted to undertake a RCT of commonly prescribed emollients for the treatment of childhood eczema in primary care. However, the feasibility of being able to conduct such a trial was questionable, because of key issues such as whether parents/carers would be willing to be assigned and use a randomly allocated emollient for several months, and uncertainty about optimal methods of recruitment and data collection. Therefore, we conducted a trial to determine the feasibility of recruiting, retaining and collecting outcome data on young children with eczema in a primary care setting, to inform the design of a full trial.

Methods

Design, participants and interventions

Full details can be found in the protocol paper.[6] In brief, COMET was a feasibility study of a pragmatic, observer masked, RCT to compare the clinical and cost-effectiveness of 'leave on' emollients in the treatment of children with eczema. Throughout this paper we will use the term 'parent' to denote all carers/guardians with parental responsibility.

Between July 2014 and April 2015, participants were recruited in primary care (general practice) via two pathways: 'self-referral' (usually in response to a letter sent by their practice inviting them to take part) or 'in-consultation' (an approach during a surgery visit by General Practitioner (GP)/Practice Nurse (PN), who also received consent and undertook randomisation). GPs/PNs were asked to record all approaches to potentially eligible participants on a 'recruitment log'. At the end of the study practices also undertook searches to identify the number of potentially eligible children who had at least one contact with the practice during the recruitment period.

To be eligible, children had to have eczema, be aged one month to under five years and not be known to be sensitive or allergic to any of the study emollients or their constituents. Participants

were randomly allocated by a web based system (1:1:1:1 ratio) to one of four emollients (Aveeno® lotion 400ml, Diprobase® cream 500g, Doublebase® gel 500g, Hydromol® ointment 500g) to use as their leave-on emollient with the directions to 'Use twice daily and when required'. Study emollients were prescribed for the duration of the study by participants' GP surgeries and issued by pharmacies, as per usual care. The trial manager telephoned participants one week after randomisation to ensure that the allocated treatment had been received and started. All other care (appointments, prescriptions, referrals) was as per usual care. Research team members ('observers') undertaking the baseline and follow-up visits (but not clinicians, parents or participants) were masked to emollient allocation.

Three key changes to the original protocol were implemented in the final four months of recruitment. First, the diagnostic criterion was relaxed from 'doctor diagnosis of eczema' to 'diagnosed by a doctor or an appropriately qualified health care professional with oversight from a medically qualified doctor'. Second, the upper age limit was raised from under three years to under five years of age. Third, the number of practices was increased from 16 to 22. These additional practices were only asked to do the mail-out, not utilise the in-consultation recruitment pathway as well.

Outcomes

Participants were followed-up for 12 weeks (84 days). During this time study visits were scheduled to take place 28, 56 and 84 days after baseline and parents were asked to complete a daily diary (paper and electronic 'app' versions were offered). In addition, the primary care electronic medical records (EMR) were reviewed for the three months participants were in the study.

Data were collected on:

- Use of study emollient and other eczema treatments (daily parent reported)
- Eczema severity: weekly parent reported (Patient Orientated Eczema Measure, POEM[7]; parent global assessment) and monthly observer completed (Eczema Area Severity Index, EASI;[8] Six Area, Six Sign Atopic Dermatitis, SASSAD;[9] Three Item Severity, TIS[10]) assessments
- Quality of life: Atopic Dermatitis Quality of Life (ADQoL)[11] and Dermatitis Family Impact (DFI)[12] (both monthly parent reported)
- Skin hydration using a corneometer (see below) (monthly observer collected)
- Eczema-related prescriptions and healthcare resource use (weekly parent reported and EMR review)
- Eczema-related personal costs, parent time off work and child time away from school/day care (weekly parent reported)

Parents who withdrew from the study at any point were asked to complete a withdrawal questionnaire. At the end of the study, parents were asked to complete an exit questionnaire which included questions about their experience of taking part in the study.

The primary outcome of this feasibility study was the proportion of parents who reported use of the allocated study emollient every day for the duration of follow-up (12 weeks). Secondary outcomes were participant recruitment and retention, data collection and completeness (including health economic), and the extent to which the observers were kept masked to the intervention. Outcome data itself and other feedback will be presented elsewhere.

Corneometry

Skin hydration was measured at two sites on the body (antecubital fossa and forearm) using a corneometer (Corneometer® CM825, Courage & Khazaka electronic GmbH, Cologne, Germany), in arbitrary units of 0 to 100, with a higher measurement representing greater hydration. Presented measurements were adjusted for ambient temperature and humidity, to give the prediction of what each measurement would have been had it been taken in the average conditions seen in the study; 22°C and 48.6% relative humidity. This adjustment was based on an equation estimated by regressing the corneometry measurements taken in the study on the corresponding temperature and humidity readings (see appendix).

Sample size

Because this was a feasibility study a formal sample size calculation was not required. We aimed for a target sample size of 160 participants. With this number, a true consent rate of 50% (160 children participating having invited 320 potentially eligible children) would be estimated with 95% confidence interval of the order 44% to 56%.

Analysis

We conducted linear or logistic regression (as appropriate) to compare the characteristics of participants recruited via the two recruitment pathways and those who withdrew/stayed in the study. Observer masking was assessed using the Bang Blinding Index,[13] which takes a value between -1 and +1: +1 indicates complete lack of masking and 0 is consistent with perfect masking. Negative values indicate the respondent is wrong more often than would be expected by chance, which can arise, for example, if all participants are said to be on one particular treatment irrespective of what they receive.

Health care resource use and prescribed medications were costed using relevant unit costs[14-17] valued in pound sterling and at 2014 prices. The cost of the intervention emollients were estimated using three alternative methods; firstly via the Prescription Cost Analysis (PCA),[15] secondly using the British National Formulary (BNF),[18] and thirdly using the Drug Tariff (DT)[19] and Dictionary of Medicines and Devices (DMD).[20] The final method aimed to estimate the true cost to the NHS of prescribed medications by estimating the amount community pharmacists are reimbursed for dispensing prescriptions. This method incorporates a deduction for any discount the pharmacy may have received, dispensing fees and payments for containers, consumables or other associated costs.

Health state utility values were estimated at each time point using scores from the ADQoL.[11] QALYs were derived using the area under the curve approach[21] and by multiplying to an annual equivalent.

Ethics

The study was approved by Central Bristol Research Ethics Committee (REC reference: 13/SW/0297), Clinical Trial Authorisation given by the Medicines and Healthcare products Regulatory Agency (MHRA reference: 03299/0017/001-003) and research governance approvals obtained across all areas prior to the start of recruitment. Written informed consent was received from all participants.

Results

Recruitment of participants

Between July 2014 and May 2015, 197 children were recruited via 22 practices. The flow of the participants through the trial is shown in the CONSORT diagram (figure 1), which distinguishes between the two recruitment pathways.

[Insert 'Figure 1: CONSORT diagram – recruitment by referral pathway' with accompanying text: [a] Data from 13 GP practices (8 practices had no exclusions, 1 practice had 3 exclusions with no reasons given); [b] Data from 6 GP practices whose GPs returned recruitment logs; [c] One participant withdrew after visit 3 from the in-consultation pathway]

Recruitment by self-referral pathway: 2026 potentially eligible children were screened and GPs excluded 9% (177/2026), the most common reason being 'no longer has eczema' (37%, 66/177). Of the 1849 invitation letters sent, responses were received from 20% (374/1849) with 66% (246/374) declining to take part. Again, the most common reason for not taking part was the child having either no or only mild eczema (62%, 152/246). A further four children were recruited by word-of-mouth or after seeing a study poster/being given a study flyer, giving a total of 132 potentially eligible participants who were screened by the research team. Of these, 19% (25/132) were not recruited, mainly because the carer could not be contacted (12/25, 48%).

Recruitment by in-consultation pathway: Retrospective searches identified 2552 potentially eligible children who had at least one contact with their practice, and therefore could have been approached via this pathway. Recording of these contacts by clinicians was poor, with only six practices returning 'recruitment logs', which detailed 66 encounters. Of these, the most common reasons given for not recruiting were that clinicians either forgot to ask or were too busy (47%, 31/66).

The majority of participants (62%, 54/87) recruited during the first six months came via the self-referral pathway (figure S1). However, during the final four months of recruitment, the number of in-consultation referrals increased so that by the end of the study 90 (46%) of the total 197 participants came via this route. Practices 1 to 16 sent reminder letters to families who did not respond to the initial invitation and still met the eligibility criteria, which resulted in the recruitment of four additional participants.

Characteristics of participants

The mean age (SD) of participants at baseline was 21.7 months (12.8), with 85 (43%) female, 155 (85%) white and a mean Index of Multiple Deprivation (IMD) score (SD) of 21.8 (14.2) (generated from participant postcode). Mean (SD) eczema severity scores were as follows: POEM 8.8 (5.9), EASI 2.9 (3.8), SASSAD 8.8 (8.4) and TIS 2.0 (1.7). Mean (SD) DFI and ADQoL were 3.6 (4.8) and 0.787 (0.084) respectively.

However, as can be seen from table 1, participants recruited in-consultation were younger (mean age in months 17.0 versus 25.7, $p<0.031$), and had higher mean POEM (10.3 vs 7.6, $p=0.012$) scores than those who were recruited via self-referral.

Table 1: Characteristics of participants at baseline by referral pathway

	Self-referral (N=107)		In-consultation (N=90)		P-value
		n		n	
Mean age in months (SD)	25.7 (11.6)	107	17.0 (12.6)	90	0.031[a]
Number female (%)	46 (43%)	107	39 (43%)	90	0.868[b]
Number white (%)	98 (93%)	108	57 (74%)	77	0.088[b]
Mean IMD score (SD)	15.7 (10.5)	104	25.4 (13.8)	88	0.201[a]
Mean eczema severity scores (SD)					
- POEM [min 0, max 28, high = worse]	7.6 (5.7)	107	10.3 (5.8)	89	0.012[a]
- EASI [min 0, max 72, high = worse]	2.8 (4.1)	105	3.1 (3.4)	79	0.841[a]
- SASSAD [min 0, max 108, high = worse]	9.0 (8.7)	107	8.5 (7.9)	79	0.918[a]
- TIS [min 0, max 9, high = worse]	2.1 (1.9)	107	2.0 (1.5)	79	0.571[a]
Skin hydration[#] [high = better]					
- Forearm	31.3 (11.8)	98	32.9 (10.1)	70	0.719[a]
- Antecubital fossa	36.5 (14.8)	98	39.5 (12.6)	71	0.325[a]
Mean DFI score (SD) [min 0, max 30, high = worse]	2.9 (4.0)	107	4.6 (5.6)	79	0.224[a]
Mean ADQoL (SD) [min 0.356, max 0.841, high = better]	0.799 (0.065)	105	0.770 (0.103)	75	0. 239[a]

[a] Linear regression model adjusting for GP practice; [b] Logistic regression model adjusting for GP practice; [#]Measurements adjusted to average study conditions of temperature (22°c) and humidity (48.6%) (model described in methods/appendix). Data presented in arbitrary units ([min 0, max 100, high = more hydrated).

Participant retention

28 (14%) participants withdrew from the study and 151 (77%) attended the final follow-up visit. Most participants who withdrew were recruited in-consultation (21/90, 23%, compared to 7/107, 7%, of self-referrals), including five children who did not attend their baseline visit. All bar one participant (who was recruited in-consultation) returned a withdrawal questionnaire, and the most commonly cited reason for withdrawing was lack of time (table 2).

Table 2: Reasons for participant withdrawal by recruitment pathway

	Recruitment pathway	
Reasons for withdrawal†	Self-referral (n=7)	In-consultation (n=21)
Study emollient not working/effective	0	2
Adverse reaction to study emollient	2	0
Disliked emollient given	0	2
Just simply changed my mind	0	2
Don't have enough time	4	10
My child's skin has improved – no longer need emollient	0	4
Other	2	7

†More than one reason could be cited.

Collection and completeness of outcome data

22/185 (12%) of parents started using the app version of the daily diary but only 11 people used it for the duration of the study. Technical problems meant that it was not promoted after the first three months of recruitment. Of 150 parents completing an exit questionnaire, 121 (81%) said they liked the daily diary, 22 (15%) said they weren't sure and 7 (5%) disliked it.

Table 3 shows that completeness of daily, weekly and monthly data collected via the parent diary was generally good. However, completion rates for individual sections varied from 70% to 95% among those who returned the diaries and from 57% to 78% of all participants. The most poorly completed sections were daily record of eczema treatment use and weekly time off school & work. Due to the cumulative nature of health care costs, complete costing of health care resources was possible for only 62% (122/197) of participants despite the relevant section of each diary having been completed by at least 70% (138/197).

Completeness of data collected by the observers was also good, with the median number (IQR) of visits with complete data (maximum 4) for EASI, TIS and SASSSAD all being 4.0 (3.0 to 4.0). The completeness for corneometry was lower and differed by site (forearm 3.0 (2.0 to 4.0), antecubital fossa 4.0 (2.0 to 4.0)), as it was not possible to use the one available corneometer at concurrent follow-up visits. A greater proportion of observer visits occurred ±10 days than ±5 days of the scheduled date, and baseline visits were more likely to be timely for participants who self-referred (table S1).

Table 3: Completeness of data collected by parent-completed daily diary

		Diary 1 (days 1-28)			Diary 2 (days 29-56)			Diary 3 (days 57-84)		
Frequency of question item completion	Question items	n	% of returners (n=162)	% of participants (n=197)	n	% of returners (n=151)	% of participants (n=197)	n	% of returners (n=150)	% of participants (n=197)
Daily	Eczema treatments	113	70	57	129	85	65	128	85	65
	POEM	145	90	74	139	92	71	139	93	71
Weekly	HCP contacts	141	87	72	138	91	70	138	92	70
	Time off school & work	130	80	66	114	75	58	124	83	63
Monthly	ADQoL	150	93	76	135	89	69	140	93	71
	DFI	153	94	78	141	93	72	143	95	73

POEM: Patient Orientated Eczema Measure; HCP: Health Care Professional; ADQoL: Atopic Dermatitis Quality of Life; DFI: Dermatitis Family Impact

The Bang-Blinding Indices for observer unmasking to the different emollients are shown in table 4 (observer guess and treatment assignment for each assessment, by which this index was calculated, are show in tables S2 to S5). Observers reported not knowing which study emollient the participants were using at most visits. They correctly identified the study emollient in eight participants at both the baseline and first follow-up visits. The most common reasons given for unmasking were the parent telling them (6/8 baseline and 6/8 visit 1) or the observer seeing the study emollient during the visit (2/8 baseline and 1/8 visit 1).

Table 4: Bang blinding index with 95% two sided Confidence Interval (comparing correct treatment response with incorrect treatment or don't know response)

	Visit			
Study emollient	Baseline	1	2	3
Aveeno® lotion	0.2 (0.0, 0.4)	0.0 (0.0, 0.1)	CE	CE
Hydromol® ointment	0.1 (-0.1, 0.2)	0.0 (-0.1, 0.1)	CE	CE
Diprobase® cream	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	CE	CE
Doublebase® gel	0.1 (0.0, 0.2)	0.0 (-0.1, 0.0)	CE	CE

CE: cannot be estimated due to lack of data (see supplementary Tables S2-S5)

Adherence to intervention

Of the 197 participants, parents of 20 (10%) reported using their allocated emollient daily for 84 days (primary outcome). However, 38 (19%) did not give any data on study emollient use. Therefore, of the 159 parents of participants who completed this question at least once, 49 (31%) said they used the study emollient on each occasion that they completed the question.

The majority (156/162, 96%) of parents reported some use of a non-study emollient: 25% (41/162) reported use every day (that data were provided) and 51% (82/162) reported using an 'other' emollient on up to 50% of days. 53% (85/159) of parents reported using an 'other' emollient *instead* of the study emollient at least once. Of these 85 parents, 86% (73/85) used an 'other' emollient rather than the study emollient half of the time.

Analysis of the EMRs revealed that while the mean (SD) number of intervention emollient prescriptions was 1.44 (0.78), the number of eczema-related prescriptions for non-intervention emollients was 1.28 (2.13). This included a mean (SD) number of 0.48 (0.99) non-study emollients, 0.43 (0.93) topical corticosteroid and 0.31 (0.69) bath/shower product prescriptions.

Economic evaluation

The main cost driver as recorded in the EMRs was GP appointments with a mean cost of £11.77 over the follow-up period (table S6). On average the cost of eczema-related prescribed medications excluding trial emollients equated to £6.97. Health care and intervention emollient costs did not appear to differ considerably between treatment arms (table 5). The mean (SD) cost to the NHS of each of the trial emollients using the DT and DMD was £11 (£5), £9 (£5), £9 (£5) and £8 (£5), for Aveeno® lotion, Diprobase® cream, Doublebase® gel and Hydromol® ointment, respectively. Emollient costs were slightly higher using this method in comparison to the PCA or BNF (table 5). Complete ADQoL data for 119 participants allowed estimation of mean (SD) annual QALYs of 0.799 (0.061).

Parents reported additional expenditure due to their child's eczema on items including: eczema treatments (n=25), clothes (n=14), household items (n=12), toiletries (n=11) and food and drink (n=9). Time off paid employment or school/day care was reported infrequently: over the entire follow-up period only 3 days off paid employment and 2 days off school/day care were reported across all participants.

Table 5: Total healthcare cost (£) and QALYs, by treatment allocation

	Aveeno® lotion (N=51)			Diprobase® cream (N=53)			Doublebase® gel (N=46)			Hydromol® ointment (N=47)		
	n	Mean cost	SD	n	Mean cost	SD	n	Mean cost	SD	n	Mean cost	SD
Total health care cost - EMR only	51	23	(50)	53	28	(50)	46	32	(85)	47	62	(258)
Total health care cost – EMR plus diary	30	25	(97)	32	32	(54)	33	35	(93)	27	16	(21)
Intervention emollient cost (PCA)	51	8	(4)	53	9	(5)	46	9	(5)	47	7	(4)
Intervention emollient cost (BNF)	51	8	(4)	53	9	(5)	46	8	(4)	47	7	(4)
Intervention emollient cost (DT & DMD)	51	11	(5)	53	9	(5)	46	9	(5)	47	8	(5)
Total cost (EMR, diary and DT & DMD emollient)	30	38	(98)	32	42	(57)	33	43	(94)	27	24	(23)
Annual QALYS	32	0.798	(0.061)	29	0.812	(0.055)	33	0.790	(0.061)	25	0.800	(0.070)

Discussion

This is the first study to show that it is feasible in a primary care setting to recruit and randomise young children with eczema to 'leave-on' emollients and follow them up, keeping observers masked to their allocation. We exceeded our recruitment target, although in the final four months we enlisted the help of six more practices than originally planned and relaxed the age and diagnostic eligibility criteria. Reported daily use of the study emollients was low however, and use of other emollients was common.

We conducted a well-executed, pragmatic trial overcoming many practical and logistical challenges, meeting regulatory requirements of a Controlled Trial of an Investigational Medicinal Product (CTIMP). More detail on trial conduct can be found in the published trial protocol[6] and we report the findings in accordance with the CONSORT guidelines.[22] These findings have implications for future trials of emollients and other treatments for children with eczema, but also for trials of treatments of other long-term conditions in primary care with medium-term follow-up.

A strength of this study is its exploration of the two possible recruitment pathways and their feasibility in a main trial. By asking most practices to try and recruit via the two routes, we now have a strong understanding of the number (and characteristics) of children likely to be recruited in a definitive trial, and the proportion likely to withdraw (and reasons why). While having the two pathways into the study helped the trial meet its recruitment target, we are mindful that the characteristics of participants, and their commitment to staying in the trial differed for participants recruited via these two routes. Of 90 participants recruited via the in-consultation pathway, 21 (23%) withdrew and 53 (59%) attended their final appointment, compared with 7 (7%) and 98 (92%) respectively for participants recruited via self-referral (most mail-out). With respect to the mail-out invitation, the high number of children identified with mild or no eczema reflects the fact that for many their diagnosis will be historical and for others, erroneous. One way to improve this may be to limit invitations to children with a recent relevant prescription (suggesting 'active' disease), as per the BATHE study.[23] The rise in the rate of children recruited in-consultation may reflect both the staggered nature in which the practices came into the study but also a learning and confidence effect among recruiting clinicians. Although all practices were members of the Clinical Research Network, they had variable levels of experience in recruiting to studies of this type and each study has its unique processes that have to be followed.

In addition to investigating recruitment and retention, we have also collected important adherence, outcome (including corneometry) and health economic data. We found that it is feasible to both collect and cost the data required to perform an economic evaluation in this setting. EMR records provided a rich source of complete healthcare resource use data, indicating that in further studies healthcare resource use collected from diaries could be reduced. Given that time away from paid employment and school were very rarely reported, capturing these data in a future trial would likely be less important. Our assessment of additional items bought due to eczema has highlighted a list of important categories to include in future studies. At inception, no generic measure of health-related quality of life that was psychometrically and conceptually robust enough for young children under the age of three was available. For this reason we used the ADQoL, from which we were able to estimate QALYs. However, given that this is a condition-specific preference-based measure, the results may not be comparable across conditions.

Reported use of study emollients was low and use of other emollients either alongside or instead of the allocated treatment common, but our ability to interpret these findings is limited by missing data. While completion of the daily diary was generally good, questions on the use of eczema treatments (including study emollient) were the most poorly completed. We think this is because parents left an item blank when a treatment was not used, rather than recording 'None' or '0', meaning it was classed as 'missing'. For example, if missing data on 'other' emollient use is treated as 'no use' on those days for which complete data are available on use of the study emollient, then only 6% (10/162) (compared with 25%) of parents of participants used a non-study emollient every day and 71% of parents of participants (115/162) (compared with 51%) reported using another emollient on up to 50% of days. Another limitation in the data on emollient use is that we are unable to distinguish between use as leave-on therapy (in the same way as the study emollients)

and use as soap substitute. Missing data would have been less of a problem had the 'app' version of the diary worked better and been used by more parents – one of the attractions of collecting data from parents this way is the ability to automatically monitor data entry in real time and prompt parents to answer all the questions.

Although initial interest among parents in using our 'app' was high, its development and incorporation in this study was challenging because: a) regulatory requirements for CTIMPs meant, additional and time consuming testing to ensure that data were transmitted securely; and b) the cost required to develop a fully functional app for the most common smart phone and tablet platforms (iOS and Android). Therefore, while we cannot conclude that studies similar to ours should not consider data collection via bespoke apps, we would certainly caution against under-estimating the time, cost and technical implications of doing this. In future studies, automatic email prompts to parents to complete online questionnaires are probably a safer and more cost effective way of maximising data collection. For parents who would still prefer paper questionnaires, clear instructions should be given about the importance of positively indicating 'no treatment use' (as opposed to leaving an answer blank). We also recommend that future studies involving young children should be realistic about parents' ability to adhere to strict follow-up schedules, with study protocols providing realistic 'windows' (e.g. ±10 days if permissible) within which to expect data collection; and where it is desirable to keep the observer masked, giving unambiguous instructions to parents to avoid accidental disclosure.

For future trials comparing emollients, researchers should be encouraged that participants who consent to taking part generally stay in the trial, although they may wish to recruit participants using just the self-referral pathway. Researchers also need to be aware that co-use of emollients appears to be common, and the extent to which this matters will depend on where future studies sit on the efficacy-effectiveness spectrum. Whatever the design, this study provides the foundations for future definitive studies to answer the prioritised research question "Which emollient is the most effective and safe in treating eczema?"[5]

Acknowledgements

We would like to thank all the children, parents and surgeries who took part in the study and the joint Trial Steering/Data Monitoring Committee (TS/DM-C) and Dr Stephanie MacNeill for her assistance in analysing the adherence data. This study has been designed and delivered in collaboration with the Bristol Randomised Trials Collaboration (a UKCRC Registered Clinical Trials Unit in receipt of National Institute for Health Research CTU support funding) and the sponsor, University of Bristol.

Declarations

Authors contribution

MJR proposed the original study idea its design, and NB, NMR, SH, SP, RG and LS helped develop this idea and obtain funding for the project. Specific input provided by authors included: NB and LS on the choice and use of emollients in eczema and assessment of eczema severity; RG on collection and interpretation of skin hydration data; DMG and CM on analysis, development of skin hydration model and reporting of main feasibility findings; SH and KG on analysis and reporting health economic data; KP and VW assisted with collation, cleaning and reporting of findings; NMR and SP input on study design and delivery; CM on trial methodology and conduct. MJR wrote the first draft and led on all subsequent revisions; NMR, KG, VW, SH, SP, KP, CM, DMG, NB, LS and RG all

commented on and contributed to revised versions of the manuscript. All authors have read and approved the final manuscript.

Competing interests statement

All authors have completed the ICMJE uniform disclosure form atwww.icmje.org/coi_disclosure.pdf. NB has been an employee of Galderma (UK) Ltd since May 2015; all other authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

The COMET study independent research funded by the National Institute for Health Research (Research for Patient Benefit Programme, PB-PG-0712-28056). The views expressed in the publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Data sharing statement

The research team will consider reasonable requests for sharing of patient level data. Requests should be made to MJR. Consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low.

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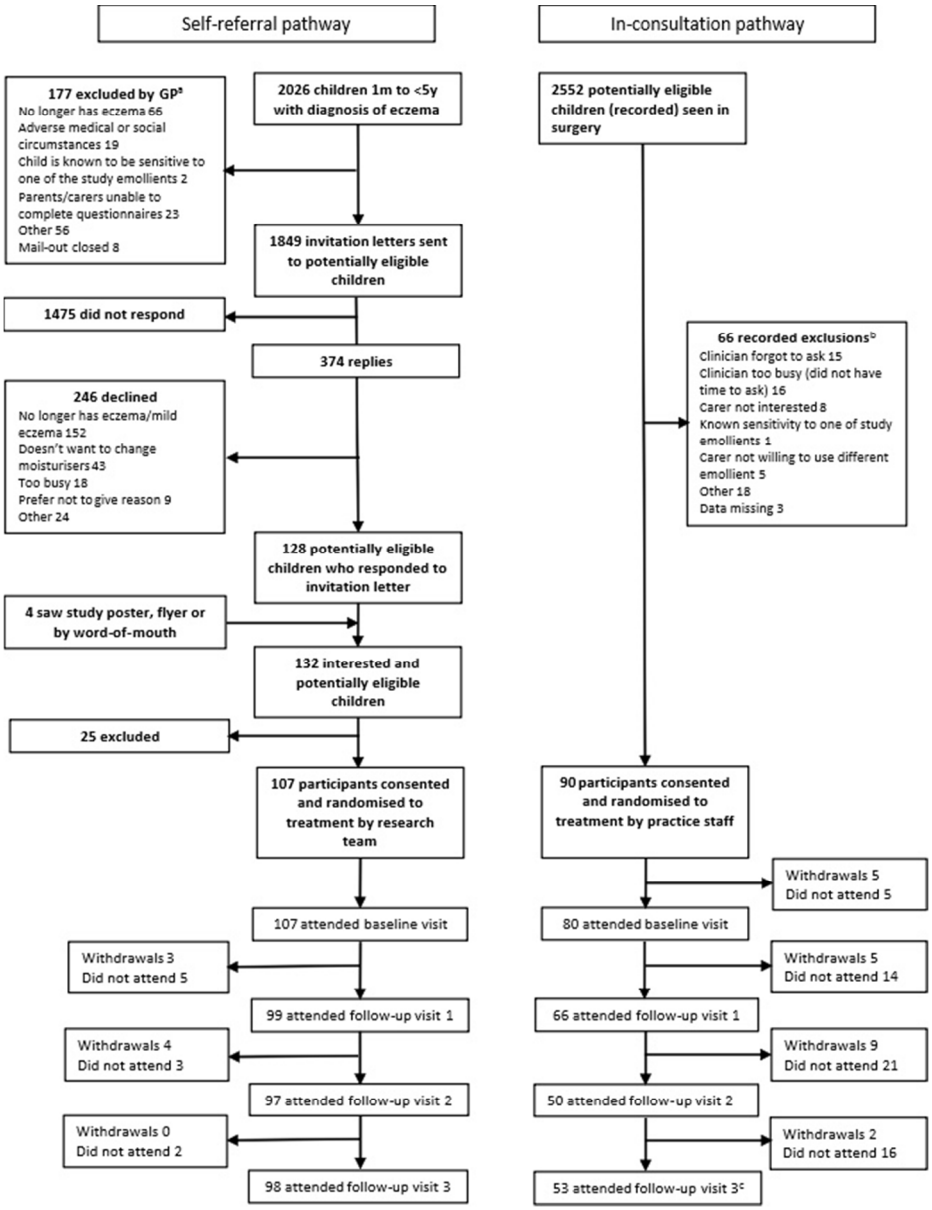

Figure 1: CONSORT diagram – recruitment by referral pathway

173x225mm (96 x 96 DPI)

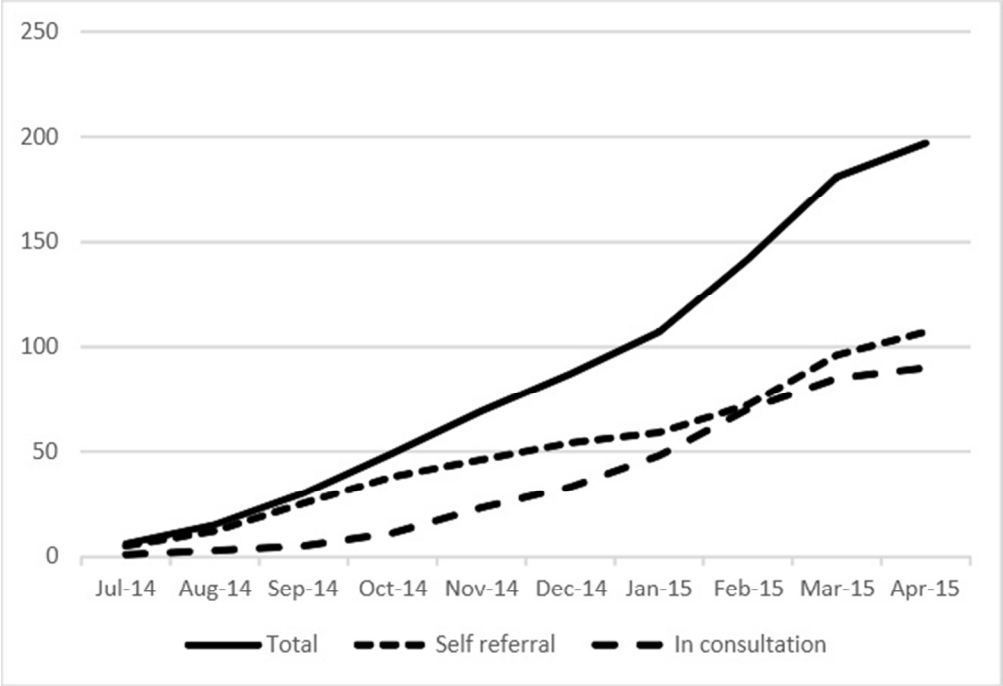

Figure S1: Cumulative participant recruitment: total and by referral pathway

175x120mm (96 x 96 DPI)

Manuscript ID bmjopen-2016-012021

Choice of Moisturiser for Eczema Treatment (COMET): feasibility study of randomised controlled parallel group trial in children recruited from primary care

Supplementary figure & tables

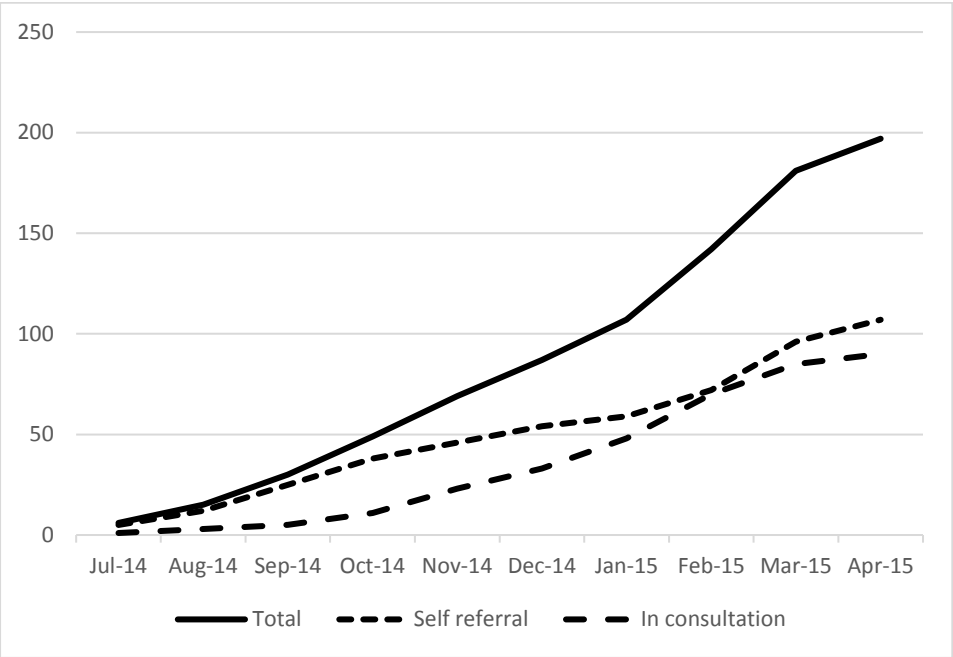

Figure S1: Cumulative participant recruitment: total and by referral pathway

	n/N (%)				
Appointment window	±5 days		±10 days		Number of assessments with complete date data‡
Recruitment pathway	Self-referral	In-consultation	Self-referral	In-consultation	
Baseline†	102/107 (95)	26/80 (33)	104/107 (97)	64/80 (80)	187
Visit 1	72/99 (73)	55/68 (81)	99/99 (100)	68/68 (100)	167
Visit 2	75/97 (77)	41/51 (80)	94/97 (97)	49/51 (96)	148
Visit 3	67/97 (69)	39/49 (80)	90/97 (93)	49/49 (100)	146

† Baseline visit fell within +/- 5/10 days of referral date

‡ Missing date of assessment or referral date possible

Table S1: Number (proportion) of researcher baseline and follow-up visits taking place within ±5 and ±10 days of planned scheduled dates by recruitment pathway

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	Researcher guess					
Assignment	Aveeno® cream	Hydromol® ointment	Diprobase® cream	Doublebase® gel	Don't know	Total
Aveeno® cream	3	0	0	0	14	17
Diprobase® cream	0	0	2	0	20	22
Doublebase® gel	0	0	0	2	18	20
Hydromol® ointment	0	1	0	0	16	17
Total	3	1	2	2	68	76

The 109 participants who self-referred were prescribed their study emollient after the baseline visit; and 1 participant was recorded as an "other" response.

Table S2: Number of subjects by treatment assignment and guess at baseline visit

	Researcher guess					
Assignment	Aveeno® cream	Hydromol® ointment	Diprobase® cream	Doublebase® gel	Don't know	Total
Aveeno® cream	1	0	0	0	37	38
Diprobase® cream	0	0	3	1	39	43
Doublebase® gel	0	0	1	0	37	38
Hydromol® ointment	0	1	0	1	33	35
Total	1	1	4	2	146	154

CSOs recorded 5 participants as "other" response.

Table S3: Number of subjects by treatment assignment and guess at visit 1

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	Researcher guess					
Assignment	Aveeno® cream	Hydromol® ointment	Diprobase® cream	Doublebase® gel	Don't know	Total
Aveeno® cream	1	0	0	0	36	37
Diprobase® cream	0	0	0	0	39	39
Doublebase® gel	0	0	0	0	36	36
Hydromol® ointment	0	1	0	0	30	31
Total	1	1	0	0	141	143

CSOs recorded 3 participants as other responses.

Table S4: Number of subjects by treatment assignment and guess at visit 2

	Researcher guess					
Assignment	Aveeno® cream	Hydromol® ointment	Diprobase® cream	Doublebase® gel	Don't know	Total
Aveeno® cream	0	0	0	0	39	39
Diprobase® cream	0	0	0	0	38	38
Doublebase® gel	0	0	0	0	38	38
Hydromol® ointment	0	0	0	0	32	32
Total	0	0	0	0	147	147

CSOs recorded 2 participants as other responses.

Table S5: Number of subjects by treatment assignment and guess at visit 2

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EMR resource use for all participants (N=197)				
	Mean no contacts	(SD)	Mean cost	(SD)
GP face-to-face	0.31	(0.71)	11.77	(27.16)
GP telephone	0.10	(0.36)	2.22	(8.24)
GP out of hours	0.02	(0.12)	1.04	(8.39)
Nurse face-to-face	0.08	(0.27)	0.92	(3.11)
Nurse telephone	0.02	(0.17)	0.11	(0.91)
Other/unknown	0.04	(0.21)	10.63	(116.20)
Outpatient appointments	0.02	(0.12)	2.29	(20.06)
Prescribed medications	-		6.97	(12.05)

Table S6 Mean health care contacts and costs (£) from electronic medical records

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1 & 2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4 & 5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4 & 5 (see protocol also)
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	7 & 9
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8 (in text) & table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Not applicable (feasibility study)
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	6-12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3 & 12-13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-13
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.