PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Choice of Moisturiser for Eczema Treatment (COMET): feasibility study of a randomised controlled parallel group trial in children recruited from primary care
AUTHORS	Ridd, Matthew; Garfield, Kirsty; Gaunt, Daisy; Hollinghurst, Sandra; Redmond, Niamh; Powell, Kingsley; Wilson, Victoria; Guy, Richard; Ball, Nicola; Shaw, Lindsay; Purdy, Sarah; Metcalfe, Chris

VERSION 1 - REVIEW

REVIEWER	Robert Boyle Imperial College London, UK
REVIEW RETURNED	14-Apr-2016

GENERAL COMMENTS	Thank you for the opportunity to review this interesting manuscript. The authors describe a pilot feasibility study designed to inform the development of a definitive RCT comparing different types of emollient for treating eczema in preschool children in primary care. The rationale for the work is a James Lind Alliance priority setting exercise which identified choice of emollient as an important research question. The findings suggest that there are differences in participant characteristics and retention rates according to source of recruitment, and provide some details to inform design of a larger trial. My main concern is that the trial primary outcome is not very clearly defined in the manuscript or trial registry, and the reasons why it wasn't achieved in the majority of participants are not fully explored. Comments for the authors to consider in revising their manuscript: 1. Please define the primary outcome more precisely - was this intended to be the proportion of participants using the allocated emollient at least once daily for at least xx days in the first 84 days post - randomisation? 2. Overall the figures for adherence to the intervention seem disappointing, but the authors present them as quite positive. I suppose interpretation depends slightly on the response to query #1 ie the definition of success; but the degree of contamination looks to me like a significant problem for designing a larger trial. My suggestion is to interpret the study findings as negative ie although there were positive findings in terms of recruitment, acceptability of assessments etc, the primary outcome of adherence to the intervention at 3 months was disappointing - and to use this to make a concrete suggestion for the design of a future emollient study eg one might suggest that future studies randomised participants to a choice of emollient A, B or C; versus D, E or F to mitigate against poor adherence.

	3. In relation to the above, it would be really nice to know why adherence was poor and other emollients were introduced - some of this seems to be related to prescription medicated ointments eg corticosteroids; but it would be helpful to see any data the group have on reasons for poor adherence to the allocated emollient. 4. Abstract - Conclusions section last sentence - should this be 'older', since earlier in the abstract it is suggested that in-consultation recruits were younger. 5. Introduction - second paragraph - 'Emollients are recommended for all..' There are some relative contraindications, and some patients don't like using emollients, so this should perhaps read 'for most patients' or similar. In the same sentence 'to improve skin comfort' - perhaps 'hydration' or 'skin health' or 'reduce skin dryness and other eczema symptoms' might read better. 6. Table 1 - footnote - data for b and c are not shown, so either they should be added into the table, or these footnotes deleted. 7. Results - 'Participant retention' - 77% retention is ok, but over a 3-month period one might hope for slightly better than this, so I think the authors could be more critical of this outcome and discuss further how to optimise retention in this sort of study eg by focussing recruitment on self-referral. 8. Results - 'Adherence to intervention' - as mentioned above, this should be clearly presented as a disappointing outcome. Reasons for poor adherence need to be explored where data exist; and implications for future study design need to be discussed. 9. Results section final sentence - the infected eczema cases are of interest. Would data be available on these patients for the previous 3 months via GP records; and if so would it be worthwhile looking at those to explore whether the emollient intervention might have increased risk of an episode of infected eczema. This might be important hypothesis-generating information. 10. Discussion - how was emollient delivered in this study - and could that be used to monitor adherence to the study intervention in a future trial eg if all emollient is delivered to participant homes following an online order. 11. Discussion - how do the authors think that adherence and retention will be in a longer duration trial ie beyond 3 months of treatment? 12. It would be nice to see some clear conclusions about how a future trial might be designed - what would the primary outcome measure look like; is safety or efficacy/effectiveness the most important outcome, have you got signals from this study which push you towards one or the other? When the James Lind group formulated the key question about emollient choice, was there clear interest in emollient type as compared in this COMET study, or was there interest in specific brand names, or specific frequencies or methods of application for using emollient? 13. There are quite a few minor typos and grammatical errors through the manuscript which would be worth a read-through to

	correct.

REVIEWER	Dr Jonathan Batchelor Centre of Evidence-Based Dermatology, University of Nottingham, UK
REVIEW RETURNED	03-May-2016

GENERAL COMMENTS	An interesting and well-reported feasibility study, on an important topic which has been identified as a research priority through a Priority Setting Partnership. Use of core outcome measures (POEM and EASI) is another strength of this work. Major comments Primary outcome features clearly only in the abstract. It needs to be clearly stated in the methods and results as well. Secondary outcomes could also be presented more clearly in main body of manuscript Results section, paragraph 2: Please clarify how participants were screened at each stage and make sure the figures correspond with those in the CONSORT flow chart CONSORT flow chart: It says that 90 participants were consented in the GP/PN referral pathway but how many were approached? Discussion needs a comment on the high use of non-study emollients and therefore the potential for contamination in the main trial. Discussion Page 12 line 40. The problem with limiting invitations to those with a recent prescription is that they don't necessarily need to have been reviewed before having a repeat prescription and so might no longer have eczema Discussion page 13 line 6-19. The under-reporting of use of treatment is a significant issue. Please expand on what measures are going to be taken in the main trial to avoid this. Minor comments I would change the term 'researcher masked' to 'observer masked' throughout the manuscript Page 5 line 5 Participants were not masked to emollient allocation either- please add this Outcomes section: rather confusing to have a mixture of days and months in this section. Could it not all be expressed in 'weeks'? You could comment that participants recruited in consultation were younger perhaps because their parents area less likely to have time to self refer?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

	Reviewer's comments	Authors' response
1.	Please define the primary outcome more precisely - was this intended to be the proportion of participants using the allocated emollient at least once daily for at least xx days in the first 84 days post - randomisation?	We have clarified the definition of the primary outcome in the Abstract and in the section "Methods – Outcomes": The primary outcome was the proportion of parents who reported use of the allocated study emollient every day for the duration of follow-up (12 weeks).
2.	Overall the figures for adherence to the intervention seem disappointing, but the authors present them as quite positive. I suppose interpretation depends slightly on the response to query #1 ie the definition of success; but the degree of contamination looks to me like a significant problem for designing a larger trial. My suggestion is to interpret the study findings as negative ie although there were positive findings in terms of recruitment, acceptability of assessments etc, the primary outcome of adherence to the intervention at 3 months was disappointing - and to use this to make a concrete suggestion for the design of a future emollient study eg one might suggest that future studies randomised participants to a choice of emollient A, B or C; versus D, E or F to mitigate against poor adherence.	We have made revisions to the Abstract and Discussion sections, acknowledging that reported use of study emollients was low and use of other emollients high, but also pointing out that problems with missing data in the relevant section of participants' diaries has limited our ability to interpret this finding; and that this problem should be minimised in future trials by use of online questionnaires and clearer instructions for participants.
3.	In relation to the above, it would be really nice to know why adherence was poor and other emollients were introduced - some of this seems to be related to prescription medicated ointments eg corticosteroids; but it would be helpful to see any data the group have on reasons for poor adherence to the allocated emollient.	Our ability to make further comment on this is limited by missing data in participant diaries (see above). We do have data from participants in the form of questionnaires (completed at the end of their time in study, rating different aspects of the study emollients) and free text comments. However, there is not enough space within this "feasibility" paper to present this as well and this will form a separate publication. We think many of the issues warrant formal exploration, and we plan to do this with a nested qualitative sub-study in a future, definitive trial.
4.	Abstract - Conclusions section last sentence - should this be 'older', since earlier in the abstract it is suggested that in-consultation recruits were younger.	Thank you for spotting this – as part of the revisions to the Abstract (in light of the above comments, to keep within the word limit) this sentence has now been removed, but the differences are/were correctly reported in the Results section.
5.	Introduction - second paragraph - 'Emollients are recommended for all..' There are some relative contraindications, and some patients don't like using emollients, so this should perhaps read 'for most patients' or similar. In the same sentence 'to improve skin comfort' - perhaps 'hydration' or 'skin health' or 'reduce skin dryness and other eczema symptoms' might read better.	Thank you for this suggestion – this sentence now reads: "Emollients are recommended for the majority of patients and they are primarily used as a "leave on" treatment to reduce eczema symptoms."
6.	Table 1 - footnote - data for b and c are not shown, so either they should be added into the	Footnote "b" relates to the rows reporting number (%) female and number (%) white.

	table, or these footnotes deleted.	Footnote “c” has now been removed.
7.	Results - 'Participant retention' - 77% retention is ok, but over a 3-month period one might hope for slightly better than this, so I think the authors could be more critical of this outcome and discuss further how to optimise retention in this sort of study eg by focussing recruitment on self-referral.	We agree with this observation and have highlighted the differences between the recruitment pathways with the following additional sentence in the Discussion section: “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).” We suggest that researchers in future may choose to recruit using just the self-referral pathway in the final paragraph of the Discussion section also.
8.	Results - 'Adherence to intervention' - as mentioned above, this should be clearly presented as a disappointing outcome. Reasons for poor adherence need to be explored where data exist; and implications for future study design need to be discussed.	As discussed above, both the Abstract and Discussion sections have been significantly modified in the light of this and points 2 & 3.
9.	Results section final sentence - the infected eczema cases are of interest. Would data be available on these patients for the previous 3 months via GP records; and if so would it be worthwhile looking at those to explore whether the emollient intervention might have increased risk of an episode of infected eczema. This might be important hypothesis-generating information.	We do have more detailed information on the different types of adverse events (including skin infections) by emollient. However, by raising this point we now feel that this section is a distraction from the focus of this paper (on the feasibility of the trial itself) so for this reason, we have now removed it. We will present this information, along with other outcome data, in a “sister” paper.
10.	Discussion - how was emollient delivered in this study - and could that be used to monitor adherence to the study intervention in a future trial eg if all emollient is delivered to participant homes following an online order.	As detailed in the study protocol and protocol paper (Ridd et al Trials 2015; 16: 304 DOI: 10.1186/s13063-015-0830-y), all study emollients were prescribed for the duration of the study by the participant’s GP surgery and issued by High Street pharmacies. Neither the issuing of a prescription nor delivery of an emollient means the emollient is used, however. For this reason, we: 1) telephoned participants one week after randomisation to ensure safe receipt of the correct allocated treatment; 2) asked participants to record use, by participant diaries; and 3) collected prescription data, via participant’s electronic medical record. Detail of step 1 have been added to the section “Methods – Design, participants and interventions”.
11.	Discussion - how do the authors think that adherence and retention will be in a longer duration trial ie beyond 3 months of treatment?	While we suspect that a significant proportion of participants would be willing to take part in a trial with follow-up longer than 3 months, we have no data to support this and to say so would be extrapolating beyond the limits of the present study.
12.	It would be nice to see some clear conclusions about how a future trial might be designed - what would the primary outcome measure look like; is safety or efficacy/effectiveness the most important outcome, have you got signals from	The sections added in the Discussion section, in response to the earlier comments, mean that the following key lessons for a future definitive trial are identified: recruitment (and follow-up) of

	this study which push you towards one or the other? When the James Lind group formulated the key question about emollient choice, was there clear interest in emollient type as compared in this COMET study, or was there interest in specific brand names, or specific frequencies or methods of application for using emollient?	children with eczema to a trial of similar interventions is feasible, especially by the mail-out method (with search criteria modified to maximise the number of invitations being sent to children with active disease); medium-term data collection (including resource use and costs) via participant diaries is feasible but strategies to minimise "missing data" (using of online questionnaires and clear instructions for paper diary completion) are needed; researchers can be kept masked to the allocated treatment, for the purpose of collection of "objective" signs of eczema severity.
13.	There are quite a few minor typos and grammatical errors through the manuscript which would be worth a read-through to correct.	Thank you for pointing this out – we have re-proof read the manuscript and are now satisfied that it is error-free.

Reviewer 2

	Reviewer's comments	Authors' response
	"Major"	
1.	Primary outcome features clearly only in the abstract. It needs to be clearly stated in the methods and results as well. Secondary outcomes could also be presented more clearly in main body of manuscript	A paragraph has been added to the "Methods – Outcomes" section: "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 research assistants were kept masked to the intervention. Outcome data itself and other feedback will be presented elsewhere." The sub-headings in the "Results" section have been revised to clearly identify the outcomes relating to "Recruitment of practices and participants", "Retention of participants", "Collection and completeness of outcome data", "Adherence to intervention" and "Economic evaluation". We think the most logical way to present the findings is in this order, so the primary outcome is reported under "Adherence to intervention" and is now flagged as such.
2.	Results section, paragraph 2: Please clarify how participants were screened at each stage and make sure the figures correspond with those in the CONSORT flow chart.	Although the numbers in the text correctly tally with the originally presented CONSORT diagram, we have revised the flow chart to make it clearer.
3.	CONSORT flow chart: It says that 90 participants were consented in the GP/PN referral pathway but how many were approached?	Two sentences describing the practice searches (which identified 2552 contacts with potentially eligible children) and the clinician recruitment logs have been added to the "Methods – Design, participants and interventions" section and reporting of these findings clarified in "Results – Recruitment of participants: Recruitment by in-consultation pathway").
4.	Discussion needs a comment on the high use of non-study emollients and therefore the potential for contamination in the main trial.	Please see responses to Reviewer 1's similar comments (points 2, 3, & 8)

5.	Discussion Page 12 line 40. The problem with limiting invitations to those with a recent prescription is that they don't necessarily need to have been reviewed before having a repeat prescription and so might no longer have eczema	While it is true that patients in primary care do not necessarily need to be reviewed before receiving a repeat prescription, it is also unlikely that parents would continue to request treatment for their child's skin if the eczema was no longer active. In any future trial, disease status can be established through eligibility criteria, before consent is received and the child is randomised.
6.	Discussion page 13 line 6-19. The under-reporting of use of treatment is a significant issue. Please expand on what measures are going to be taken in the main trial to avoid this.	Please see the response to Reviewer 1's similar comment (point 2).
	"Minor"	
7.	I would change the term 'researcher masked' to 'observer masked' throughout the manuscript.	This has been done as requested.
8.	Page 5, line 5: Participants were not masked to emollient allocation either- please add this	This has been added as requested.
9.	Outcomes section: rather confusing to have a mixture of days and months in this section. Could it not all be expressed in 'weeks'?	As suggested, where possible we have changed it here (and elsewhere in the manuscript for consistency) from "3 months" to "12 weeks", but in some sections we think it still makes more sense to present findings in terms in days (i.e. where 84 days, not 12 weeks, is the denominator)
10.	You could comment that participants recruited in consultation were younger perhaps because their parents are less likely to have time to self-refer?	This is one of several possible reasons (for example, parents being less likely to consult with their older children – hence less likely to be invited; parents of/children with worse eczema suffering more distress/worry so being more likely to consult, and hence be recruited into the study via that pathway) so for this reason we have chosen not to speculate further.

VERSION 2 – REVIEW

REVIEWER	Robert Boyle Imperial College London, UK
REVIEW RETURNED	29-Jul-2016

GENERAL COMMENTS	The authors have addressed my comments well. There is one remaining minor issue, which may be a typo. The last sentence of the Abstract Conclusions reads 'However, reported use of emollients (study and others) has design implications for future trials'. I think the authors mean 'However, the low reported use of emollients (both study and others) has design implications for future trials.'

REVIEWER	Jonathan Batchelor University of Nottingham, UK
REVIEW RETURNED	19-Jul-2016

GENERAL COMMENTS	The authors have responded clearly and adequately to previous

	comments and have made suitable amendments to the manuscript.