BMJ - Decision on
Manuscript ID
BMJ.2017.042841

Body: 07-Feb-2018

Dear Dr. Santer

Manuscript ID BMJ.2017.042841 entitled "Emollient bath additives for the treatment of childhood eczema (BATHE): multi-centre pragmatic parallel group randomised controlled trial of clinical and cost-effectiveness"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

dr. Wim Weber
European editor, The BMJ
wweber@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (Chair), Julie Morris (Statistics advisor), Robin Baddeley, Sophie Cook, John Fletcher, José Merino, George Rőggla, Tiago Villanueva, Wim Weber.

Decision: Put points

Detailed comments from the meeting:

We thought your study addresses an interesting and potentially important research question.

We had the following concerns:

How often was the intervention used? 92% of parents said they used it "every time" but what does that mean? How often were the children bathed? With topical treatments we would expect daily or near-daily use is needed to obtain benefit, yet we could not find any description of how frequently baths were supposed to be taken. This seems a major limitation.

Conversely, are these additives available without prescription ? And could this have led to contamination, so that both group used these ?)

We are not sure bath emollients do not work, based on this trial, only that they don't work when baths are intermittent. At a minimum we think we need information about the frequency of bathing in each group and a discussion of this matter.

Likewise, as some reviewers point out, it remains possible additives are effective in some subgroups such as those with more severe disease. Yous need to defend pooling patients with varying degrees of disease severity.

We agree with reviewer who says we need a better description of what emollient bath additives are.

More information on how adverse events (AEs) were collected would be useful. It is unclear, from the AE table, how many individual participants experienced an AE. You report 44 slips, for example, but in how many people?

What does "pragmatic" mean? The patient reviewer makes a good point about this. Flow diagram says 265 were in the intervention group, but Table 1 says 264. Is this flow diagram up to Consort standards? You assert this is an ITT analysis but the flow diagram doesn't have explicit numbers for the final analysis, just reports how many filled out forms at various points. Can you add this information?

A very small proportion of eligible participants decided to participate in the trial. This doesn't seem a particularly burdensome study, so what is the reason for the reluctance? Is the trial population representative of the wider population of children with eczema or is there something unusual about those who agreed to participate? Can you comment?

We probably do not need an extended Cost-effectiveness analysis, when intervention was not effective.

There are differences in secondary outcomes as listed in the trial registry vs. protocol vs. paper.
Within the paper there are differences between the list on p. 6-7 and Tables 2-3.
See attached list.
Please reconcile.

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
Reviewer's comments
Manuscript ID BMJ.2017.042841, entitled "Emollient bath additives for the treatment of childhood eczema (BATHE): multi-centre pragmatic parallel group randomised controlled trial of clinical and cost-effectiveness."
Thank you for asking me to review this pragmatic RCT of 483 children with eczema that sought to answer whether or not bath emollients are effective across a range of outcomes. The Investigators are internationally recognized in primary care and dermatology research. As the authors state, this is an important study for a very common condition. Use of bath emollients is one three treatment strategies in primary care used for managing this condition, alongside use of topical emollients/steroids and soap substitutes. The results of this RCT have widespread implications for patients and clinicians managing childhood eczema. I do not have substantive concerns about the conduct, analysis and reporting of this RCT.
My additional comments are as follows:

- More detail and explanation about co-interventions- both groups continued standard eczema management- topical (leave on) emollients and steroids when required. Table 2 reports on TCS and TCI- I am unsure what TCI stands for (topical emollient). Was there a differential use of these co-interventions in the proportion of children using them during the course of the RCT? Did adjustment for topical emollient and/or steroid have any impact on the primary and/or secondary outcomes when measured as a continuous variable and/or categorical variable?
- Formatting issues- Table 1, last column is redundant; Figure 1, abbreviation for "BA" and "No BA" is needed.

Additional Questions:
Please enter your name: Tom Fahey

Job Title: Professor of General Practice

Institution: RCSI Medical School

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

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Reviewer: 2

Recommendation:

Comments:
This is a great paper. Great research questions and very well done by an experienced team. While the negative results are disappointing a having confidence in a negative result and this will mean that parents will no longer pursue this line of treatment. Eczema is a huge problem for children in NZ and the profession will welcome the findings of this study. This is a definite yes to being published and I hope the research group continues to answer pragmatic primary care research questions

Additional Questions:
Please enter your name: Bruce Arroll

Job Title: Professor of General Practice

Institution: University of Auckland

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 3

Recommendation:

Comments:
This is an interesting and well-written paper examining the difference in several eczema (outcome) parameters and cost-effectiveness between patients who used bath additives and those who did not, over the course of one year. The study was well-designed and had an appreciable number of participating and compliant subjects considering the duration of the study. There are a few points that came to mind during my reading that could potentially improve the manuscript:

1. Data from the 3 emollient bath additives in the study were pooled despite that they differ in composition. A few additional comments/information would be helpful to a reader interested in understanding the contribution of non-drug interventions in eczema management:
   a. Please provide the numbers of subjects that used the various bath additives,
   b. Provide a few words about the composition of each (Aveeno (oatmeal bath) varies significantly from Balneol).
   c. Assuming no between-treatment subanalysis of the various interventions was conducted (or possible?), please mention why. It's possible that there could be influences/differences related to composition, which should be at least mentioned in the discussion.
2. The manuscript mentions the range of possible scores for the POEM evaluation. However I could not find a similar range for the DFQI. The median values are fairly low at baseline and unchanged, but without the range the reader has no idea of how impacted the patients were.
3. The study included mostly patients with mild and moderate eczema, but also some with more severe eczema (POEM scores in Table 1). This begs the question as to whether there might be differences between those with low eczema impact, and those with a higher POEM scores. It might be worth commenting on this.
4. The cost-effectiveness is important and nicely evaluated and discussed in the manuscript. Besides a potential for cost savings, omitting bath additives could be a welcome simplification in bath-time for care-givers, who bear additional burdens caring for children with eczema – another possible benefit.
5. Under "What is already known on this subject" perhaps line 32 and 33 could be modified, e.g. "The efficacy of emollient bath additives for the treatment of childhood eczema has not been convincingly assessed due to a lack of adequately powered studies."
6. Under "What this study adds" statement seems to be missing a word: "This is a large…"

Also, page 8, line 37, should be "…additives with (not and) no difficulty"

Additional Questions:
Please enter your name: Teresa M Weber

Job Title: Director, US R&D

Institution: Beiersdorf Inc

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 4

Recommendation:

Comments:
Originality - does the work add enough to what is already in the published literature? If so, what does it add? If not, please cite relevant references. Yes, existing literature does not provide a clear definitive answer about whether bath additives have any benefits and are effective in managing childhood eczema. There is no reference for "widespread clinical consensus around soap substitutes... ", which weakens the argument.

* Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it? Childhood eczema is a common condition, and many children are affected by it. It causes discomfort and distress to children, and in extreme cases put children at risk of acquiring infections via open sores. For parents it is difficult and upsetting to see children in discomfort and pain. Most of these children will be taken to GPs for diagnosis and treatment, so the BMJ is the right journal to publish an article on this topic. The researchers have considered patient involvement and worked with the James Lind Alliance to ensure this. They have also considered how they will report back to parents.

* Scientific reliability
Research Question - clearly defined and appropriately answered? the question is clear and terms are defined. It thoroughly and appropriately answered.

Overall design of study - adequate ?The question is clearly defined - it is a randomised control trial with two groups. However, it is also described as a "Pragmatic randomised open-label superiority trial with two parallel groups" and referred to as pragmatic later in the text, which was confusing. Although, I have undertaken postgraduate study in research methods I was not completely clear how this differs from an RCT.

Participants studied - adequately described and their conditions defined? The selection criteria is clear: age, criteria for childhood eczema (UK diagnostic criteria) and exclusion criteria.

Methods - adequately described? Complies with relevant reporting

standard - Eg CONSORT for randomised trials ? Ethical ? Yes, very thoroughly described and CONSORT checklist has been completed. Research was approved by Ethics board, and further ethical approval sought when needed.

Results - answer the research question? Credible? Well presented? Yes, results answered the research question - data was well presented and described. I liked the inclusion of QALYs in the measures.

Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear? Yes, the interpretations are warranted and sufficiently derived from the data.

References - up to date and relevant? Any glaring omissions? References appear to contain current literature. As I am not an expert in the field I am unable to comment about omissions.

Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says? This is very clear and easy to read reflecting accurately what the paper says.

Additional Questions:
Please enter your name: Helen Castledine

Job Title: patient reviewer

Institution: n/a

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 5

Recommendation:

Comments:
This RCT assesses the clinical benefit of using emollient bath additives in the management of childhood eczema. The overall statistical analysis approach (multilevel modelling) is appropriate, but there are a number of issues relating to the design methodology and the primary outcome which need to be addressed.

1. The percentage of parents/carers who responded to the study invite was quite small (7%). Hence the study sample is select group of 'positive healthcare' families. This should be acknowledged.

2. The sample size statement relates to a repeated measures ANOVA, but insufficient information is given to be able to replicate the power calculation. More details should be provided about, for example, the assumed within and between subject variability.

3. The disparity in the randomised group sizes (218 vs 264) seems rather large. Was a blocked randomisation method not used?

4. Exactly how were missing values dealt with in the statistical analysis?

5. What was the frequency of use of the bath emollient? Adherence to using the emollient (every bath time) is not necessarily a good indicator of the effective use of the emollient if not all parents are bathing their child every day. It would seem more appropriate to measure frequency of use (every day, every two days?) and carry out a sensitivity analysis which takes account of this factor.

6. Insufficient details of the economic analysis are reported. Perhaps this could be omitted from the paper?

Additional Questions:
Please enter your name: Julie Morris

Job Title: Head of Medical Statistics

Institution: UHSM

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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