PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for an outcome assessor-blinded pilot randomised controlled trial of an ion-exchange water softener for the prevention of atopic eczema in neonates, with an embedded mechanistic study: The SOFtened waTER for eczema prevention trial (SOFTER)
AUTHORS	Jabbar-Lopez, Zarif; Gurung, Nikeeta; Greenblatt, Danielle; Briley, Annette; Chalmers, Joanne; Thomas, Kim; Frost, Tony; Kezic, S; Common, John; Kong, Heidi; Segre, Julie; Danby, Simon; Cork, Michael; Peacock, Janet; Flohr, Carsten

VERSION 1 – REVIEW

REVIEWER	Adrian Lowe Allergy and Lung Health Unit. University of Melbourne I have corresponded with K Thomas to discuss the possibility of visiting her unit to explore collaborations in the future. I have also corresponded with J Common to seek advice on infant skin biome sampling protocols. I have not published with either author and do not hold any grants.
REVIEW RETURNED	18-Oct-2018

GENERAL COMMENTS	Jabbar-Lopez and colleagues describe the pilot trial of their intervention study to use an ion exchange water softener for the prevention of eczema in children who live in areas where the domestic water supply is hard (>250 mg/L of calcium carbonate). The work is of interest and builds on the observational data suggesting a relationship between water hardness and incidence of eczema in a number of studies. While the study is of limited scope (80 infants to be recruited), it will provide valuable information for the conduct of the planned clinical trial. Major comments 1. The “article summary” section is somewhat disconnected with the rest of the manuscript, as the primary outcome for this study (as opposed to the future clinical trial testing efficacy of the intervention) is the proportion of eligible families who enrol, which is not “outcome-assessor blinded”. This study also does not “address a gap in research around the primary prevention of atopic eczema”, but rather explores the key logistical issues in undertaking a trial that will address this gap, including recruitment fraction, frequency of cross-over events etc. I suggest that this section be re-written in light of what the strengths and limitations of this specific pilot trial are. 2. Please clarify and make a clear statement concerning the role of Harvey Water Softeners Ltd in the design, conduct and interpretation of the study results.

	3. Please consider raising the importance of the secondary outcome of families who are randomised, but who are eventually ineligible (pre-term or significant skin or health issues). For the full trial, these will be post randomisation losses, and should, if possible, be included in the final analyses. Exclusion of these children will potentially create the largest study design challenge for avoiding bias in the main study. In contrast, the proportion of eligible families willing to be enrolled simply will inform recruitment timeframe and resources required, rather than undermine the internal validity of the study. 4. The investigators are going to some lengths to avoid intervention families from using the soft water as the source of drinking water. Could you please clarify why this is the case? Is it due to concern that the intervention may cause excess sodium intake, or lack of dietary minerals? The rationale for making this purely a bathing water intervention needs to be made clear. 5. Related to this, a description of where, in the water supply line, the water softeners are to be installed is required. That is, are all potential outlets going to be running softened, other than the kitchen tap? 6. I suggest adding a clear statement that the causes for incidence of eczema are not necessarily the same as those for exacerbations/severity of eczema, so the negative results in treatment trials does no exclude a role for water softeners in prevention trials. 7. Please provide greater detail as to how the sample size of 80 was determined. A 50% uptake rate with 80% will give a 95%CI with a span of ~22% points rather than 10. Minor points: 1. Please clarify what is meant by the phrase “given a favourable opinion” for the ethics committee. Has the project been approved at this time, or is it still working through the review process? 2. Can you provide a value in mg/L for what a 5 unit “German degrees of hardness” means? Is it per 50 mg/L increase? 3. Citation details for ref 9 need to be updated. 4. There is lot of repetition for the description of the study visits, particularly the mechanistic assessments. I suggest you could revise to “as per baseline and …” 5. For the main trial, I suggest you use a secure computerised package for randomisation. We are using RedCap for our trials and it is working well.

REVIEWER	Lone Skov Dept of Skin and Allergy Herlev and Gentofte Hospital Copenhagen, Denmark Atopic dermatitis is part of my field of research but I have no studies in relation to this study
REVIEW RETURNED	22-Oct-2018

GENERAL COMMENTS	I my view it is a well-planned and important study

REVIEWER	Julian Crane University of Otago, Wellington
REVIEW RETURNED	22-Nov-2018

GENERAL COMMENTS	Review BMJ-Open-2018-027168

	This is a carefully considered protocol for a pilot study plus a mechanistic eczema evaluation (n=80) to inform a larger multicentre RCT of in-home water softening in a group of infants at high family risk of developing eczema. The authors already have considerable experience of observational studies of the association between water hardness and eczema and with a soft water eczema treatment trial of short duration amongst children with established eczema. The pilot trial has been in the field since Feb 2018 and will complete at the end of Spring 2019. Despite the editorial instructions to reviewers of protocols it is somewhat difficult to refrain from discussing issues that now clearly cannot be altered at least for the pilot – otherwise it doesn't leave very much to say! Issues that come to mind in no special order: 1. I am quite surprised to see a pilot study (albeit with a mechanistic add-on) submitted for publication though I note views on this are mixed. Presumably the full protocol will also be published. 2. No power calculations are given for the mechanistic add-ons. They would be helpful and is 40 in each group realistic for any of them? In fact presumably it will be less than 40/group given that some assessments are only being undertaken at Guy's and Thomas' hospital site. How many other sites are there? 3. The primary outcome of this pilot is the proportion of eligible families screened who are willing and able to be randomised. Would this not have bene best done by discussion and theoretical agreement – it would have been much cheaper. The 'able' part of the question is already answered from SWET – 27% (this seems rather large proportion and are they more likely to be in lower SES groups? The authors also have a pretty good idea of willingness to participate from EAT and BEEP, 40-60% of 70%. What will prospective families be told? That they can halve their risk by intensive use of moisturisers from birth? That some evidence suggests they can halve their risk by taking certain strains of probiotics? Presumably those that plan to do either will be excluded? The Association of British Dermatologists suggests that regular moisturisers can help prevent the development of eczema and many other groups suggest it especially for high risk infants. While I appreciate there is a large national study underway we would seem to be close to a lack of equipoise here in terms of advice. Presumably if that study confirms the many smaller ones it will be important to include this treatment in any future study. 4. At face value one would have thought that it might be quite straightforward to blind participants to the intervention – plumbing but no salt. The authors have tried this and in their Health Technology Assessment report of SWET (2011) of the intervention trial they do mention the difficulty

	in that participants can easily tell in terms of water feel, lather and soap use. But is that the only difference – does it taste or smell very different and they will still be drinking hard water. Given that those with the water softening will either change soaps/detergents or use much less – how will this be disentangled from the water hardness per se? Will both groups be advised not to use any soaps? 5. Similarly in SWET they mention the difficulty of measuring chlorine – yet they have shown this to be important. Is it really that difficult to measure just because it is volatile? Can they assume it is pretty constant over time in all water supplies? 6. Participants will likely Google Harvey Water Softeners where they will be informed that they will get '7 wonders' from softened water including a view that "Research has proved what all of us here at Harvey have known for years; that when it comes to alleviating chronic skin conditions such as eczema, softened water can make all the difference". They also mention that eczema can be caused by hard water and that softened water can lower the risk of eczema developing in the first place. 7. Should the plumbing be done earlier in pregnancy so that the family gets used to it before the baby arrives? 8. I note that both groups can purchase the water softener at a discount, I would hope this is pretty generous especially for the non-intervention group who seem to be doing a lot for the study for little in return and the company already seems to be benefiting from their involvement. Having made these comments (which of course are much easier than developing the protocol) this is in general a very well thought out protocol for a pilot study based on a lot of previous experience and this group would have more expertise in this area than anyone else.

VERSION 1 – AUTHOR RESPONSE

Reviewer Comments to Author:

Reviewer: 1
Comment 1:
"Jabbar-Lopez and colleagues describe the pilot trial of their intervention study to use an ion exchange water softener for the prevention of eczema in children who live in areas where the domestic water supply is hard (>250 mg/L of calcium carbonate). The work is of interest and builds on the observational data suggesting a relationship between water hardness and incidence of eczema in a number of studies. While the study is of limited scope (80 infants to be recruited), it will provide valuable information for the conduct of the planned clinical trial."

Response: Thank you.

Comment 2:
“The “article summary” section is somewhat disconnected with the rest of the manuscript, as the primary outcome for this study (as opposed to the future clinical trial testing efficacy of the intervention) is the proportion of eligible families who enrol, which is not “outcome-assessor blinded”. This study also does not “address a gap in research around the primary prevention of atopic eczema”, but rather explores the key logistical issues in undertaking a trial that will address this gap, including recruitment fraction, frequency of cross-over events etc. I suggest that this section be re-written in light of what the strengths and limitations of this specific pilot trial are.”
Response:
This is a good point and we thank the reviewer for highlighting this disconnect. We have re-written the section to focus specifically on the strengths and limitations of the pilot trial, rather than the definitive study, as per the response above to the Editor’s comment. We appreciate the point regarding ‘outcome-assessor blinded’. Whilst it is correct that the primary outcome of the pilot is not outcome-assessor blinded, secondary outcomes considered in the study are outcome-assessor blinded and we feel that this description is appropriate as we are piloting an outcome-assessor blinded trial design.”

Comment 3:
“Please clarify and make a clear statement concerning the role of Harvey Water Softeners Ltd in the design, conduct and interpretation of the study results.”
Response:
We have added the following statement to the Competing Interests Statement:
“Harvey Water Softeners contributed to the design and operational running of the study (supply and installation of water softeners, testing of water samples). Final decisions around design and conduct were made independently by investigators. HWS will not be involved in the analysis or interpretation of the results.”

Comment 4:
“Please consider raising the importance of the secondary outcome of families who are randomised, but who are eventually ineligible (pre-term or significant skin or health issues). For the full trial, these will be post randomisation losses, and should, if possible, be included in the final analyses. Exclusion of these children will potentially create the largest study design challenge for avoiding bias in the main study. In contrast, the proportion of eligible families willing to be enrolled simply will inform recruitment timeframe and resources required, rather than undermine the internal validity of the study.”
Response:
We completely agree that post-randomisation losses are an important source of bias in any trial. The secondary outcomes are not intended to be listed hierarchically. Whilst we do not have a catch-all secondary outcome for post-randomisation losses, we have included the specific reasons for post-randomisation drop out that we consider important, for example families randomised that withdraw due to infant eligibility.

Comment 5:
“The investigators are going to some lengths to avoid intervention families from using the soft water as the source of drinking water. Could you please clarify why this is the case? Is it due to concern that the intervention may cause excess sodium intake, or lack of dietary minerals? The rationale for making this purely a bathing water intervention needs to be made clear.”
Response:
The reviewer is correct. We have designed the study so that families will not use the water as a source of drinking water. This is because of the risk of excess sodium intake if newborn babies were to receive formula prepared with softened water that could potentially exceed the recommended

sodium intake limits set in the UK by the Department of Health. There is also a possible effect on cardiovascular health of household members through removal of magnesium from drinking water. Therefore, out of an abundance of caution, we felt that it would be safest to require families to have a hard domestic drinking water source available. This is not purely for bathing, as the softened water would be available for washing clothes and other household uses.

Comment 6:
“Related to this, a description of where, in the water supply line, the water softeners are to be installed is required. That is, are all potential outlets going to be running softened, other than the kitchen tap?”
Response:
Yes, all potential outlets other than the kitchen tap. This point has been clarified in the manuscript (page 9): “Standard procedure will be to soften all water in the home except the drinking water tap. Unsoftened mains drinking water will be delivered through the existing kitchen tap wherever possible, or otherwise through an extra (faucet-style) tap installed at the side of the kitchen sink.”

Comment 7:
“I suggest adding a clear statement that the causes for incidence of eczema are not necessarily the same as those for exacerbations/severity of eczema, so the negative results in treatment trials does no exclude a role for water softeners in prevention trials.”
Response:
We agree with this point and have made it clearer in the text on page 6.

Comment 8:
“Please provide greater detail as to how the sample size of 80 was determined. A 50% uptake rate with 80% will give a 95%CI with a span of ~22% points rather than 10.”
Response:
We anticipated uptake of around 65% and so with 80 subjects this would be estimated +/- 10 percentage points. This is what we meant by saying ‘within 10 percentage points’.

Comment 9:
“Please clarify what is meant by the phrase “given a favourable opinion” for the ethics committee. Has the project been approved at this time, or is it still working through the review process?”
Response:
This is standard phrasing used in the UK and means that the study has been ‘approved’.

Comment 10:
“Can you provide a value in mg/L for what a 5 unit “German degrees of hardness” means? Is it per 50 mg/L increase?”
Response:
The following clarification has been added on page 5:
“…for each 5 unit increase in domestic water hardness (equivalent to 89.2 mg/L calcium carbonate) over a range of 6.60-35.90 German degrees of hardness [118-641 mg/L calcium carbonate]).”

Comment 11:
“Citation details for ref 9 need to be updated.”
Response:
This has been updated.

Comment 12:
“There is lot of repetition for the description of the study visits, particularly the mechanistic assessments. I suggest you could revise to “as per baseline and …”
Response:

This is a good suggestion, and we have updated the study visit descriptions accordingly.

Comment 13:
“For the main trial, I suggest you use a secure computerised package for randomisation. We are using RedCap for our trials, and it is working well.”
Response:
We are using an FDA-compliant validated database, Medscinet, which is available within our institution.

Reviewer: 2

Comment 1:
“I my view it is a well-planned and important study.”
Response:
Thank you.

Reviewer: 3

Comment 1:
“I am quite surprised to see a pilot study (albeit with a mechanistic add-on) submitted for publication though I note views on this are mixed. Presumably the full protocol will also be published.”
Response:
We hope that the pilot study protocol will be of interest to readers. This abridged summary of the protocol provides readers with the scientifically relevant sections of the pilot study.

Comment 2:
“No power calculations are given for the mechanistic add-ons. They would be helpful and is 40 in each group realistic for any of them? In fact presumably it will be less than 40/group given that some assessments are only being undertaken at Guy’s and Thomas’ hospital site. How many other sites are there?
Response:
No formal power calculations have been performed for the mechanistic add-ons, however, this sample size is larger than those typically seen in other studies of mechanistic aspects of atopic eczema.

Comment 3:
“The primary outcome of this pilot is the proportion of eligible families screened who are willing and able to be randomised. Would this not have bene best done by discussion and theoretical agreement – it would have been much cheaper. The ‘able’ part of the question is already answered from SWET – 27% (this seems rather large proportion and are they more likely to be in lower SES groups? The authors also have a pretty good idea of willingness to participate from EAT and BEEP, 40-60% of 70%. What will prospective families be told? That they can halve their risk by intensive use of moisturisers from birth? That some evidence suggests they can halve their risk by taking certain strains of probiotics? Presumably those that plan to do either will be excluded? The Association of British Dermatologists suggests that regular moisturisers can help prevent the development of eczema and many other groups suggest it especially for high risk infants. While I appreciate there is a large national study underway we would seem to be close to a lack of equipoise here in terms of

advice. Presumably if that study confirms the many smaller ones it will be important to include this treatment in any future study."
Response:
We agree that the highlighted studies all provide useful insights into potential recruitment metrics, however, in designing the study we felt that there were sufficient differences that meant a pilot would be useful. Of course, if the pilot is a success and there is no need for modification of the protocol then we could consider going directly to a definitive trial (i.e. an internal pilot). In terms of information provided to participants around skincare, we discussed this extensively and felt that at present there is still equipoise around the role of moisturisers and/or probiotics for primary prevention of atopic eczema. We appreciate that further studies may change the weight of evidence in the future and we will, of course, consider this in the design of the definitive trial.

Comment 4:
"At face value one would have thought that it might be quite straightforward to blind participants to the intervention – plumbing but no salt. The authors have tried this and in their Health Technology Assessment report of SWET (2011) of the intervention trial they do mention the difficulty in that participants can easily tell in terms of water feel, lather and soap use. But is that the only difference – does it taste or smell very different and they will still be drinking hard water. Given that those with the water softening will either change soaps/detergents or use much less – how will this be disentangled from the water hardness per se? Will both groups be advised not to use any soaps?"
Response:
The difference in the 'feel' of the water and the effect on wash products are the reasons that blinding is not likely to be effective. Hard water tastes different from softened water. We decided not to give participants any specific skincare advice and so there will be a mixture of approaches that are adopted by participants. We will collect detailed data on a monthly basis of soap and detergent use to evaluate this further.

Comment 5:
Similarly, in SWET they mention the difficulty of measuring chlorine – yet they have shown this to be important. Is it really that difficult to measure just because it is volatile? Can they assume it is pretty constant over time in all water supplies?"
Response:
The role of chlorine co-exposure with hard water remains unclear, however, recent experimental work by our group (Danby et al. J Invest Dermatol 2017) suggests that the additional role of chlorine at levels likely to be encountered in drinking water on skin irritation is less than previously thought.

Comment 6:
"Participants will likely Google Harvey Water Softeners where they will be informed that they will get '7 wonders' from softened water including a view that "Research has proved what all of us here at Harvey have known for years; that when it comes to alleviating chronic skin conditions such as eczema, softened water can make all the difference". They also mention that eczema can be caused by hard water and that softened water can lower the risk of eczema developing in the first place."
Response:
We agree that this is an important point for participants in the study. As Harvey Water Softeners is a separate company we cannot directly control what is placed on their website. We will direct participants to the information within the approved study participant information sheet.

Comment 7:
"Should the plumbing be done earlier in pregnancy so that the family gets used to it before the baby arrives?"
Response:

With the current design pregnant women can be enrolled at any point following an anomaly scan, which is usually performed around 21 weeks gestation up until late in the third trimester. Accordingly, some women will potentially have several months with the softener prior to giving birth and others may just have a few weeks. We felt that it would be best to avoid enrolment in the first trimester because of the higher risk of pregnancy complications in the early stages of pregnancy.

Comment 8:
"I note that both groups can purchase the water softener at a discount, I would hope this is pretty generous especially for the non-intervention group who seem to be doing a lot for the study for little in return and the company already seems to be benefiting from their involvement."
Response:
We have added further details on the level of the discount offered on page 9:
"At the end of the study, all participants will be given the option to purchase the water softener from Harvey Water Softeners Ltd. at a reduced price of £399.00 inclusive of VAT, installation and warranty; this is approximately a quarter of the full retail price £1,678.80)."

Comment 9:
"Having made these comments (which of course are much easier than developing the protocol) this is in general a very well thought out protocol for a pilot study based on a lot of previous experience and this group would have more expertise in this area than anyone else."
Response:
Thank you.

VERSION 2 – REVIEW

REVIEWER	Adrian Lowe University of Melbourne, Australia I have joined a consortium (lead by Bob Boyle from Imperial College London), to conduct an individual patient data on the impact of skin barrier interventions for the prevention of eczema and food allergy. I have become aware that Carsten Flohr is also part of this consortium. I have not had any direct contact or communications with Prof Flohr to date. I have also met John Common at a conference in 2017 in Portland (USA). We have discussed potential collaborations, and he has shared his protocol for collecting skin microbiome with me, which we are using within one of our projects. We intend to collaborate on the analyses of these data in future. To date, we have not published together or hold any grant funds together.
REVIEW RETURNED	06-Jun-2019

GENERAL COMMENTS	Thank you for your responses to my comments. Most of the issues I have raised have been adequately addressed. 1. For the statement in the article summary, I suggest that it be stated which outcomes will be measured in a blinded fashion, or that this statement be removed. 2. I recommend that a brief sentence be added to indicate that the softened water is not for drinking, and the reasons that this is the case. For the "naive" reader (including myself to be honest), it took some thinking to understand why drinking softened water may be problematic.

REVIEWER	Julian Crane

	University of Otago NZ
REVIEW RETURNED	07-Jun-2019

GENERAL COMMENTS	I am happy with authors responses to my queries

VERSION 2 – AUTHOR RESPONSE

Comment 1:

"For the statement in the article summary, I suggest that it be stated which outcomes will be measured in a blinded fashion, or that this statement be removed."

Response: We are unfortunately at the word limit for the summary. However, we already state on page 11: "Skin examinations and measurements will be performed by research team members who will be blinded to treatment allocation." All skin examinations and measurements are conducted in a blinded fashion, as our team is not aware of which study arm the participants are in.

Comment 2:

"I recommend that a brief sentence be added to indicate that the softened water is not for drinking, and the reasons that this is the case. For the "naive" reader (including myself to be honest), it took some thinking to understand why drinking softened water may be problematic."

Response: This has been done.

We now explain on page 8, lines 3-4:

"Standard procedure will be to soften all water in the home except the drinking water tap, as the water softening process exchanges calcium with sodium ions and will therefore increase the water sodium concentration, making the water unsuitable for drinking purposes."