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ORIGINAL ARTICLE

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Randomized controlled pilot trial with ion-exchange water softeners to prevent eczema (SOFTER trial)

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Abstract

Background: Observational studies suggest an increased risk of eczema in children living in hard versus soft water areas, and there is, therefore, an interest in knowing whether softening water may prevent eczema. We evaluated the feasibility of a parallel-group assessor-blinded pilot randomized controlled trial to test whether installing a domestic ion-exchange water softener before birth in hard water areas reduces the risk of eczema in infants with a family history of atopy.

Methods: Pregnant women living in hard water areas (>250 mg/L calcium carbonate) in and around London UK, were randomized 1:1 antenatally to either have an ion-exchange water softener installed in their home or not (ie to continue to receive usual domestic hard water). Infants were assessed at birth and followed up for 6 months. The main end-points were around feasibility, the primary end-point being the proportion of eligible families screened who were willing and able to be randomized. Clinical end-points were evaluated including frequency of parent-reported doctor-diagnosed eczema and visible eczema on skin examination. Descriptive analyses were conducted, and no statistical testing was performed as this was a pilot study.

Results: One hundred and forty-nine families screened were eligible antenatally and 28% (41/149) could not have a water softener installed due to technical reasons or lack

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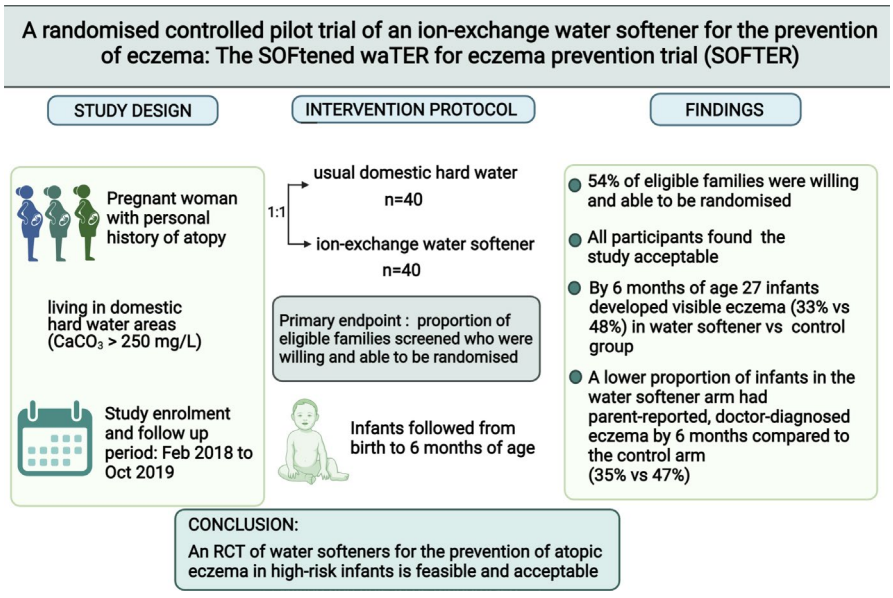
Trial registration number: NCT03270566

of landlord approval. Eighty of 149 (54%) were randomized, the primary end-point. Two participants withdrew immediately after randomization, leaving 39 participants in each arm (78 total). Attrition was 15% (12/78) by 6 months postpartum. All respondents ($n = 69$) to the study acceptability questionnaire reported that the study was acceptable. Fifty-six of 708 (7.9%) water samples in the water softener arm were above the hard water threshold of 20 mg/L $CaCO_3$. At 6 months of age 27/67 infants (40%) developed visible eczema, 12/36 (33%) vs. 15/31 (48%) in the water softener and control groups, respectively, difference −15% (95% CI −38, 8.3%), with most assessments (≥96%) remaining blinded. Similarly, a lower proportion of infants in the water softener arm had parent-reported, doctor-diagnosed eczema by 6 months compared to the control arm, 6/17 (35%) versus 9/19 (47%), difference −12% (95% CI −44, 20%).

Conclusion: A randomized controlled trial of water softeners for the prevention of atopic eczema in high-risk infants is feasible and acceptable.

KEYWORDS
atopic eczema, hard water, prevention trial, water softener



GRAPHICAL ABSTRACT

In the SOFTER trial, approximately half of eligible families were willing and able to be randomized to a water softener. There were less infants that had visible or parent-reported doctor-diagnosed eczema in the water softener group in comparison with the control group, which had their usual hard domestic water supply. Lastly, this pilot trial showed that a trial of water softeners for preventing eczema in high-risk infants is feasible and acceptable.

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1 | INTRODUCTION

Eczema (syn. atopic eczema, atopic dermatitis) is a common inflammatory skin condition affecting around 20% of UK children.[1] It is associated with significant morbidity and affects health-related quality of life. The cause of eczema is not fully understood. It is likely to be multifactorial, and several genetic and environmental factors have been identified.[2] No primary prevention strategy has been established.[3] However, several approaches have been proposed such as probiotics during pregnancy, dietary

Key Messages

- Approximately half of the eligible families were willing and able to be randomized.
- Less infants in the water softener arm developed a visible eczema or parent-reported doctor-diagnosed eczema.
- An RCT of water softeners for preventing eczema in high-risk infants is feasible and acceptable.

supplementation, house dust mite avoidance, intensive emollient use and domestic water softening.[4]

Hard water is the result of dissolved minerals, mainly calcium carbonate and magnesium carbonate, from the percolation of water through rock in the environment. England, especially the south, has very hard (>250 mg/L calcium carbonate) domestic water. A cross-sectional study conducted in the 1990s found that primary school-aged children living in hard water areas had an increased risk of eczema, compared to children living in softer water areas around Nottingham, UK.[5] Two further cross-sectional studies amongst school children conducted in Japan and Spain confirmed this association.[6,7] Subsequently, a cross-sectional analysis from a cohort study amongst over 1300 infants in England and Wales has also confirmed this relationship in early life, even after adjusting for likely confounders.[8] The same study suggested a possible interaction with loss-of-function mutations in the skin barrier gene, filaggrin (*FLG*). Most recently, a large study from a Danish birth cohort found a 5% increase in the prevalence of eczema within the first 18 months of life for each 5 unit increase in domestic water hardness (equivalent to 89.2 mg/L calcium carbonate)[9] over a range of 6.60–35.90 German degrees of hardness [118–641 mg/L calcium carbonate]).[10]

Several potential mechanisms have been proposed for how hard water may lead to eczema development: increased deposition of detergents such as sodium lauryl sulphate (SLS) on the skin, altered calcium signalling in the epidermis, and a rise in skin surface pH, resulting in increased protease activity could all have a detrimental effect on skin barrier function.[8] Experimental work has demonstrated an increased deposition of SLS in skin washed with hard water versus softened water.[11] In animal studies using a hairless mouse model, low extracellular concentrations of calcium ions in the upper epidermis led to exocytosis of lamellar bodies, required for skin barrier repair, independent of skin barrier disruption.[12]

Eczema is associated with a preponderance of *Staphylococcus aureus* and a reduction in microbial diversity.[13] Recent work has identified a synergistic relationship between the human cathelicidin-related antimicrobial peptide LL-37 and antimicrobial peptides produced by coagulase-negative staphylococcal species that selectively kill *Staphylococcus aureus*.[14] Human LL-37 activity against some bacterial species is decreased by the presence of calcium, but not magnesium, ions.[15]

The multi-centre Softened Water Eczema Trial (SWET), completed in 2011, examined the role of water softeners in treating children with established, moderate-to-severe eczema and found no overall benefit in terms of eczema severity reduction.[16] Early life is likely to be an important time in the development of eczema, particularly as most eczema develops before 2 years of age. Early interactions between genes and the environment may be crucial in instigating the cycle of inflammation and skin barrier dysfunction seen in eczema. Indeed, skin barrier dysfunction in early infancy, as measured by transepidermal water loss, is a predictor of subsequent eczema risk.[17,18] A small pilot randomized controlled double-blind crossover trial of 12 patients aged 3–6 years with mild-moderate eczema compared ultra-pure soft water to tap water. After 6 weeks, no statistically significant differences in eczema area severity index (EASI) or transepidermal water loss (TEWL) were observed between the groups, although there was a statistically significant improvement in pruritus as measured by visual analogue score.[19] To date, there are no studies examining the role of water softeners in the prevention of eczema.[20]

The overall rationale was that by installing a domestic water softener around the time of birth, the infant would be exposed to softened water rather than hard water for bathing and that this would be less irritating to the skin than hard water and so associated with a lower risk of eczema development. Such a study would require a large number of participants and before embarking on this it was important to determine whether the planned trial recruitment and assessment procedures are possible and workable, or whether they required adapting or changing.[21]

This pilot trial built on the experience gained from the SWET trial[16] and a trial of emollients in early life (Barrier Enhancement for Eczema Prevention; BEEP).[22] It was a 'version of the main study that is run in miniature to test whether the components of the main study can all work together' (UK National Institute for Health Research[23]). The objective of this pilot trial was, therefore, to determine the feasibility of undertaking a large-scale definitive trial on eczema prevention using a domestic water softener. The trial was not designed or powered to definitively answer the question of whether the installation of a domestic water softener prevents eczema.

2 | MATERIALS & METHODS

2.1 | Study design

This was a multi-centre parallel-group assessor-blinded randomized (1:1) controlled pilot trial of an ion-exchange water softener for the prevention of eczema in neonates at high risk of developing eczema, with an embedded mechanistic study.

2.2 | Participants

The study recruited pregnant women living in hard water areas ($CaCO_3$ >250 mg/L) identified from antenatal services at two public hospitals in London, UK: a teaching hospital with secondary and tertiary care maternity services located in urban central London; and a community hospital with secondary care maternity services serving a mixed urban and rural area in south-west London. Participants were recruited between February 2018 and October 2019. Participants with a domestic water softener already installed were not eligible. Infants needed to be born at term (≥37 weeks' gestation) and have a parent or sibling with a history of doctor-diagnosed atopy (eczema, asthma or hay fever) and were excluded if they had a significant inflammatory skin disease at birth that would make the detection and assessment of eczema difficult, or any other serious health issue that would interfere with their ability to participate in the study.

2.3 | Intervention

Pregnant women in the intervention arm had a domestic ion-exchange water softener (model HV3, Harvey Water Softeners, Woking, UK) (Figure 1) installed at their usual place of residence after enrolment and before the child's birth. Ion-exchange water softeners exchange calcium and magnesium, amongst other divalent cations, for monovalent sodium cations, typically reducing downstream water hardness to close to zero. The sodium ions come from common salt that needs to be topped up every 3–4 weeks. Standard procedure was to soften all water in the home except the drinking water tap to avoid the risk of excessive sodium in the drinking water being used for infant feed preparation. Unsoftened main drinking water was to 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. At the end of the study, all participants were given the option to purchase the water softener from Harvey Water Softeners Ltd. at a reduced price or have it removed (if in the intervention arm). The control group had no water softener installed and continued to receive their usual domestic hard water supply. There were no restrictions on the use of concomitant treatment or skincare products for the infant.

2.4 | Primary and secondary outcomes

The primary purpose of this study was to determine the feasibility and acceptability of installing a water softener prior to birth of the baby to inform the design of a definitive multi-centre prevention RCT. The primary end-point was the proportion of eligible families screened who were willing and able to be randomized. Secondary feasibility outcomes (proportions, unless stated) were: pregnant women approached who agreed to be screened; families eligible on screening that could not have a water softener installed (eg due to landlord or local authority refusal, technical (plumbing) reasons); families randomized that withdrew due to infant ineligibility; families in intervention arm who found the intervention acceptable; participants in the control arm who became exposed to softened water (eg by moving to a new home in a soft water area, or moving to a home with an active water softener installed, before the end of follow-up); participants that had the water softening unit removed or disabled prior to end of follow-up; participants with one or more home water samples with hardness >20 mg/L calcium carbonate in the intervention arm; participants who withdrew from the trial prior to end of follow-up; median number of nights spent away from the participant's main home during follow-up; clinical outcome assessments that remained blinded at 4 weeks, 3 and 6 months.

FIGURE 1 Image of a water softener

Secondary clinical outcomes: participants with visible eczema status (yes/no) recorded at each time point (baseline, 4 weeks, 3 and 6 months); proportion with patient-reported, doctor-diagnosed atopic eczema by 6 months of age; proportion with visible eczema according to the UK diagnostic criteria-based photographic protocol for visible flexural dermatitis[24] (4 weeks, 3 and 6 months); severity of eczema (if present) assessed using the Eczema Area and Severity Index (EASI; 4 weeks, 3 and 6 months); patient-reported eczema symptoms (Patient-Orientated Eczema Measure – POEM) score, monthly from 4 weeks to 6 months. Time to onset of patient-reported doctor-diagnosed eczema.

Skin hydration, TEWL and skin surface pH were measured on the volar forearm. Skin hydration was measured using a CM 825 Corneometer (Courage and Khazaka electronic GmbH,). TEWL was measured using an AquaFlux AF200 condensing chamber probe (Biox Systems Ltd,). Skin surface pH was measured using a PH905 Skin-Surface-pH probe fitted with a Mettler and Toledo flat surface electrode (Courage and Khazaka electronic GmbH,). Additional mechanistic outcomes were also evaluated in a sub-study and the analyses of these will be reported separately.

2.5 | Visit schedule, randomization and blinding

Participants were randomized antenatally at the time of the engineer home visit to receive either a water softener or not, once:

- Antenatal eligibility criteria had been fulfilled;
- Fully informed written consent had been provided; and
- The engineer was satisfied that the softener could technically be installed.

The independent online randomization service was provided by Guy's and St Thomas' Biomedical Research Centre (BRC) and used the MedSciNet database system. When a patient was recruited, an independent BRC administrator who was not involved in patient assessment, obtained the allocation from the online system. This information was relayed by telephone to the water softener installation engineer so they knew whether to install a softener or not in that participant's home. The randomization sequence was designed to allocate equally, that is, 1:1 and with randomly permuted blocks to prevent the research team guessing the next allocation whilst providing balance in numbers in the two arms.

Experience from the SWET trial has shown that the effects of a functional water softener are too noticeable to allow participants

to be blinded.[16] Skin examinations and measurements were performed by research team members who were blinded to treatment allocation. Participants were encouraged not to disclose allocation. Study team members in direct contact with study participants were trained on the study protocol and the importance of demonstrating equipoise.

An enrolment visit occurred up until 36 weeks gestation to allow time for the home installation visit. Eligibility was confirmed at this visit. The water softener engineer's home visit occurred up until 40 weeks gestation to check the home's suitability for water softener installation. If the home was deemed suitable, the engineer telephoned the central randomization service to determine the allocated randomization group. If the participant was randomized to the water softener arm, the engineer proceeded to install the water softener and provide water sampling materials.

The baseline visit occurred within 1 week of birth. After confirming infant eligibility criteria and postnatal consent, birth details and health status were collected and then neonates had a skin examination to look for visible flexural dermatitis.

Infants were followed up for up to 6 months from birth with similar assessments performed at 1, 3 and 6-month visits. Participants who completed the study were asked to complete a short acceptability questionnaire. Also, monthly from the birth of the child, a secure web-based questionnaire link using the Snap Surveys platform (Snap Surveys) was emailed to mothers to determine whether the child had received a diagnosis of eczema from a healthcare professional and to check current skincare, hygiene, confirm residence/time away from the main residence and the infant's general health.

2.6 | Approvals and registration

This study was given a favourable ethics opinion by the North West—Liverpool East Research Ethics Committee (Ref: 17/NW/0661). The trial was registered at Clinicaltrials.gov: NCT03270566. The study protocol has been published.[25]

2.7 | Sample size

This was a pilot study and, therefore, not powered to establish the efficacy of the intervention. A total of 80 families (40 per group) was judged to provide a sufficiently precise (within 10 percentage points for a 95% confidence interval) estimate of the proportion of families who are willing to be randomized and who will go on to complete the trial. Findings from the Enquiring About Tolerance (EAT) study[8] and the Barrier Enhancement Eczema Prevention (BEEP) feasibility study,[26] allowed us to make a conservative estimate that approximately 70% of families screened will have a history of atopy that predisposes to a high risk of eczema in their offspring. Of these, 40%–60% would be expected to be willing and able to participate. In addition, the SWET study reported that 27% of eligible families could not participate because their home was not suitable for installation.[16]

2.8 | Statistical analysis

As this was a pilot and feasibility trial, the focus was on descriptive statistics by randomized group with no hypothesis testing. Binary data are presented as frequencies and proportions, continuous data as means and SDs and scores as median and interquartile range. 95% confidence intervals are calculated where possible. The time to patient-reported doctor-diagnosed eczema was shown as a Kaplan-Meier curve, overall and by group.

3 | RESULTS

Baseline characteristics are given in Table 1 and were mostly well balanced between the randomized groups. The mean overall level of water hardness at baseline was 272 mg/L $CaCO_3$ and was similar in the two arms. Levels of parental atopy were also similar by study arm. A higher proportion of female infants was seen in the water softener arm. Just over half of all participants lived in flats and 93% lived in urban locations.

3.1 | Feasibility end-points

A total of 500 pregnant women were approached who expressed an interest in the study and were pre-screened, of which 231 (46%, 95% CI 42, 51%) were potentially eligible. Of those potentially eligible on pre-screening, 154 agreed to consider the study further and had a mean gestation of 31 weeks (SD 6 weeks). One hundred and fifty-two women then signed an informed consent form at an enrolment visit, of these 149 women were fully eligible for the study. Of the 149 eligible women, 80 (54%, 95% CI: 45, 62%) were randomized, the primary end-point of the study. The most common reason for ineligibility on pre-screening was no history of atopy (49%) (See CONSORT flow diagram, Figure 2). Of the 69 confirmed as eligible, but who were not subsequently randomized, 36 (52%) had a home that was not suitable for installation of a water softener due to technical (plumbing) reasons. 11 (16%) participants gave birth before the installation visit could take place. Four (5.8%) were unable to have a water softener installed due to landlord or local authority refusal or subsequently discovered technical problems. Of those randomized, two were immediately lost in each group: one in the water softener arm where the device could not be installed, and one in the hard water control arm who withdrew, leaving 39 in each arm of the trial (78 participants). No participants in the intervention arm had the water softening unit removed before the end of follow-up.

Potential contamination of the intervention, based on the mean (SD) number of nights spent away from the main residence in the 6 months of follow-up, was 12 (12) and was similar in both groups (Table 2).

Out of 708 analysed water samples received from the 39 participants in the intervention arm, 56 samples (7.9%) were above 20 mg/L $CaCO_3$. Sixteen participants (41%) had at least 1 water sample with

TABLE 1 Baseline characteristics of the infant trial population

Characteristic of the infant		Water softener % (*n*/*N*)	No water softener % (*n*/*N*)
Number in group		40[a]	40[b]
Sex	Female	64% (25/39)	46% (18/39)
Ethnicity	White British	33% (13/39)	33% (13/39)
	Other White	15% (6/39)	18% (7/39)
	White and Asian	18% (7/39)	15% (6/39)
	Other Mixed	15% (6/39)	15% (6/39)
	Chinese	10% (4/39)	5.1% (2/39)
	Other	7.7% (3/39)	13% (5/39)
Birth history			
Birth weight, g, mean (SD)		3513.4 (446.8)	3429.5 (399.1)
Mode of delivery	Vaginal	67% (26/39)	72% (28/39)
	C-section	33% (13/39)	28% (11/39)
Born in a bathing pool		0 (0/26)	0 (0/28)
Maternal antibiotic exposure during pregnancy		26% (10/39)	21% (8/39)
Family atopy status (self-reported)		100% (39/39)	100% (39/39)
Maternal			
Eczema		46% (18/39)	49% (19/39)
Atopy*		82% (32/39)	82% (32/39)
Paternal			
Eczema		36% (14/39)	21% (8/39)
Atopy*		59% (23/39)	62% (24/39)
Sibling			
Eczema		21% (8/39)	18% (7/39)
Atopy*		21% (8/39)	18% (7/39)
Home environment			
Property type	House	36% (14/39)	46% (18/39)
	Flat	64% (25/39)	54% (21/39)
Home location type	Urban	92% (36/39)	92% (36/39)
	Rural non-farm	7.7% (3/39)	7.7% (3/39)
Domestic water $CaCO_3$ mg/L, mean (SD)		274.6 (25.0) *N* = 40	269.5 (17.5) (*N* = 38)
Skin physiological parameters			
Skin surface hydration, arbitrary units, mean (SD)		17.9 (8.1) (*n* = 31)	17.4 (8.1) (*n* = 30)
Transepidermal water loss ($g{\cdot}m^{-2}{\cdot}h^{-1}$ mean (SD)		13.1 (2.8) (*n* = 27)	14.6 (4.2) (*n* = 28)
Skin pH, mean (SD)		5.7 (0.6) (*n* = 30)	5.9 (0.7) (*n* = 28)

Note: *Eczema, asthma or hay fever.

[a]Softener could not be installed following randomization of one participant.

[b]One participant withdrew consent immediately after randomization.

increased water hardness levels (>20 mg/L $CaCO_3$). No faults were found with the units, other than a lack of salt. One participant in the intervention arm experienced water hardness exposure >100mg/L (104.5 mg/L $CaCO_3$).

By 6 months postpartum, 4 participants in the water softener arm and 8 in the control arm were lost to follow-up or withdrew (15% attrition). A total of 69/78 (88%) families completed the study acceptability questionnaire, all of whom reported that they found the study acceptable and 67/69 (97%) said that they would take part in the same study again.

3.2 | Clinical end-points

At 6 months of age, 27/67 infants (40%) developed visible eczema and 15/36 infants (42%) had parent-reported doctor-diagnosed eczema. Of those with parent-reported doctor-diagnosed eczema, 13/15 (87%) also had visible eczema on examination, however, only 68% (13/19) of those with visible eczema on examination had corresponding parent-reported doctor-diagnosed eczema. Blinding was maintained for 96% of completed assessments at 4 weeks and 3 months and 100% at 6 months.

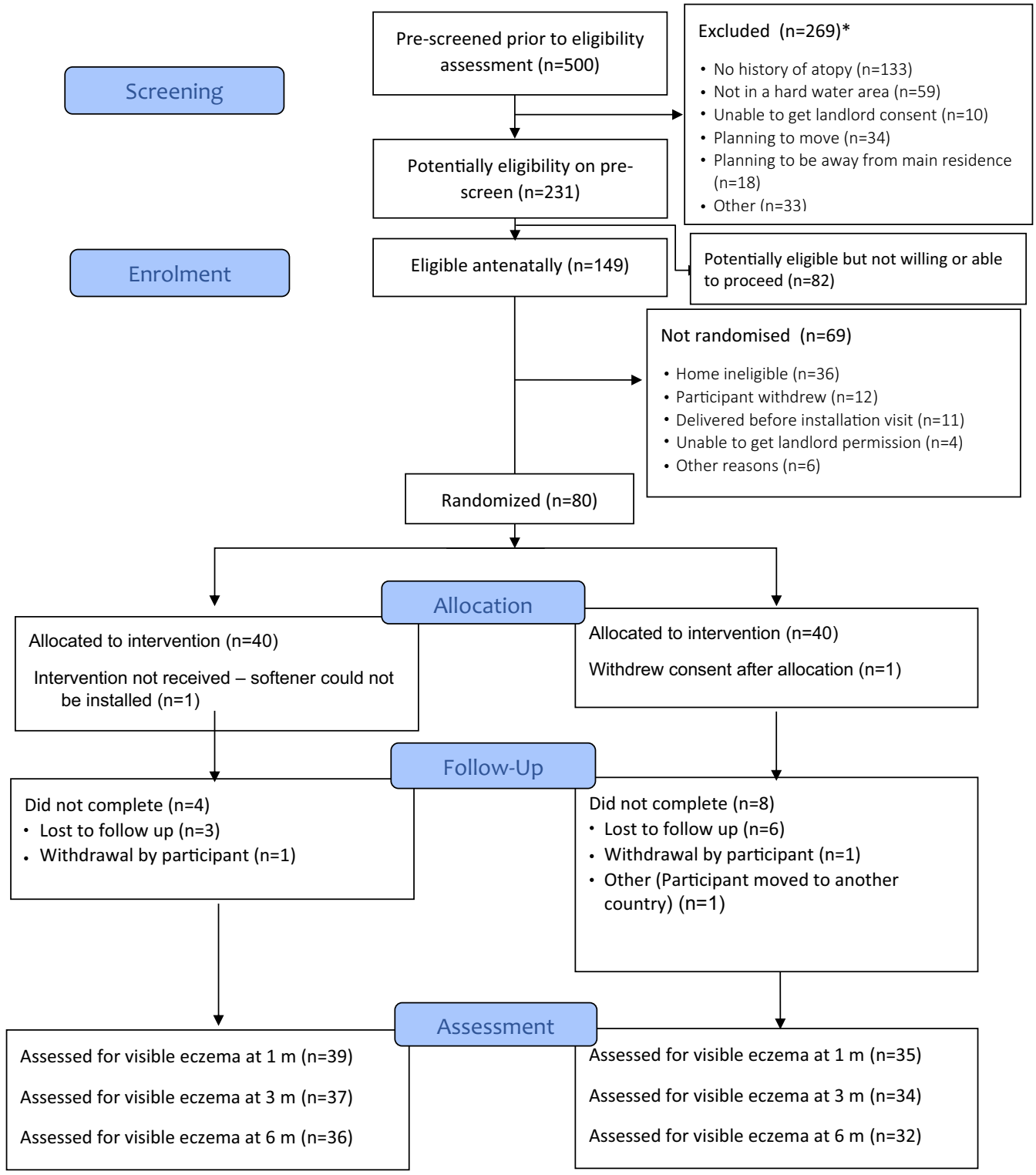

FIGURE 2 CONSORT flow diagram

A lower proportion of infants in the water softener arm (6/17, 35%) had parent-reported, doctor-diagnosed atopic eczema by 6 months of age compared to those in the control arm (9/19, 47%) exposed to hard water (difference −12%, 95% CI −44, 20%). This magnitude of effect was also observed in the proportion of infants with visible eczema by 6 months of age (difference −15%, 95% CI −38, 8.3%) (Table 3). Time to onset of parent-reported doctor-diagnosed eczema was similar in the two arms (Figure 2) and Figure 3. Trends in EASI and POEM scores were generally consistent. Median EASI scores beyond 4 weeks were lower in the water softener arm than the control arm. Median POEM scores beyond 4 weeks were lower in the water softener arm than the control arm (Table 3).

TABLE 2 Feasibility outcomes

Outcome	Estimate (95% CI) (n/N)
Proportion of eligible families screened who are willing and able to be randomized (95% CI)	54% (45, 62%) (80/149)
Proportion of pregnant women approached who agree to be screened (95% CI)	45% (41, 49%) (225/500)
Proportion of families eligible on screening that cannot have a water softener installed (eg due to landlord or local authority refusal, technical (plumbing) reasons) (95% CI)	28% (21, 35%) (41/149)
Proportion of families randomized that withdraw due to infant ineligibility	0% (0/80)
Proportion of families in intervention arm who found the study acceptable	100% (36/36)
Proportion of participants that have the water softening unit removed or disabled prior to end of follow-up	0% (0/39)
Proportion of water samples with hardness >20 mg/L calcium carbonate in the intervention arm	7.9% (56/708)
Proportion of subjects in the intervention arm with at least 1 water sample with hardness >20 mg/L calcium carbonate	41% (16/39)
Proportion of participants that withdraw from the trial prior to end of follow-up (95% CI)	15% (8.9, 25%) (12/78)
Mean (SD) number of nights spent away from the participant's main home during follow-up	12 (12) ($n = 36$)
Proportion of clinical outcome assessments that have remained blinded at 4 weeks, 3 & 6 months (95% CI), [N#]:	
• 4 weeks	96% (88, 99%) (72/75)
• 3 months	96% (88, 98%) (69/72)
• 6 months	100% (69/69)

Abbreviations: [N#], Number of assessments completed; CI, Confidence interval; N, Number of water samples received; SD, standard deviation.

TABLE 3 Clinical outcomes

Outcome	Water softener (n/N)	No water softener n(n/N)	Difference (water softener – hard water) (95% CI)*
Parent-reported, doctor-diagnosed atopic eczema by 6 months of age,	35% (6/17)	47% (9/19)	−12% (−44, 20%) ($n = 36$)
Time to onset of patient-reported doctor-diagnosed eczema (weeks), mean (SD)	24.0 (4.9) ($n = 37$)	23.5 (5.7) ($n = 34$)	0.55 (−1.9, 3.1) ($n = 71$)
Visible eczema at 4 weeks	2.6% (1/39)	17% (6/35)	−15% (−28, −1.1%) ($n = 74$)
Visible eczema at 3 months of age	24% (9/37)	8.8% (3/34)	−16% (−1.29, 32%) ($n = 71$)
Visible eczema at 6 months of age,	8.3% (3/36)	28% (9/32)	−20% (−38, −1.8%) ($n = 68$)
Visible eczema by 6 months of age	33% (12/36)	48% (15/31)	−15% (−38, 8.3%) ($n = 67$)
EASI at 4 weeks, median (IQR)#	17 (0) ($n = 1$)	1.2 (1.8) ($n = 5$)	16 ($n = 6$)
EASI at 3 months, median (IQR)#	0.8 (0.4) ($n = 9$)	1.3 (12.5) ($n = 3$)	−0.5 ($n = 12$)
EASI at 6 months, median (IQR)#	0.8 (0.4) ($n = 2$)	2.0 (1.0) ($n = 9$)	−1.2 ($n = 11$)
POEM at 4 weeks, median (IQR)#	16 (0) ($n = 1$)	10 (0) ($n = 1$)	6 ($n = 2$)
POEM at 2 months, median (IQR)#	1.0 (0) ($n = 1$)	4.5 (1.0) ($n = 2$)	−3.5 ($n = 3$)
POEM at 3 months, median (IQR)#	4.0 (0) ($n = 6$)	8.5 (9.5) ($n = 4$)	−4.5 ($n = 10$)
POEM at 4 months, median (IQR)#	3.0 (1.0) ($n = 3$)	16 (15) ($n = 2$)	−13 ($n = 5$)
POEM at 5 months, median (IQR)#	2.0 (4.0) ($n = 2$)	8.5 (8.5) ($n = 8$)	−6.5 ($n = 10$)
POEM at 6 months, median (IQR)#	1.0 (1.0) ($n = 2$)	10 (9.0) ($n = 7$)	−9 ($n = 9$)

*Only calculated for differences in means.

#Only completed when the mother reported that the infant had eczema.

EASI—Eczema Area and Severity Index, IQR—interquartile range, N: total number of participants, [N] number of participants with complete data, POEM—patient-oriented eczema measure, SD standard deviation.

4 | DISCUSSION

This pilot study assessed the feasibility of installing home water softeners for the prevention of eczema in high-risk neonates. Overall, around half of eligible pregnant women were willing and able to be randomized. This is consistent with the proportion (42%) of eligible families who were randomized into the Barrier Enhancement Eczema Prevention (BEEP) pilot study[26] that informed the design of the full-scale BEEP study. The most common reason for failure to proceed to randomization was that the participant's home was not suitable for the installation of a water softener. Potential contamination of the intervention was low, with a low number of nights (mean 12

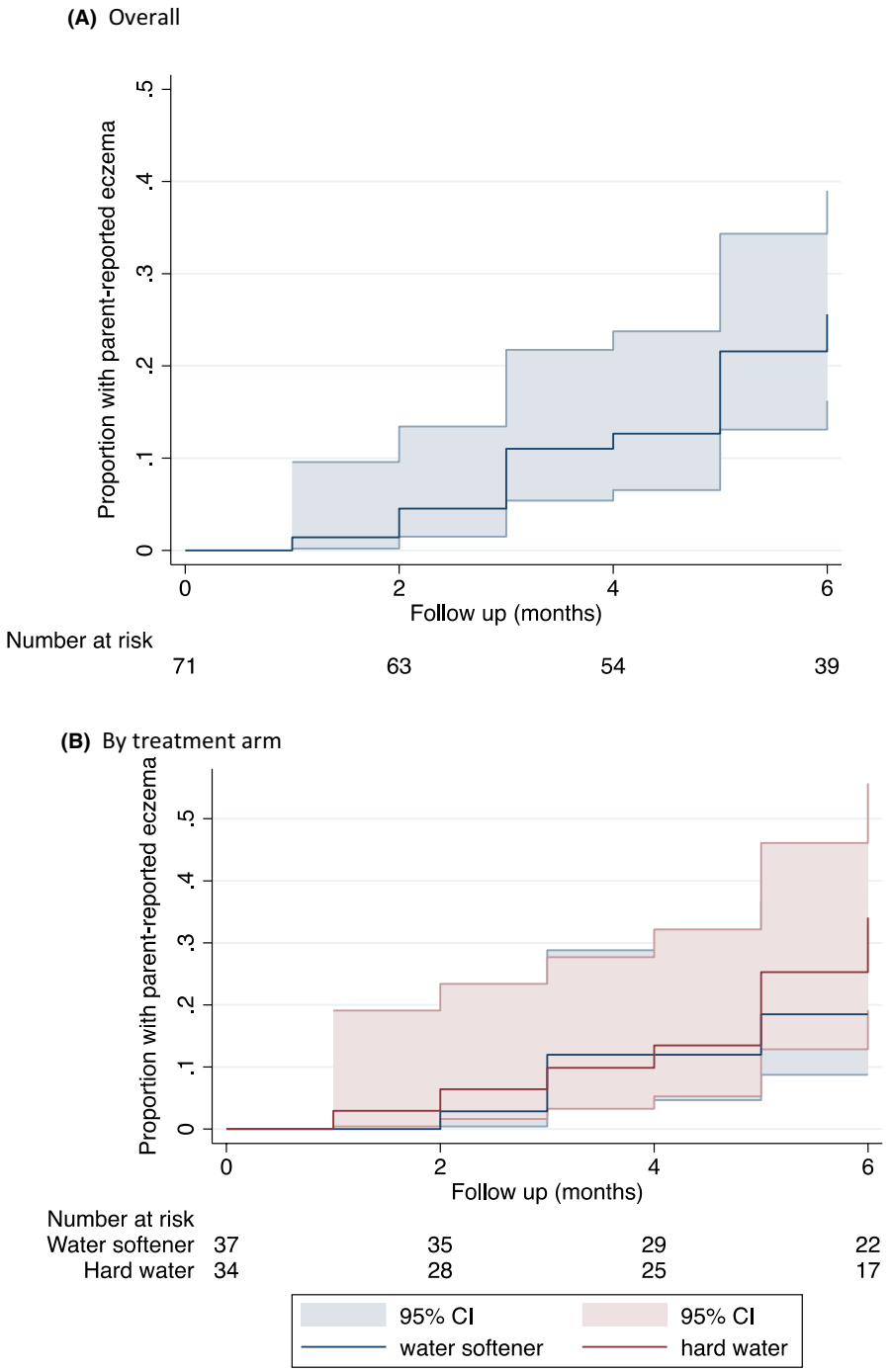

FIGURE 3 Kaplan-Meier curves for time to onset of parent-reported doctor-diagnosed eczema

nights, SD 12) on average spent away from the main residence over the 6 months follow-up period. 41% ($n = 39$) of participants in the water softener arm had at least one water sample out of the softer water range (>20 mg/L $CaCO_3$) with a low proportion of total water samples (7.9%, $n = 708$) out of the soft water range, despite the need for participants to top-up the unit with salt.

These findings suggest that the current study design could be scaled-up in a fully powered RCT prevention study. The question is then how large such a study would need to be. Approximately one-third of infants developed eczema over the first 6 months of life in this high-risk population, and this is consistent with other estimates in the literature.[8] There was some discordance between parent-reported doctor-diagnosed eczema and those with visible eczema on skin examination, the latter detecting more 'cases' than the former, suggesting that both end-points would probably need to be measured in a future study.

This study is the first randomized controlled trial testing the effect of water softeners on infant eczema providing data on the likely magnitude of effect, and therefore, sample size requirements for an adequately statistically powered prevention study. Based on the observed difference in visible eczema of 15% and attrition of 16%, the sample size requirement for a study with 80% power is likely to be >860 participants, allowing for attrition. Based on the data generated in this study, roughly 6 pregnant women had to be approached

and pre-screened for every randomized participant, suggesting around 5200 pregnant women would need to be approached about the study.

There were 27 infants who developed visible eczema by 6 months. The magnitude of the point estimate of the relative risk (softened water/control) is 0.68 (95% CI 0.38, 1.2), which is consistent with the magnitude of risk reduction that might be expected by softening water based on the increased odds identified with hard water exposure in children in a recent systematic review and meta-analysis conducted by our group (OR 1.28).[20] However, there is uncertainty around the relative risk and, as observed in studies of emollient use for the prevention of eczema, encouraging findings from pilot data may not hold in a fully powered study.[26,27] Additionally, in the absence of longer-term follow-up, there is the possibility that use of a water softener in early life simply delays the onset of eczema rather than preventing it. Given that approximately 80% of eczema cases occur before 2 years of age, this would seem an appropriate follow-up period for a definitive prevention trial.

Infants in the water softener arm who developed eczema appeared to have lower severity scores, both in terms of clinician- (EASI) and parent-assessed (POEM) measures, compared to those in the hard water arm. Lower POEM scores were also seen with the addition of a water softener to usual care versus usual care alone in the SWET trial. However, in this study as with the SWET trial, there is a high risk of biased POEM assessments as parents were unblinded to the intervention status.

5 | CONCLUSIONS

In summary, the results from this pilot RCT indicate that a definitive RCT to assess the prevention of atopic eczema in high-risk infants may be feasible in a mixed urban and suburban setting in England. However, many clinical sites would be needed to recruit enough pregnant women over a 1 year period. The outcome, eczema, is a binary variable and as such requires a considerably larger sample size to detect differences. Overall, pregnant women found the study design acceptable. Adjustments to the study design may help to reduce the proportion of eligible pregnant women who do not go on to be randomized, in particular, around the timing and organization of the water softener installation visit and so improve the efficiency of the trial.

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CONFLICT OF INTEREST

C.F. has received investigator-led research funding from Sanofi. His department has received clinical trial funding from Sanofi and AbbVie to test novel therapeutics in paediatric atopic eczema patients. M.J.C. is an Investigator and Consultant for Regeneron, Sanofi Genzyme, Pfizer, Leo, Galapagos, Novartis, Boots, L'Oreal, Dermavant, Menlo, Reckitt Benckiser, Oxagen, Johnson&Johnson, Hyphens, Astellas, Amlar, Abbvie, Galderma, Procter&Gamble. The other authors declare that they have no competing interests. Harvey Water Softeners contributed to the design and operational running of the study (supply and installation of water softeners, testing of water samples). Z.J.-L. is an employee of Galderma SA. Final decisions around design and conduct were made independently by investigators. HWS will not be involved in the analysis or interpretation of the results.

AUTHORS' CONTRIBUTIONS

CF was the Chief Investigator with overall responsibility for the SOFTER trial. He conceived the idea for the study, contributed to the writing of the trial protocol, oversaw the conduct of the study and reviewed this manuscript. ZKJ-L was the Senior Co-investigator responsible for designing and running the SOFTER pilot trial. He led on writing of the trial protocol, analysing the results and drafting the manuscript. JLP was the Senior Statistician who contributed to the trial design, writing the trial protocol, oversaw the statistical analysis and contributed to drafting the manuscript. BE contributed to the statistical analysis and writing of the manuscript. NG coordinated the study and reviewed the trial protocol. DG, AB, JC, KT, TF, SK, HHK, JAS, JEAC, SD, MJC were involved in finalizing the study protocol. All authors reviewed the final version of the manuscript.

DISCLAIMER

The views expressed are those of the authors and not necessarily those of the UK National Health Service, the UK Department of Health and Social Care or the National Institute of Health Research.

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