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A multicentre randomised controlled trial and economic evaluation of ion-exchange water softeners for the treatment of eczema in children: the Softened Water Eczema Trial (SWET)

KS Thomas,[1*] K Koller,[1] T Dean,[2] CJ O'Leary,[3] TH Sach,[4] A Frost,[5] I Pallett,[6] AM Crook,[3] S Meredith,[3] AJ Nunn,[3] N Burrows,[7] I Pollock,[8] R Graham-Brown,[9] E O'Toole,[10] D Potter[11] and HC Williams[1]

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 05/16/01. The contractual start date was in September 2006. The draft report began editorial review in June 2010 and was accepted for publication in October 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

A multicentre randomised controlled trial and economic evaluation of ion-exchange water softeners for the treatment of eczema in children: the Softened Water Eczema Trial (SWET)

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Objectives: To determine whether installation of an ion-exchange water softener in the home could improve atopic eczema in children and, if so, to establish its likely cost and cost-effectiveness.

Design: An observer-blind, parallel-group randomised controlled trial of 12 weeks duration followed by a 4-week observational period. Eczema was assessed by research nurses blinded to intervention at baseline, 4 weeks, 12 weeks and 16 weeks. The primary outcome was analysed as intent-to-treat, using the randomised allocation rather than actual treatment received. A secondary per-protocol analysis excluded participants who failed to receive their allocated treatment and who were deemed to be protocol violators.

Setting: Secondary and primary care referral centres in England (UK) serving a variety of ethnic and social groups and including children living in both urban and periurban homes.

Participants: Three hundred and thirty-six children (aged 6 months to 16 years) with moderate/severe atopic eczema, living in homes in England supplied by hard water (≥200 mg/l calcium carbonate).

Interventions: Participants were randomised to either installation of an ion-exchange water softener plus usual eczema care (group A) for 12 weeks or usual eczema care alone (group B) for 12 weeks. This was followed by a 4-week observational period, during which water softeners were switched off/removed from group A homes and installed in group B homes. Standard procedure was to soften all water in the home, but to provide mains (hard) water at a faucet-style tap in the kitchen for drinking and cooking. Participants were therefore

exposed to softened water for bathing and washing of clothes, but continued to drink mains (hard) water. Usual care was defined as any treatment that the child was currently using in order to control his or her eczema. New treatment regimens used during the trial period were documented.

Main outcome measures: Primary outcome was the difference between group A and group B in mean change in disease severity at 12 weeks compared with baseline, as measured using the Six Area, Six Sign Atopic Dermatitis (SASSAD) score. This is an objective severity scale completed by blinded observers (research nurses) unaware of the allocated intervention. Secondary outcomes included use of topical medications, night-time movement, patient-reported eczema severity and a number of quality of life measures. A planned subgroup analysis was conducted, based on participants with at least one mutation in the gene encoding filaggrin (a protein in the skin thought to be important for normal skin barrier function).

Results: Target recruitment was achieved ($n = 336$). The analysed population included 323 children who had complete data. The mean change in primary outcome (SASSAD) at 12 weeks was –5.0 [standard deviation (SD) 8.8] for the water softener group (group A) and –5.7 (SD 9.8) for the usual care group (group B) [mean difference 0.66, 95% confidence interval (CI) –1.37 to 2.69, $p = 0.53$]. The per-protocol analysis supported the main analysis, and there was no evidence that the treatment effect varied between children with and without mutations in the filaggrin gene. No between-group differences were found in the three secondary outcomes that were assessed blindly (use of topical medications; night-time movement; proportion showing reasonable, good or excellent improvement). Small, but statistically significant, differences in favour of the water softener were found in three of the secondary outcomes that were assessed by participants [Patient-Oriented Eczema Measure (POEM); well-controlled weeks (WCWs); Dermatitis Family Index (DFI)]. The results of the economic evaluation, and the uncertainty surrounding them, suggest that ion-exchange water softeners are unlikely to be a cost-effective intervention for children with atopic eczema from an NHS perspective.

Conclusions: Water softeners provided no additional benefit to usual care in this study population. Small, but statistically significant, differences were found in some secondary outcomes as reported by parents, but it is likely that such improvements were the result of response bias. Whether or not the wider benefits of installing a water softener in the home are sufficient to justify the purchase of a softener is something for individual householders to consider on a case-by-case basis. This trial demonstrated overwhelming demand for non-pharmacological interventions for the treatment of eczema, and this is something that should be considered when prioritising future research in the field.

Trial registration: Current Controlled Trials ISRCTN71423189.

Funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 15, No. 8. See the HTA programme website for further project information.

Results of this trial are also published at www.plosmedicine.org.

Contents

List of abbreviations

CI	confidence interval
CTU	Clinical Trials Unit
DFI	Dermatitis Family Impact (questionnaire)
eczema	atopic eczema/atopic dermatitis
EQ-5D	European Quality of Life-5 Dimensions
GCP	good clinical practice
GP	general practitioner
HTA	Health Technology Assessment
IgE	immunoglobulin E
ITT	intention to treat
MRC	Medical Research Council
MREC	Multicentre Research Ethics Committee
NIHR	National Institute for Health Research
OR	odds ratio
POEM	Patient-Oriented Eczema Measure
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SASSAD	Six Area, Six Sign Atopic Dermatitis
SD	standard deviation
SWET	Softened Water Eczema Trial
TCW	totally controlled week, i.e. a week in which symptoms are controlled throughout the week without the need to 'step up' treatment beyond normal maintenance care (such as emollients)
TIS	Three-Item Severity
TMG	Trial Management Group
TSC	Trial Steering Committee
UKWTA	UK Water Treatment Association
WCW	well-controlled week, i.e. a week in which symptoms and the need for 'step-up treatment' occurred on ≤ 2 days of the week
WRAS	Water Regulations Advisory Scheme
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Atopic eczema (also known as atopic dermatitis, or eczema) is a chronic, itchy, inflammatory skin condition that mainly affects young children.

Eczema is very common, affecting around 20% of school children in developed countries, and appears to be on the increase worldwide. Eczema can cause intractable itching, leading to thickened skin, bleeding, secondary infection, sleep loss, poor concentration and psychological distress to the child and the entire family. The cost of treating eczema is substantial, both for the health provider and for families.

Evidence linking increased water hardness with increased prevalence of eczema was first reported in a large study of primary school children living around Nottingham, UK. Similar results have since been reported in Japan and Spain. In addition, there are widespread anecdotal reports of the benefits of water softeners for the treatment of eczema. However, reviews of eczema treatments have failed to identify any relevant clinical trials looking at the potential benefits of water softeners for eczema sufferers. In view of the limited evidence for water softeners in eczema and the high public interest in their potential benefit, along with the added benefits of protecting against scale deposition in household appliances and the low risk of adverse events, the UK National Institute for Health Research Health Technology Assessment programme commissioned the Softened Water Eczema Trial (SWET).

Objectives

The aim of SWET was to test whether installation of an ion-exchange water softener in the home could reduce the severity of eczema in children and, if so, to establish its likely cost and cost-effectiveness.

Methods

The Softened Water Eczema Trial (SWET) was a pragmatic randomised controlled trial (RCT) of children aged 6 months to 16 years with moderate or severe atopic eczema. All lived in hard water areas (≥ 200 mg/l calcium carbonate) in England. Participants were randomised to receive either immediate installation of an ion-exchange water softener plus their normal eczema care for 12 weeks (group A) or normal eczema care alone for 12 weeks (group B).

At 12 weeks the main (primary) outcome was assessed, after which time water softeners were removed for participants in group A, or installed for a period of 4 weeks for those in group B. Additional data were collected between weeks 12 and 16 to conduct within-group comparisons in order to determine the possible duration of benefit effects in group A and speed of onset of possible benefit in group B.

The primary outcome of change in eczema severity at 12 weeks was measured using the Six Area, Six Sign Atopic Dermatitis (SASSAD) score, which, as the name suggests, records six physical signs of eczema in six areas of the body. The SASSAD scale ranges from 0 to 108, with high scores

representing more severe eczema. SASSAD score was measured by research nurses who were unaware of treatment allocation (blinded). Previous pilot work had demonstrated that blinding participants with a sham unit was only partially successful, owing to the different feel of softened water and the amount of soap suds generated. As a result, participants and their families were not blinded to allocation group in the main SWET study.

Three hundred and thirty-six children aged 6 months to 16 years were enrolled into the trial. All had a diagnosis of eczema, according to the UK working party's diagnostic criteria, and a minimum eczema severity score of 10 points using SASSAD. Outcomes were collected by the research nurse during clinic assessments at baseline and 4, 12 and 16 weeks.

Secondary outcomes were (i) the proportion of time spent moving during the night (captured using wrist accelerometers); (ii) the amount of topical medications used (corticosteroids and calcineurin inhibitors); (iii) Patient-Oriented Eczema Measure (POEM) score; (iv) Dermatitis Family Impact (DFI) score; (v) European Quality of Life-5 Dimensions (EQ-5D); (vi) the proportion of children who had a no change or reasonable, good or excellent improvement in SASSAD score; and (vi) how well the child's eczema was controlled on a week-to-week basis (captured from symptom diaries kept by the participants). In addition, saliva samples were taken from consenting participants and screened for mutations of the gene coding for filaggrin – a protein in the skin that is thought to be important for normal skin barrier function. A planned subgroup analysis was based on participants with at least one mutation in the gene coding for filaggrin.

The intervention was a standard ion-exchange water softener that was assembled specifically for the trial and carried the SWET logo. Ion-exchange water softeners use a synthetic resin to remove calcium and magnesium ions from household hard water, replacing them with sodium ions. The resin becomes depleted of sodium and is recharged using sodium chloride (common salt). Sufficient salt was supplied for the duration of the installation.

For those allocated to group A, a water softener unit was installed in the child's main residence as soon as possible after randomisation into the trial. All water entering the home was softened, with the exception of a drinking water tap at the side of the kitchen sink. Participants continued with their usual eczema treatments and were asked to bathe and wash their clothes in the usual way. Participants were encouraged to reduce their soap use in line with general advice on the use of water softeners in the home. Participants allocated to group B (delayed installation) received an active unit after the primary outcome had been collected at 12 weeks.

Both groups continued to receive their usual eczema care throughout the trial. 'Usual care' was defined as any treatment that the child was currently using in order to control his or her eczema (e.g. topical corticosteroids, emollients, contacts with health professionals). In order to minimise performance bias, participants in both groups had the same amount of contact with trial personnel, including a support telephone call from the co-ordinating centre at 8 weeks.

Results

Of the 336 children enrolled into the trial, 323 (96%) had complete data at baseline and 12 weeks (159 in group A and 164 in group B). Participants were recruited from eight UK centres, and included families of diverse socioeconomic backgrounds. The groups were broadly balanced at baseline in both clinical and demographic characteristics.

The primary outcome was the difference in mean change in eczema severity between groups A and B at 12 weeks, as measured using SASSAD. A reduction in the SASSAD score represents a reduction in the severity of eczema. There was no difference in baseline SASSAD score between groups [group A: 25.3 (standard deviation, SD, 13.4) and group B: 26.0 (SD 13.9)]. We found no difference between the groups in the primary outcome of change in disease severity. The mean change in the SASSAD score at 12 weeks compared with baseline was –5.0 (SD 8.8) in group A and –5.7 (SD 9.8) in group B. The difference between the two groups in mean reduction in disease severity at 12 weeks was small and not significant. The mean difference in score in favour of the control group was 0.66 [95% confidence interval, (CI) –1.37 to 2.69, $p = 0.53$].

Overall, there were no statistically significant differences between the groups for any of the objective (blinded) secondary outcomes. These included time spent moving during the night, the amount of topical medications used, and the eczema severity scores, grouped into no change (or worse), or reasonable, good or excellent improvement. Small, but statistically significant, differences in favour of water softeners were observed in three of the four unblinded secondary outcomes that were reported by the participants or their carers (POEM, number of well-controlled weeks and the DFI score).

Subgroup analyses including the 92 patients with at least one mutation on the gene coding for filaggrin showed no additional benefits for this group. The difference in mean change in disease severity between the two groups at 12 weeks in the subgroup was 1.05 in favour of the control group (95% CI –2.36 to 4.47, $p = 0.54$).

Analyses exploring speed of onset of benefit and duration of effects were not conducted as there was no overall treatment effect.

The results of the economic evaluation, and the uncertainty surrounding them, suggest that ion-exchange water softeners are unlikely to be a cost-effective intervention for children with atopic eczema from an NHS perspective.

Conclusions

Main findings

The SWET study found no benefit of using an ion-exchange water softener in addition to usual care in this study population. There were no clinically important differences between the treatment groups for any of the objective (blinded) outcomes. Furthermore, the 95% CIs around the primary efficacy estimates were narrow. An improvement of 1.37 points in favour of water softeners (the lower 95% CI) to 2.69 points in favour of usual care (the upper 95% CI) makes it unlikely that a clinically useful benefit has been excluded by chance.

Even though there was no change in disease severity, it is possible that water softeners could have proved beneficial if they resulted in reduced use of the topical medications needed to control the eczema (e.g. a steroid-sparing effect). However, measurement of the amount of topical steroid creams or calcineurin inhibitor creams applied showed that both groups used approximately equivalent amounts throughout the 12-week study period.

Of the four unblinded secondary outcomes, all except EQ-5D showed small, but statistically significant, differences in favour of the water softener group. However, the improvements seen were small and unlikely to be clinically significant. It is most likely that these differences were a result of response bias.

Of the children involved in the study, just under 30% had at least one filaggrin mutation. There was no difference in response between those with and without the mutation.

We believe that this pragmatic study has good external validity because participants were recruited from eight UK centres, and included families of diverse socioeconomic backgrounds. Every effort was made to include participants who lived in rented accommodation as well as owned homes. Nevertheless, the results are applicable only to children aged 6 months to 16 years with moderate or severe eczema. It is possible that water softening is beneficial for milder forms of eczema, or in adults with other eczema types such as asteatotic or seborrhoeic types. We are not able to comment on the impact of other types of water-softening devices such as physical water devices.

This trial demonstrated overwhelming demand for non-pharmacological interventions for the treatment of eczema, and this is something that should be considered when prioritising future research in the field.

Strengths and weaknesses

The Softened Water Eczema Trial (SWET) was an RCT with sufficient recruits to detect clinically important differences in eczema improvement between the groups. The motivation of families who participated in the study was high, as shown by the low number of dropouts (96% follow-up to 12 weeks; 94% follow-up to 16 weeks). Particular emphasis was placed on objective outcome measures to minimise observer bias, given that it was not possible to blind participants to the intervention. It is possible that our emphasis on objective outcomes meant that some important potential benefits were not captured in the primary analysis. Other factors, such as improvements in quality of life, or a reduction in symptoms (e.g. dry skin), may be important in determining whether or not parents choose to buy a water softener. Indeed, many parents in the trial reported small health benefits, and 55% from group A and 55% from group B chose to buy the water softener at the end of the trial. The reasons people gave for purchasing the units were perceived health benefits and the wider benefits of using softened water in the home.

It is also possible that small treatment effects were concealed by the usual eczema care that the children received, or that the moderate duration of the trial was insufficient to capture any longer-term treatment effect. However, there is no suggestion that either of these is the case from the data collected.

The continued use of soap and soap products during the trial may have limited the observed benefits if families were using too much soap in conjunction with the water softener. However, this was a pragmatic study that aimed to capture the effects of water softeners as they are normally used, according to standard advice. Evidence of how much soap was actually used was not collected, as we did not want to change participants' behaviour by intensive monitoring.

Interpretation

The primary end point results of this study are clear. We found no evidence of an objective benefit of ion-exchange water softeners for the treatment of moderate or severe eczema in children. Whether or not the wider benefits of installing a water softener in the home are sufficient to justify the purchase of one is something for individual householders to consider on a case-by-case basis.

Trial registration

This trial is registered as ISRCTN71423189.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1

Introduction

Background

The problem of eczema

Atopic eczema (atopic dermatitis) is the most common inflammatory skin disease in childhood, with a prevalence of around 20% in England, Australia and Scandinavia. There is recent evidence of a worldwide increase in atopic eczema symptoms in primary school-aged children.[1] The term atopic eczema is synonymous with atopic dermatitis. The World Allergy Organization now suggests that the phenotype of atopic eczema should be called just eczema unless specific immunoglobulin E (IgE) antibodies are demonstrated, and we will use the term eczema throughout this report.

The burden of eczema is wide-ranging. The child's life is affected in many ways, including the suffering of intractable itch, sleep disturbance and ostracism by other children. Family disturbance is also considerable, including sleep loss and the need to take time off work for visits to health-care professionals.[2–4] Wider economic costs are considerable. Reviews of the socioeconomic impact of eczema reveal significant burdens worldwide, including the UK,[5,6] the USA[7] and Australia.[8]

Treatment options for childhood eczema have traditionally focused on topical medications, with topical corticosteroids being the mainstay of treatment of skin inflammation and regular use of emollients for dry skin.[9] However, many parents of children with atopic eczema worry about the side effects of conventional topical medications.[10] Although the degree of public concern about the side effects of corticosteroids, such as skin thinning and growth retardation, has not been supported by long-term studies,[2] it is important to recognise these concerns and continue to look for other ways of treating atopic eczema. Options that avoid the possible side effects of conventional pharmacological treatments would be a welcome addition to the management of eczema.

Water hardness and eczema

There is evidence from ecological studies linking increasing water hardness with increasing eczema prevalence in children of primary school age. This was first demonstrated in the UK in a study of 4141 primary school children.[11] The 1-year period prevalence of eczema was 17.3% in the hardest water category and 12.0% in the lowest [odds ratio (OR) 1.54, 95% confidence interval (CI) 1.19 to 1.99 after adjustment for confounders]. Such a gradient was not seen in secondary school children in the same study. Similar results were subsequently reported in a large study in Japan of 458,284 children aged 6–12 years, in which the prevalence was 24.4% in the hardest water category and 22.9% in the lowest,[12] and in a study in Spain of 3907 children aged 6–7 years, in which the lifetime prevalence was 36.5% in the hardest water category and 28.6% in the lowest.[13] There are also anecdotal reports from the patients themselves that water softeners are of benefit to eczema sufferers.

Hardness in water is due to a high mineral content, primarily calcium and magnesium ions. Calcium usually enters the water supply as calcium bicarbonate as the water passes through

limestone or chalk rocks. Water hardness varies across the UK, but is generally classified as hard to very hard (> 200 mg/l calcium carbonate) throughout southern and central England (*Figure 1*).

If the association between water hardness and eczema prevalence is a causative one, a number of possible mechanisms can be put forward to suggest why hard water could exacerbate eczema. Perhaps the most likely explanation is increased soap usage in hard water areas, the deposits of which ('soap scum') can cause skin irritation in eczema sufferers.[14,15] This could be from direct skin contact with soap scum during washing or from the irritant effect of residual deposits in clothes and bedding. A direct chemical irritant effect from calcium and magnesium salts is also possible, or an indirect effect of enhanced allergen penetration from skin barrier disruption[16] and increased bacterial colonisation of the skin.[14]

Water softeners

Ion-exchange water softening is a well-understood and widely available technology. Water softeners are mainly used in households for reducing calcium deposits in appliances. They are usually installed under the kitchen sink and plumbed into the water supply to soften water to the whole house. A typical purchase price, including installation, would be approximately £600 ($900, €700). Ion-exchange water softeners remove calcium and magnesium ions, replacing them with sodium ions (from common salt). They reduce water hardness to < 20 mg/l calcium carbonate.

To fully soften water, calcium and magnesium ions must be removed, and domestic ion-exchange water softeners are the only products specifically designed to do this. Other technologies include water conditioners (also called 'physical water conditioners'), which reduce limescale build-up by altering the physical properties of calcium and magnesium ions, but they do not affect the chemical composition of the water and therefore do not affect its hardness. For this reason ion-exchange water softeners were installed in the Softened Water Eczema Trial (SWET), and throughout this report the term 'water softeners' refers to ion-exchange technology.

FIGURE 1 Water hardness in the UK. Soft, < 100 mg/l calcium carbonate; medium, 100–200 mg/l calcium carbonate; hard, > 200 mg/l calcium carbonate.

Despite interest from people with eczema using water softeners, a Health Technology Assessment (HTA) systematic review of eczema treatments failed to identify any trials evaluating the use of water softeners for patients with eczema.[12] The only trials of possible relevance were an inconclusive one looking at the benefits of salt baths and another that examined the use of biological versus non-biological washing powders. The search for new, relevant studies was updated in 2010 and no new evidence on the use of softened water was found (see *Appendix 1* for search strategy). The HTA systematic review identified a randomised controlled trial (RCT) of water softeners as one of six urgent research priorities in eczema. As a result of this, a feasibility study was run by the University of Nottingham in 2002 involving 17 families living in Nottingham, UK. This informed the design of SWET, in which ion-exchange water softeners were compared with usual eczema care in over 300 children recruited from seven hard water areas across England.

Objectives of the trial

The Softened Water Eczema Trial (SWET) had two main objectives: (i) to assess whether installation of an ion-exchange water softener reduces the severity of eczema in children with moderate-to-severe eczema; and, if so, (ii) to establish the likely cost and cost-effectiveness of this intervention.

Chapter 2

Methods

Trial design

See also *Chapter 3, Pilot study*.

The Softened Water Eczema Trial (SWET) was a pragmatic, observer-blinded, parallel-group RCT of 12 weeks' duration, followed by a 4-week observation period (*Figure 2*).

All participants were randomised to receive either immediate installation of an ion-exchange water softener, plus usual eczema care (group A), or usual eczema care, with delayed installation of a water softener after week 12 (group B). The primary outcome (eczema severity) was assessed at 12 weeks. The final 4-week period was included to provide further information on speed of onset of any effects, and to measure how quickly any benefits were lost once treatment was stopped. Feedback from the pilot study indicated that all participants would have liked to experience the intervention; hence, the inclusion of the opportunity for those not allocated to active treatment in the first 3 months to experience water softeners for the last month of the trial. In addition to helping recruitment, the provision of a water softener to group B after 12 weeks allowed a within-group comparison of speed of onset in group B if the softener was effective.

All families had the option of purchasing the water softener at reduced cost at the end of their child's 16-week study period.

Recruiting centres

Recruitment took place at secondary and primary care referral centres in England, serving a variety of ethnic and social groups, and including both urban and periurban homes. All sites had predominantly hard water (> 200 mg/l calcium carbonate).

At the start of the trial children were recruited through four secondary care referral centres: Queen's Medical Centre (Nottingham), Addenbrooke's Hospital (Cambridge), Barnet and Chase Farm Hospitals NHS Trust (London) and David Hide Asthma and Allergy Research Centre, St

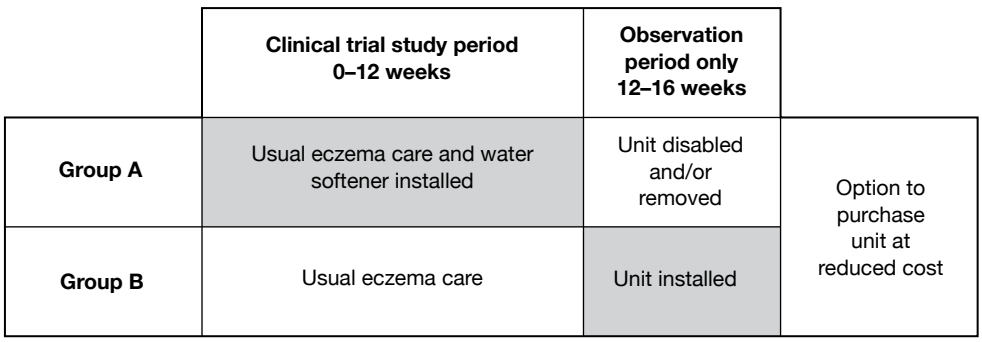


FIGURE 2 Trial design.

Mary's Hospital (Newport, Isle of Wight). As the trial progressed, a further four secondary care referral centres were opened: Leicester Royal Infirmary, United Lincolnshire Hospitals, the Royal London Hospital and St Mary's Hospital (Portsmouth). All centres held designated paediatric clinics in which children with eczema were seen.

Participants were informed of the trial in a variety of ways. Principal investigators at each centre sent letters of invitation and information sheets to parents of children with eczema referred to these centres over the previous 12–18 months. Posters were displayed in centres, and SWET research nurses attended designated outpatient clinics, informing interested families about the trial. The National Eczema Society website included a link to the trial website. Information was included in primary school newsletters. Individual research nurses advertised the study through local radio and short articles in local newspapers. In addition, recruitment was obtained from primary care trusts local to three of the recruiting centres (Isle of Wight, Leicester and Cambridge), with letters of invitation and information sheets sent to targeted families by general practitioners (GPs) at practices within these primary care trusts.

Ethical considerations

The trial was approved by the North West Multicentre Research Ethics Committee (MREC, reference number 06/MRE08/77) and the local ethics research committee (LREC) for each participating centre prior to entering participants into the trial.

Participants

Eligibility criteria

Children were candidates for inclusion in the trial if they were aged 6 months to 16 years at recruitment visit, with moderate-to-severe eczema, and living in a property supplied by hard water. Eczema was defined by the UK refinement of the Hanifin and Rajka diagnostic criteria.[17]

BOX 1 Criteria for presence of eczema

In order to qualify as a case of atopic eczema with the UK diagnostic criteria, the child must have:

- an itchy skin condition in the last 12 months
- plus three or more of:
- onset below age 2 years (not used in children under 4 years)
- history of flexural involvement
- history of a generally dry skin
- personal history of other atopic disease (in children under 4 years, history of atopic disease in a first degree relative may be included)
- visible flexural dermatitis as per photographic protocol.

Eczema was assessed using the Six Area, Six Sign Atopic Dermatitis (SASSAD) score. Moderate-to-severe eczema was defined as a SASSAD score of 10 or above. Children with a SASSAD score of < 10 were excluded in order to avoid floor effects, i.e. they had the potential to improve. Although children with a SASSAD score < 10 at baseline were not randomised into the trial, they were invited to contact the nurse again if their eczema worsened. The home where the child lived was assessed by a water engineer for technical suitability for the installation of an ion-exchange

water softener, during a 'home screening' visit carried out prior to recruitment. Hard water was defined as containing ≥ 200 mg/l calcium carbonate, and was measured in the home by water engineers using the drop-count titration Hach test (counting the number of drops required to change the solution colour to determine water hardness). In order to be as inclusive as possible, approval for water softener installation was sought from local council housing departments, housing associations and private landlords.

Children were not admitted to the trial if:

- they planned to be away from home for > 21 days during the 16-week study period, or had holidays scheduled during the 4 weeks prior to the primary outcome assessment date (to ensure adequate exposure to the intervention)
- they had taken systemic medication (e.g. ciclosporin A, methotrexate) or ultraviolet light for their eczema within the previous 3 months (because of these treatments' long-lasting effects)
- they had taken oral steroids within the previous 4 weeks, or, as a result of seeing a health-care professional, had started a new treatment regimen for their eczema within the last 4 weeks
- they lived in homes that already had a water treatment device installed, including ion-exchange softeners, polyphosphate dosing units or physical conditioners
- they lived in a home that was unsuitable for straightforward installation of a water softener.

Screening

On expression of interest in the trial, a two-stage screening process was initiated.

Families were initially contacted by telephone by their local SWET research nurse, who then administered a telephone screen checklist (*Appendix 2*) to assess eligibility for the trial. This generated a study number and a request for a home screen visit by a water engineer attached to the trial. The water engineer completed a home screen checklist (*Appendix 2*), which was faxed to the co-ordinating centre. If the home was supplied by hard water and was technically suitable for straightforward installation of an ion-exchange water softener, an appointment was made for the child to be assessed by their local SWET research nurse for recruitment into the trial.

Informed consent

Research nurses took written consent from the child's primary carer at the initial recruitment visit for all children aged 15 years or less. Children aged 16 years consented in their own right. Children aged 15 years or younger were invited to sign the consent form if they wanted to. Consent included permission for on-site inspection of the installed water softener by the relevant water supply company, under their duties within the statutory water fitting regulations, should this be requested.

Consent to take part in the genetic part of the study (filaggrin status) was additional to consent for the main study, i.e. it was not necessary to participate in the genetic study in order to participate in the main trial.

Interventions

Participants received either an ion-exchange water softener plus usual eczema care (group A) or usual eczema care alone with delayed installation of a water softener at 12 weeks (group B).

Ion-exchange water softeners use a synthetic styrene monomer resin to remove calcium and magnesium ions from hard household water, replacing them with sodium ions, thus removing the hardness. The resin becomes depleted of sodium and is recharged using sodium chloride

(common salt). The units met all necessary regulatory standards, and were installed by trained water engineers according to the Water Regulations Advisory Scheme (WRAS) Information and Guidance Note[18] and British Water's code of practice.[19] In order to avoid favouring any one company, a generic unit was produced for the trial, which carried the SWET logo. Units were usually installed under the kitchen sink (*Figure 3*).

The standard procedure was to soften all water in the home, but to provide mains (hard) drinking water through an additional faucet-style tap at the side of the kitchen sink for drinking and cooking. (Occasionally, this was refused or was technically too difficult to install, in which case participants either purchased bottled water or used softened water for drinking and cooking for the duration of the study period.) Participants were therefore exposed to softened water for all washing/bathing/showering and washing of clothes, but continued to drink mains (hard) water. Participants were asked to shower/bathe and wash their clothes in their usual way. While using the water softener, participants were encouraged to reduce their soap use in line with general advice on the use of water softeners in the home (www.ukwta.org/watersofteners.php).

For those allocated to group A, a water softener unit was installed in the child's main home as soon as possible after the baseline (recruitment) visit. Engineers were instructed to install water softeners within 10 working days, and parents were asked to be as flexible as possible when arranging suitable dates in order to achieve this. Participants allocated to group B received an active unit as soon as possible after the primary outcome had been collected at 12 weeks. Salt was supplied for all participants during the trial. Participants were reminded of the importance of replenishing the salt supply during a telephone call at 8 weeks (group A), and a weekly reminder was included in the daily symptom diary.

At week 12, group A participants were asked to switch their water softeners off, by turning three bypass levers to put the unit into 'bypass mode' (*Figure 4*) on the evening of the day they attended for their 12-week assessment (primary outcome), and reminded to do so with a telephone call the following day. A water engineer subsequently visited to remove the water softener and all associated pipework and fittings. However, if participants in group A indicated that they wished to purchase the water softener, the engineer ensured that the unit remained inactive for the final 4 weeks by removing the brine valve. Everything else remained in place, ready for subsequent reconnection.

FIGURE 3 The SWET ion-exchange water softener.

Both groups received a 'support telephone call' from the co-ordinating centre at 8 weeks, and all participants continued with their usual eczema care for the duration of the trial. 'Usual care' was defined as any treatment currently being used in order to control the child's eczema (e.g. topical corticosteroids, emollients). Newly introduced treatment regimens used during the study period were documented.

A *Water Engineer's Handbook* was compiled by the trial manager in conjunction with the UK Water Treatment Association (UKWTA) giving background information about the trial and practical information about home screening and subsequent visits. The UKWTA provided engineers with SWET water softener installation instructions, based on the WRAS guidelines.

At installation, engineers gave parents a number of sampling pots, stamped addressed envelopes, and instructions for sending weekly samples taken from the hot tap in the bathroom for hardness testing. At the start of the trial (May 2007) parents were instructed to take the weekly water sample from the cold (softened) kitchen tap. Occasionally parents confused this with the new kitchen drinking faucet (mains hard water). In September 2008 a hardness alert visit revealed a home with unusual plumbing and a hard water supply to the bathroom despite a water softener installed in the kitchen. As a result parents were asked to take weekly water samples from the hot water tap in the main bathroom from October 2008 to the end of the trial. Samples were sent to Culligan UK Ltd (High Wycombe, UK) and analysed using a Palintest wavelength selection photometer (Palintest Ltd, Kingsway, Tyne & Wear, UK). Tests were carried out within 24 hours of receipt. Samples were split for analysis. The first sample was used for 'blocking' (setting the test unit), and the second was treated with Palintest Hardicol tablets. The test method was accurate to ± 5 mg/l calcium carbonate. If a sample contained > 20 mg/l calcium carbonate an alert was faxed through to the engineer's co-ordinator, and copied to the co-ordinating centre. This triggered a standard procedure for dealing with the alert. If a unit was suspected to be malfunctioning, an engineer visited the home and replaced the unit. If there was an obvious reason for the hardness breakthrough (e.g. a bypass lever had been knocked out of position), this was rectified on site.

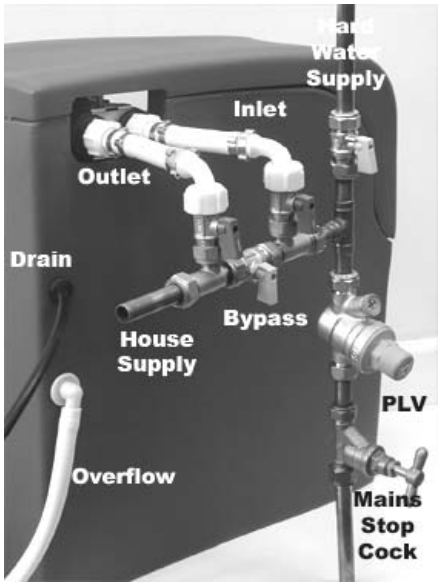


FIGURE 4 Water softener water supply and bypass levers.

Outcome measures

Primary outcome

As this was a single-blind trial, it was important to use an objective primary outcome measure that could be assessed by blinded observers (research nurses).[20] With this in mind, the primary outcome was the mean change in eczema severity at 12 weeks compared with baseline, as measured using the SASSAD severity scale –(see *Appendix 3)*. SASSAD is an objective severity scale that was completed by the research nurses; it did not involve input from the participant in any way.[21] SASSAD includes assessment of the severity of six signs – erythema (redness), exudation (oozing of fluid), excoriation (scratch marks), cracking, lichenification (skin thickening) and dryness – in each of six areas, the head and neck, trunk, hands, arms, legs and feet. The theoretical range of the scale is 0 to 108, although in practice scores rarely exceed 70.

Nurses were trained in the use of SASSAD during a 2-day training event at the co-ordinating centre. With the exception of one study centre (Chase Farm Hospital) all SASSAD scores for each participant were obtained by the same nurse. In July 2008 the nurse at Chase Farm Hospital went on maternity leave. Prior to her departure she trained two Medicines for Children Research Network (MCRN)-funded nurses in SASSAD scoring. The MCRN-funded nurses attended a number of joint assessment visits by SWET participants, during which the nurses scored SASSAD independently and compared their final scores. Training was deemed complete when scores were within 10% or less of each other for three consecutive assessments.

In addition to the SASSAD score, nurses scored a representative site using the Three-Item Severity (TIS) scale. This measures three clinical signs – excoriation, erythema and oedema/population – at a single representative site.[22] Its simplicity makes it a suitable tool for research studies and clinical practice, and it has been suggested that the score provides as much information about eczema severity as more complex scoring systems.[23] In SWET, this score was recorded for two reasons: (i) to compare with SASSAD for research purposes; and (ii) to assess integrity of observer (nurse) bias (information bias) using digital images of a representative site of the participant's eczema. These digital images were intended to be scored by two independent dermatologists using the TIS scale. The location of the representative site for TIS was agreed between the nurse, parent and child and photographed using a Samsung S630 CE digital camera (Chelsey, UK).

Secondary outcomes

Night-time movement

The difference between the groups in the proportion of time spent moving during the night was included as an objective surrogate for sleep loss and itchiness (two of the defining features of eczema). Previous research has suggested that this is a suitable objective tool for assessing itch,[24,25] and it has been shown to correlate with objective clinical scores in children with atopic dermatitis.[26] Movement was measured using accelerometers (Actiwatch Mini™, CamNtech Ltd, Cambridge, UK) for periods of 1 week at week 1 and for 1 week at week 12. The unit was worn by the child in the same way as a wrist watch. Data were stored on the unit and uploaded on to a laptop computer at the subsequent assessment visit. Pilot work using these units suggested that it was unusual for participants to record complete data for an entire week. As a result, the first three nights of evaluable data were used at baseline and the last three nights of evaluable data were used at week 12, in order to tie data collection as closely as possible to the date at which the participants' eczema severity was assessed by the research nurse. Evaluable data were defined as values > 5% and < 95% of the night spent moving to remove outliers. If there were fewer than three nights of evaluable data, this variable was considered missing.

Improvement in eczema severity

The difference between the groups in the proportion of children who had the same or worse outcome (≤ 0%) or a reasonable (> 0% and ≤ 20%), good (> 20% and ≤ 50%) or excellent (> 50%) improvement in SASSAD score at 12 weeks compared with baseline.

Topical medication use

The difference between the groups in the amount of topical corticosteroid/calcineurin inhibitors used during the study period was measured. Medications were weighed at each assessment visit, using digital scales. The scales were checked for accuracy before each visit, using standardised weights. Data were split into six types of medication: mild steroids, moderate steroids, potent steroids, very potent steroids, mild calcineurin inhibitors and moderate calcineurin inhibitors.

Patient-Oriented Eczema Measure (POEM, *Appendix 3*)

The difference between the groups in POEM data collected at baseline and at weeks 4, 12 and 16. This scale is a well-validated tool that has been developed to capture symptoms of importance to patients.[27] Parents were asked to state the number of days in the last week that their child had been affected by a range of symptoms. These were scored as follows: no days = 0, 1–2 days = 1, 3–4 days = 2, 5–6 days = 3 and every day = 4. The POEM score was then calculated as the sum of these seven individual scores (scale 0–28).

Eczema control

The difference between the groups in the number of totally controlled weeks (TCWs) and well-controlled weeks (WCWs) was recorded. This outcome was based on a systematic review looking at ways of assessing long-term control for chronic conditions such as eczema, asthma and rheumatoid arthritis.[28] The terms TCW and WCW have been adopted for use by researchers in the field of asthma and appear to be a useful and intuitive means of capturing disease activity over time. Using this definition, a TCW is one in which symptoms are controlled throughout the week without the need to 'step up' treatment beyond normal maintenance care (such as emollients). A WCW is one in which symptoms and the need for 'step-up treatment' occurred on 2 days of the week or less. Each family was asked to keep a daily symptom diary throughout the trial. The information from this diary was used to calculate the number of TCWs and WCWs.

Dermatitis Family Impact questionnaire (*Appendix 3*)

The difference was measured between the groups in the mean change in the questionnaire at 12 weeks compared with baseline. This scale measures how much the child's eczema has affected the whole family over the previous week, based on 10 questions.[29] Questions were scored as follows: not at all = 0, a little = 1, a lot = 2 and very much = 3. The Dermatitis Family Impact (DFI) score was calculated as the sum of these 10 individual scores (scale 0–30).

European Quality of Life-5 Dimensions (*Appendix 3*)

In order to assess whether the intervention had an impact on generic health-related quality of life, health utility was captured using the children's version of the EQ-5D for children aged 7 years and over, or the proxy version of the European Quality of Life-5 Dimensions (EQ-5D) for children aged 3–6 years.[30,31] A utility weight was attached to the health state descriptions using the currently accepted UK adult tariff, calculated using the York A1 tariff.[32] The mean change in utility score from baseline to 12 weeks was compared for group A against group B.

Filaggrin status

The role of filaggrin gene (*FLG*) mutations as a predictor of treatment response was assessed. Mutations of the epidermal barrier protein filaggrin have been shown to be a predisposing factor for eczema.[16,33] Saliva samples were collected during the trial. If children were unable to spit into the container, swabs were taken from inside the cheek. Samples were shipped to the Human

Genetics Unit at the University of Dundee, Dundee, UK and analysed for *FLG* genotyping for the common null alleles according to published protocols.[34]

Assessment visits

Assessment visits were carried out in paediatric dermatology clinic rooms in one of the SWET secondary care referral centres. Occasionally the research nurse agreed to see the child in the family home for the initial recruitment visit, but parents were informed that follow-up visits would all need to take place in the local SWET referral centre, to avoid unblinding of the nurse once the child had been randomised into the trial. SWET research nurses were trained in defining eczema at an initial training session run by a dermatology nurse consultant, by attending eczema clinics run by their principal investigators and consultant colleagues, and by self-testing using the online diagnostic criteria manual (www.nottingham.ac.uk/scs/divisions/evidencebaseddermatology/methodologicalresources/diagnostictools.aspx). Assessments took place at baseline and at 4 weeks and at 12 weeks (primary outcome) and at 16 weeks (*Table 1*).

Data collection and monitoring

Data generated by all centres were collected on study case report forms, which were entered on to the password-protected SWET database that was created and maintained by the Nottingham Clinical Trials Unit (CTU). Data were entered by the research nurses and by staff at the co-ordinating centre. A 100% check was conducted for the primary outcome (eczema severity) and the time spent moving, and discrepancies were resolved. All other data were subject to a 10% check, which was assumed to be adequate if the maximum error rate was, < 1 in 200 (in practice it was much lower than this). Data were also checked for consistencies in range and missing data. Missing and/or ambiguous data were queried with individual research nurses and resolved wherever possible.

Randomisation

Participants were randomised using web-based randomisation, and allocated on a 1 : 1 basis according to a computer-generated code, using random permuted blocks of randomly varying size. The program was created by the Nottingham CTU in accordance with its standard operating procedure and held on a secure server. Randomisation was stratified by disease severity (baseline SASSAD score ≤ 20 or SASSAD score > 20) and recruiting centre. Access to the sequence was confined to the CTU data manager. The allocation group was indicated to the trial manager only after baseline data had been irrevocably entered into the randomisation programme by the research nurse. The sequence of treatment allocations was concealed until interventions had all

TABLE 1 Summary of assessments carried out at each visit

Baseline	Week 4	Week 12	Week 16
Eligibility criteria checked	SASSAD/TIS	SASSAD/TIS	SASSAD/TIS
Baseline characteristics	POEM	POEM, DFI, EQ-5D	POEM
SASSAD/TIS	Medications weighed	WTP questionnaire	Medications weighed
POEM, DFI, EQ-5D	Digital photo of index site (TIS score)	Medications weighed	Digital photo of index site (TIS score)
WTP questionnaire	Week 1 Actiwatch data downloaded and watch reissued	Digital photo of index site (TIS score)	
Medications weighed	Diary 2 issued	Week 12 Actiwatch data downloaded	
Digital photo of index site (TIS score)		Diary 3 issued	
Saliva sample			
Actiwatch issued			
Diary 1 issued			
Consent taken, child randomised into trial			

WTP, willingness to pay.

been assigned, recruitment and data collection were complete, a signed-off statistical analysis plan had been received and the database locked.

Blinding/bias

Research nurses were blinded to treatment allocation throughout the trial and statisticians analysed the results based on treatment code, using an analysis plan that had been finalised prior to locking the database and prior to the blinded data analysis. The only study personnel in direct contact with study participants were the research nurses and water engineers. The trial manager and study support staff at the co-ordinating centre in Nottingham had telephone contact with parents of participants. Trial participants continued to see health-care professionals for their usual eczema care.

Participants were discouraged from discussing their treatment allocation with the research nurse and the importance of maintaining 'blinding' was highlighted in the participant information sheets. Records were kept of all instances when the nurses believed they had become unblinded.

Sample size

Sample size calculations, based on the results of the pilot study and previously published eczema trials, supported a target of 310 participants (155 in each group) in order to show a minimum clinically relevant difference of 20% in the change in SASSAD score between the two groups [assuming a mean baseline SASSAD score of 20 and a standard deviation (SD) in change scores of 10]. This sample size provided 90% power, assuming a significance level of 5% and dropout rate of 15%.

For the planned subgroup analysis, including children with at least one mutation in the gene coding filaggrin, a total of 90 children with the mutation was assumed to be sufficient to detect a 30% difference between the treatment groups in the primary outcome, with 80% power, 5% significance and a SD of 10.

Statistical analysis

Primary outcome

The full statistical analysis plan is included in *Appendix 4*. The primary efficacy end point was an intention-to-treat (ITT) analysis including all participants with evaluable data (if < 5% missing values). If > 5% of data were missing, then a general linear model was to be used to handle the missing values.

Baseline characteristics were summarised and, if any major imbalance existed, the analyses were to be adjusted to account for this, along with an adjusted analysis including the stratification variables (recruiting centre and eczema severity).

A secondary, per-protocol analysis was performed in order to establish proof of principle, and subgroup analysis was conducted, based on those with at least one mutation of the gene coding for filaggrin.

Per-protocol analysis excluded the following participants:

- those who were randomised into the study, but who failed to receive their allocated treatment
- those who were deemed to be major protocol violators as defined by the Protocol Violators Group [including independent members of the Trial Steering Committee (TSC)].

Criteria for protocol violators were defined prior to breaking of the code relating to treatment allocation. They were as follows:

- missing SASSAD score at week 12
- group A: exposed to fully softened water for < 75% of the time that their home had an active water softener in place (i.e. sleeping at home + unit fully working for < 75% of the time that their home had an installation)
- group A: participant away from home or with partially functioning water softener for > 2 days/week for each of the 4 weeks prior to the primary outcome assessment
- group B: participant away from home for > 2 days/week for each of the 4 weeks prior to the primary outcome assessment
- unblinding of research nurse prior to primary outcome measurement (which could have caused observer bias)
- participants starting new treatment prior to primary outcome assessment were examined by a dermatologist on a case-by-case basis to determine if they were violating protocol.

Sensitivity analyses

Three sensitivity analyses were planned in relation to the primary outcome: (i) including all randomised participants by replacing missing values; (ii) excluding those for whom the research nurse had become unblinded; and (iii) excluding outliers. For the analysis including all randomised participants, missing values at baseline were replaced by the maximum score from the other five areas of the SASSAD score that were completed. Missing values at week 12 were replaced by the SASSAD score at baseline or week 4, depending on which was greater. For the analysis excluding outliers, these were defined as change scores outside the range of ± 3 SD.

Secondary outcomes

Secondary end points were analysed using a complete case analysis.

In order to aid clinical interpretability, SASSAD scores were grouped into those reporting no change or worse, a reasonable reduction (> 0% and ≤ 20%), a good reduction (> 20% and ≤ 50%), or an excellent reduction (> 50%).

The average percentage of the night spent moving was calculated by taking the average of the first three nights of usable data at baseline and the last three nights of usable data at week 12. Usable data were defined as values between 5% and 95% of the night spent moving to exclude outliers.

The total amount of medication used during the 12-week study period was measured by weighing the medication at each visit. Nurses recorded how confident they were in the measurement.

The number of TCWs and WCWs were compared during the first 12 weeks of the trial. A TCW was defined as a week with zero days with an eczema bother score above 4 and zero days on which 'stepping up' of treatment was required. Stepping up of treatment was defined as treatment over and above that defined as 'normal' for an individual participant in the daily symptom diaries. Bother scores were assessed on a scale of 0–10 in answer to the following question: 'How much bother has your child's eczema been today?' A WCW was defined as a week with ≤ 2 days with an eczema bother score > 4 and ≤ 2 days on which stepping up was required.

All other outcomes were scored according to the guidelines for the scale, and compared the mean change from baseline to week 12. Continuous data were analysed using a *t*-test and categorical data were analysed using a chi-squared test for trend.

Analyses of all secondary end points and adjusted analyses were considered to be supportive to the primary analysis, so no adjustments for multiple comparisons were made.

Analyses were performed in STATA 10.1 (StataCorp LP, College Station, TX, USA) and all *p*-values reported are two sided, with a significance level of 5%.

Summary of changes to the protocol

A full copy of the final trial protocol and statistical analysis plan are given in *Appendix 4*. Changes to the protocol following MREC approval in January 2007 include minor amendments to trial documents: the inclusion of amounts of topical medications as an additional secondary outcome measure and an end of trial follow-up questionnaire. One of the secondary outcomes (patient-assessed global improvement in eczema) was replaced with broad categories as defined by the SASSAD score [the proportion of children who had a reasonable (≤ 20%), good (> 20% and ≤ 50%) or excellent (> 50%) improvement in SASSAD score], as this was felt to be more appropriate in a single-blind study. All amendments were implemented prior to breaking of the treatment allocation code and prior to finalising the analysis plan.

Trial conduct

Trial organisation

The trial was managed and co-ordinated from the Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK. Data management was conducted through the Nottingham CTU. Statistical analysis was overseen by Professor Andrew Nunn and conducted at the Medical Research Council (MRC) CTU in London.

The Trial Management Group (TMG) was responsible for overall management of the trial. The TSC had an independent chairperson and vice chairperspon and met annually to provide overall supervision of the trial on behalf of the trial sponsor (University of Nottingham). Training sessions were held for research nurses and water engineers prior to starting the trial, and ongoing training was provided at individual sites as required.

The trial manager was responsible for day-to-day management of the trial. Details of individual participants were kept in a password-protected ACCESS database (Microsoft Corporation, Redmond, WA, USA). This included unblinded information relating to home screen outcomes, installation and removal of water softeners and hardness alerts.

As the trial involved the use of a commonly available domestic water softening unit, and did not involve the use of a medicinal product, there was no need for a Data Monitoring Committee.

Membership of the TMG and the TSC are given in *Appendix 5*.

Engineer co-ordination

Water engineers were subcontracted by the UKWTA. All water engineering aspects on the Isle of Wight were handled by a single subcontractor (MG Heating Ltd, Oxford, UK). Homes on the mainland were assessed by a number of local independent subcontractors co-ordinated by Lorraine Doran at European Water Care Ltd (Essex, UK, May–October 2007) and John Kyle at Kinetico UK Ltd (Hampshire, UK, October 2007 to September 2009). Fourteen subcontractors

carried out water engineering aspects over the course of the trial. The majority of the work was done by the following nine subcontractors: Aquastream, Capital Softeners, Clearwater Softeners, European Water Care, Greens Water Systems, Kinetico UK, MG Heating Ltd, Silkstream and Simply Soft Water Softeners.

Consumer involvement

A consumer panel of five service users with experience of living with eczema assessed patient information sheets, symptom diaries and publicity material prior to submission for ethical approval. The panel members shared these documents with children with eczema aged 4 and 13 years. Mr David Potter acted as consumer panel representative on the TSC. Several participants from the trial assisted with trial publicity by agreeing to take part in media interviews (once their direct involvement in the trial was over). The National Eczema Society (NES) and the Nottingham Support Group for Carers of Children with Eczema (NSGCCE) helped with publicity during the recruitment phase of the trial.

Trial finances

This trial was funded by the UK National Institute for Health Research (NIHR) HTA programme. Subcontracts were established between the University of Nottingham and the MRC CTU, the consortium of water treatment companies (through the UKWTA) and the University of Portsmouth. In addition to the funding provided by the NIHR HTA programme, representatives from the water-softening industry covered the costs of the design, testing and supply of generic ion-exchange water softeners, salt supplies, hardness testing of water samples and supervision of water engineers.

Trial participants were offered a standard inconvenience allowance of £5–10 per visit in the form of gift vouchers.

Trial insurance and indemnity

The usual NHS indemnity arrangements for negligent harm applied. The University of Nottingham acted as sponsor for the trial and had third-party liability insurance in accordance with all local legal requirements, including cover for children under the age of 5 years. In addition, study engineers carried their own third-party liability insurance. The water softeners used in the study were covered by product warranty.

SWET website

The SWET website (www.swet-trial.co.uk, *Figure 5*) was active from May 2007 when recruitment began. The website included a password-protected researcher section where all current trial documentation was accessible for download by research nurses at individual study sites.

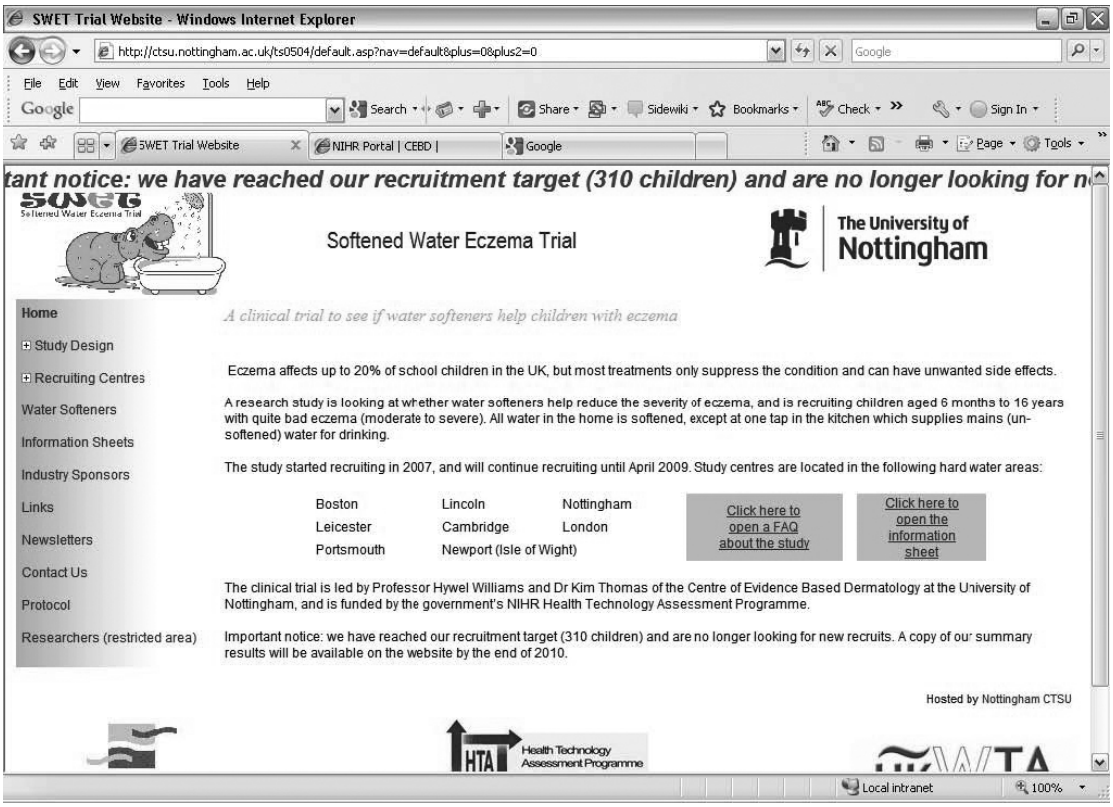


FIGURE 5 Screenshot of the home page of the SWET website.

Chapter 3

Working with industry

Pilot study

A pilot study funded by Kinetico UK Ltd was carried out in 2002 by Professor Hywel Williams and his research team at the University of Nottingham. This was a randomised, double-blind, parallel-group pilot study of 12 weeks' duration. The aims of the pilot study were (i) to test the appropriateness of the recruitment methods and trial procedures; (ii) to inform sample size calculations for the main RCT; and importantly and; (iii) to assess whether or not it was possible to blind participants to their treatment allocation (given that softened water typically produces more lather when using cleaning products).

Participants in the pilot study received either an ion-exchange water softener or a specially modified 'placebo' water softener, in which the internal resin beads had been replaced with inactive polypropylene. Technical difficulties meant that, for the purposes of the pilot trial, only homes with a gravity-fed boiler were eligible to take part (families with a combination boiler were excluded). Participants were instructed to continue treating their eczema according to their usual practice for the duration of the trial.

Seventeen children aged 1–10 years with moderate or severe eczema from the Nottingham area were randomised into one of two treatment groups for a period of 12 weeks.

At the end of 12 weeks, the children's eczema was assessed, and parents/carers were asked whether they thought they had received a real or a placebo unit.

Lessons from the pilot study.

- The pilot trial generated a lot of interest, although many families were ineligible because their homes were unsuitable for the installation of a water softener; or they had a combination boiler in the home. This led to modifications in the RCT design so that both gravity-fed and combination boiler types were eligible, and an additional home screen visit was introduced prior to randomising the participants into the trial.
- It proved to be extremely difficult to blind participants to their treatment allocation and, as might be expected, this was particularly marked for those who received the real water softener. However, there was no evidence to suggest that the research nurse had been compromised, and so a single-blind study was recommended (with mechanisms in place to record instances when the research nurses had become aware of the treatment allocation).
- In order to maximise exposure to the intervention, it was recommended that water softener units were installed as soon as possible after a child had been randomised into the study, and records kept of periods away from the home.
- The number of technical difficulties experienced with the units during the 12-week study period was higher than expected. For the full study, it was recommended that engineers be employed to work exclusively for the trial, and that regular water testing be introduced.
- Measuring chlorine content of the water proved problematic due to rapid evaporation. For the full study it was recommended that we measure water hardness only.
- Participants randomised to receive a placebo unit expressed regret at not being able to try a 'real' unit for themselves. It was felt that this might impact on our ability to recruit into the

main RCT, and so an additional 4-week period was introduced between weeks 12 and 16, when the control group would have a water softener installed.

Experiences from the main trial

The Softened Water Eczema Trial (SWET) was an unusual eczema clinical trial in that the intervention was not another skin cream, but altering one aspect of the child's normal home environment (water hardness). The intervention was a piece of widely available specialised non-medical equipment, which plumbed into the mains water supply to the child's home. This required a level of specialist knowledge and expertise that could be achieved only by close collaboration with the water-softening industry.

Water-softening industry and their trade associations

British Water is a corporate membership association covering all sectors of the water industry, and was closely involved with the pilot study and setting up the main study. Ian Pallett (Technical Director at British Water) was a co-applicant on the funding application and served as the industry representative on the TSC.

A number of meetings were held with representatives from British Water and the water-softening industry prior to setting up the main trial. These informed practical logistics, including the design of a generic water-softening unit encased in a special SWET cabinet.

Representatives from the following companies gave input to meetings prior to and during the trial: Aqua Focus Ltd (Newport, UK), Aquademic Ltd (Derby, UK), Aqua Nouveau Ltd (Basingstoke, UK), Coleman Water Ltd (Ipswich, UK), Culligan International (UK) Ltd (High Wycombe, UK), EcoWater Systems Ltd (High Wycombe, UK), Harvey Softeners Ltd (Surrey, UK), Kennet Water Components Ltd (Newbury, UK) and Kinetico (UK) Ltd (Hampshire, UK).

The UKWTA was formed in March 2006 and is a national trade organisation for companies involved in the sale and use of water treatment chemicals and equipment in the UK. The UKWTA was closely involved with delivery of the SWET trial, and Tony Frost served as the UKWTA representative on the TMG.

There was a great deal of goodwill in the industry towards the trial; an early example was the professional redrawing of a draught logo by artists working in the publicity department of Aqua Nouveau Ltd. This became the instantly recognisable SWET hippo logo, which was a great hit with children on the trial.

Engineer employment

The intention had been to employ a small number of water engineers, one for each study centre, and to pay each engineer a salary for a fixed number of days/week devoted to SWET. However, this plan was set aside in March 2006, when the UKWTA was formed. By liaising directly through the UKWTA, the trial was able to have a more flexible approach to securing water engineer expertise and cover a wider geographical area extending across south-east and central England, from the Isle of Wight to Lincolnshire. Tony Frost acted as representative on the TMG for the UKWTA, which took over responsibility for subcontracting work to a number of smaller water softener companies.

Engineer training

Over the lifetime of the study, more than 20 water engineers from over 10 companies were involved in the installation and/or removal of study units. It was felt that the advantage of increased flexibility and engineer cover outweighed the disadvantage of losing direct contact

with individual engineers. A downside was the effect on engineer training. Information about the trial was passed on through engineer co-ordinators on the Isle of Wight and the mainland, rather than directly in face-to-face training sessions with members of the TMG. In response to a few instances where engineers became involved in unwarranted discussions with parents about softened water and eczema, the trial manager wrote a SWET engineer's handbook. This was distributed to all engineers in March 2008, and included background information and a list of important 'dos' and 'don'ts'.

Individual engineers' levels of expertise and professionalism were very high. There were a few occasions when water engineers did not have the skills necessary to adequately screen homes, or to carry out installations, e.g. one engineer underestimated water hardness at home screen by not giving sufficient time for the Hach drop-count test to develop. Action to resolve the situation was swiftly implemented in all cases.

Water engineers work to tight deadlines, often driving many miles between homes and only visiting their company depot/offices as required. As a result, it was difficult for individual engineers to work to good clinical practice (GCP) standards in terms of paperwork trails. The co-ordinating centre spent many hours chasing paperwork, confirming home screens and installations/removals. In an effort to improve rapid communication between engineers and the co-ordinating centre, a dedicated telephone answering machine was introduced for engineers to leave messages whenever they had done anything for SWET.

Understanding research terminology and methodology

In order to collaborate effectively, industry colleagues needed to understand clinical methodology and terminology such as the difference between RCTs and other types of research, and the statistical interpretation of RCT blinded and unblinded outcomes. This was important both during the trial itself in terms of working to GCP standards (data protection, paperwork trails, etc.) and at the end of the trial when understanding trial results and statistical terminology. Hywel Williams, in his role of Chief Investigator, agreed to talk to a meeting of industry colleagues after the trial ended, in order to explain the results.

While the water-softening industry helped inform study design and assisted with the trial conduct by carrying out home screen visits, installing devices and monitoring water samples, it had no involvement in data collection, analysis or interpretation.

Publicity issues

The UKWTA companies involved with SWET were asked to take a responsible approach to publicity about the study on their own websites. While all additional publicity about the trial was welcomed (because it would aid recruitment) it was important that companies remained neutral and did not give any misleading information. Routine monitoring of company websites occasionally revealed problems which were rapidly resolved on our behalf by the UKWTA.

Ongoing commitment to the trial

There were numerous examples of good practice which put the needs of the trial foremost. During the first 6 months of the study the number of homes failing the 'home screening visit' was higher than expected, and this was addressed in meetings held within the industry, and in collaborative meetings with staff at the co-ordinating centre. As the trial progressed, the number of samples needing routine analysis for hardness levels increased, and this extra work was absorbed by Culligan UK Ltd. Kinetico UK Ltd had responsibility for building the generic SWET ion-exchange water softeners. Originally the company had been told that 100 units would be required across the 2-year recruitment period, but owing to higher than expected numbers of units being purchased by families, this number increased to 197. At an individual level, engineers

attached to the SWET trial were often working in very different environments from usual. This sometimes involved installing softeners into tight or unusual spaces, and finding creative ways to solve technical problems. One engineer discovered additional pipework to a bathroom during a visit to investigate a hardness 'alert'. As a result of this, the procedure for routine weekly water testing and home screening was changed. Other examples included staff at the co-ordinating centre contacting parents to let them know about a recent hardness alert only to be told that water engineer had already visited and rectified the problem.

Option to buy the water softener

All participants had the option of buying the water softener at a reduced price at the end of their child's 16-week study period.

To avoid potential conflict of interest, staff at the co-ordinating centre did not get involved in payment arrangements. Standard information was included in the letter sent out after recruitment, and all requests to purchase units were directed to the UKWTA (responsible as intermediary) and Kinetico UK Ltd (responsible for invoicing and warranty).

Chapter 4

Results

Recruitment

Recruitment took place between May 2007 and June 2009 (*Figure 6*).

Enrolment into the trial was a two-stage process (*Figure 7*). All those who passed the initial telephone screen were issued a study number ($n = 644$). Of these, 308 failed to meet the full inclusion criteria and were not randomised into the trial. The main reasons for excluding participants at this stage were that it was not possible to install a water-softening device in the child's home or that the child's eczema was too mild. Further details on home screening outcomes are given in *Appendix 6*.

A total of 336 participants were randomised into the study (170 in group A and 166 in group B). This is higher than the original target ($n = 310$), as a number of families had been issued study numbers and were in the process of having home screening visits or were awaiting landlord/council decisions when the 310th participant was recruited into the trial. The ITT population consisted of the 323 participants with evaluable data (96% of all randomised participants). This included 159 in group A (water softener + usual care) and 164 in group B (usual care). Multiple imputation of missing values was not felt to be appropriate in this context owing to the very low levels of missing data.

Baseline data

The groups were generally well balanced for all baseline characteristics, although to group A (water softener + usual care) included a slightly higher proportion of older children (aged ≥ 7 years) and members of group A, were more likely to use higher potency topical therapy (potent steroids, very potent steroids or calcineurin inhibitors) and slightly more likely to use biological washing powders (*Table 2*). The possible impact of these differences was explored in sensitivity analysis (primary outcome).

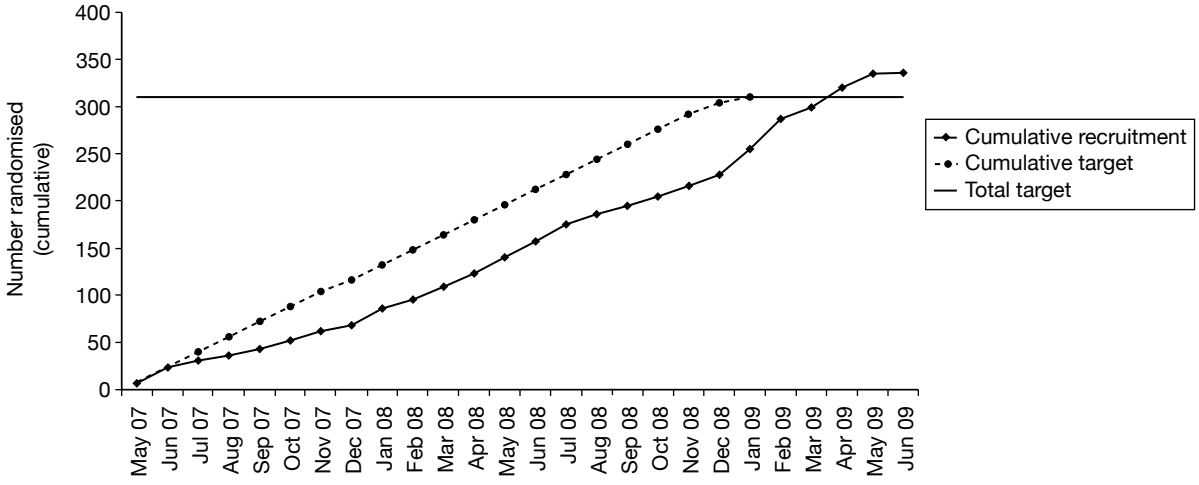


FIGURE 6 Cumulative recruitment.

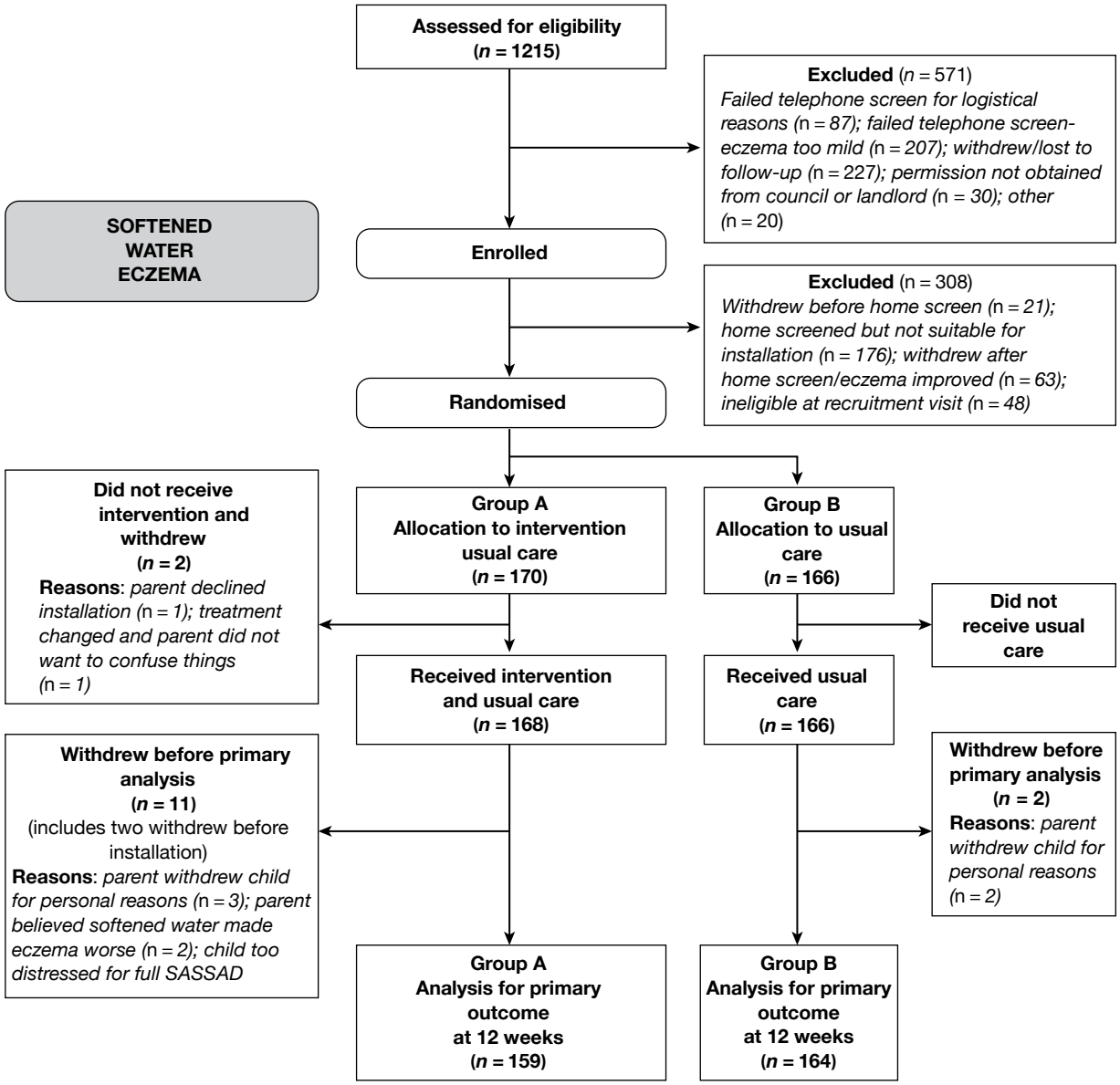


FIGURE 7 CONSORT diagram of participant flow.

Intervention – duration of exposure to softened water

Engineers were instructed to carry out installation of water softeners within a maximum of 2 weeks (10 working days); parents were asked to be as flexible as possible when arranging suitable dates, in order to achieve this. The average duration of exposure to softened water in group A was 10.6 weeks (range 7.6–16.4 weeks) (*Table 3*).

Primary analysis

Intention-to-treat analysis

The primary end point of change in disease severity is shown in *Table 4*. Group A showed a mean reduction of 20% (5.0 points) in SASSAD score from an average of 24.6 at baseline to 19.6 at week 12. Group B showed a reduction of 22% (5.7 points) in SASSAD score from an average of 25.9 at

TABLE 2 Baseline characteristics of study population included in ITT analysis

Baseline characteristics	Group A (water softener + usual care)	Group B (usual care)
Number enrolled	**170**	**166**
Number in ITT population	**159**	**164**
Age		
Mean age, years (SD)	5.8 (4.2)	5.1 (4.0)
Sex,* n *(%)		
Male	89 (56)	96 (59)
Female	70 (44)	68 (41)
Ethnicity,* n *(%)		
White	124 (78)	125 (76)
Non-white	34 (21)	38 (23)
Not stated/unknown	1 (1)	1 (1)
***Previous treatment history,* n *(%)*[a]**		
High strength corticosteroids/calcineurin inhibitors	91 (57)	80 (49)
Low strength corticosteroids/calcineurin inhibitors	57 (36)	73 (45)
None	11 (7)	11 (7)
Filaggrin status,* n *(%)		
Presence of mutation	45 (28)	47 (29)
Absence of mutation	103 (65)	109 (66)
Unknown	11 (7)	8 (5)
***Food allergy,* n *(%)*[b]**		
No	97 (63)	102 (64)
Yes	58 (37)	58 (36)
***Baseline SASSAD score,* n *(%)*[c]**		
Mean (SD)	24.6 (12.7)	25.9 (13.8)
Median (IQR)	21 (15–32)	22.5 (15.5–33.5)
10–19	72 (45)	68 (41)
> 20	87 (55)	96 (59)
Water hardness (mg/L^{-1} calcium carbonate)		
Mean (SD)	309 (50)	310 (58)
Median (IQR)	308 (274–342)	300 (270–340)
***Washing powder,* n *(%)*[d]**		
Biological	20 (13)	12 (7)
***Fabric softener,* n *(%)*[e]**		
Yes	69 (44)	81 (49)
***Bathing frequency at home, times per week*[f]**		
Median (IQR)	5 (3–7)	4 (3–7)
***Bathing frequency away from home, times per week*[g]**		
Median (IQR)	0 (0–1)	0 (0–0)

continued

TABLE 2 Baseline characteristics of study population included in ITT analysis *(continued)*

Baseline characteristics	Group A (water softener + usual care)	Group B (usual care)
Swimming frequency, **n** ***(%)***[h]		
Never	56 (35)	66 (40)
Less than once a month	53 (34)	52 (32)
More than once a month	49 (31)	46 (28)

IQR, interquartile range.
a High-strength medication consists of potent or very potent steroid, or mild or moderate calcineurin inhibitors. Low-strength medication consists of mild or moderate steroids only.
b There were eight missing values for the food allergy variable.
c There was one missing value for SASSAD score at baseline.
d There were four missing values for the washing powder variable.
e There were there missing values for the fabric softener variable.
f There was one missing value for the bathing at home frequency variable.
g There were 12 missing values for the bathing away from home variable.
h There was one missing value for the swimming frequency variable.

TABLE 3 Duration of exposure to softened water

Group	Installation status	Days (including weekends), mean ± SD
Group A[a] ($n = 168$)	Time from randomisation to installation	12.4 ± 5.5 (range 2–32)
	Duration of installation prior to primary outcome assessment	74 ± 7.6 (range 53–115)
Group B[b] ($n = 156$)	Time from week 12 visit to installation	9.2 ± 6.5 (range 0–34)
	Duration of installation prior to assessment at 16 weeks	24.5 ± 9.0 (range 0–78)

a Group A had 168 installations; 160 had both installation and week 12 assessment; eight had installation but no week 12 assessment; two had no installation or week 12 assessment.
b Group B had 156 installations; 155 had both installation and week 16 assessment; five had no installation; five had no installation and no week 16 assessment; one had installation after week 16 assessment.

baseline to 20.2 at week 12. The difference between the two groups at week 12 was 0.66 in favour of group B (95% CI −1.37 to 2.69) and was not statistically significant ($p = 0.53$). An additional analysis adjusting for stratification variables (baseline SASSAD score and centre) was performed, but this did not alter the conclusion. The difference between the two groups was reduced to 0.34 (95% CI −1.65 to 2.33, $p = 0.74$), in favour of group B.

These results are shown graphically in *Figure 8* based on those with complete data at all time points.

As a result of the slight imbalance between the two groups at baseline in relation to age, previous treatment history and use of biological washing powder, a generalised linear model (GLM) was performed that adjusted for these baseline differences. This analysis gave similar results to the univariate *t*-test analysis. The difference between the two groups was 0.54 (95% CI −1.54 to 2.62, $p = 0.61$). (More detailed information is given in *Appendix 7*.)

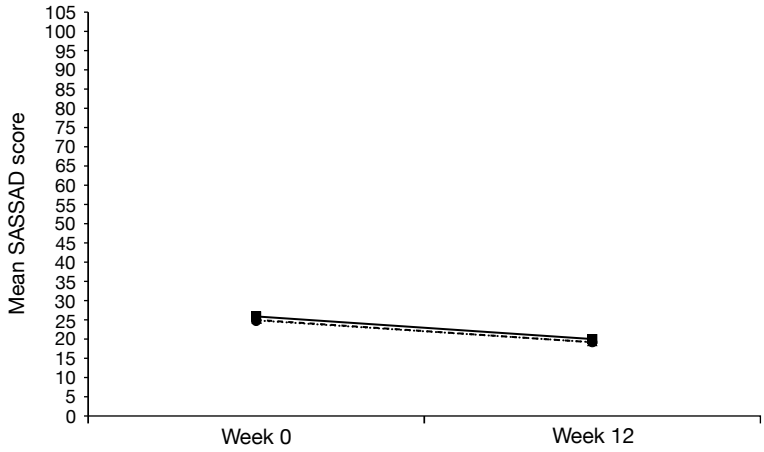
Per-protocol analysis

The planned per-protocol analysis supported the findings of the primary ITT analysis (*Table 5*). There was an 18% reduction (4.5 points) in group A and a 24% reduction (6.3 points) in group B.

TABLE 4 Change in SASSAD score – primary ITT analysis

Time assessed		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* analysed**[a]		**159**	**164**		
Week 0	Mean ± SD	24.6 ± 12.7	25.9 ± 13.8		
Week 12	Mean ± SD	19.6 ± 12.8	20.2 ± 13.8		
Change	**Mean ± SD**	**–5.0 ± 8.8**	**–5.7 ± 9.8**	**0.66 (–1.37 to 2.69)**	**0.53**

a Number of participants with evaluable data at week 0 and week 12.



	Week 0	Week 12
Group A (water softener and usual care)	24.6	19.6
Group B (usual care)	25.9	20.2
Total	25.3	19.9

FIGURE 8 Six Area, Six Sign Atopic Dermatitis scores to week 12.

This represented a difference of 1.87 in favour of group B (95% CI –0.73 to 4.47), which was not statistically significant ($p = 0.16$).

Sensitivity analyses

Sensitivity analyses were performed (i) including all randomised participants by replacing missing values; (ii) excluding participants for whom the outcome assessor had been unblinded; and (iii) excluding participants with scores that were defined as being outliers (*Table 6*).

Results from analysis of all randomised participants supported the primary result, as the mean change in SASSAD score was 0.76 in favour of group B (95% CI –1.22 to 2.74; $p = 0.45$).

Results from analysis excluding unblinded participants showed a difference between the two groups of 1.26 in favour of group B (95% CI –0.77 to 3.28), which was not statistically significant ($p = 0.22$), and again supported the primary result.

Results from analysis excluding outliers gave a mean difference of –0.11 in favour of group A (95% CI –1.93 to 1.70) and was not statistically significant ($p = 0.90$).

TABLE 5 Change in SASSAD score – per-protocol analysis

Time assessed		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* analysed**[a]		**99**	**115**		
Week 0	Mean ± SD	25.3 ± 13.7	26.3 ± 14.5		
Week 12	Mean ± SD	20.8 ± 13.6	20.0 ± 13.4		
Change	**Mean ± SD**	**–4.5 ± 9.3**	**–6.3 ± 9.9**	**1.87 (–0.73 to 4.47)**	**0.16**

a Excluding participants deemed to be protocol violators by the Protocol Violators Group.

TABLE 6 Change in SASSAD score – sensitivity analyses

Time assessed		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* – all participants**[a]		**170**	**166**		
Week 0	Mean ± SD	25.5 ± 13.7	26.0 ± 13.9		
Week 12	Mean ± SD	20.7 ± 13.8	20.4 ± 13.9		
Change	Mean ± SD	–4.9 ± 8.7	–5.6 ± 9.7	0.76 (–1.22 to 2.74)	0.45
***N* – excluding participants where nurse became unblinded**[b]		**153**	**159**		
Week 0	Mean ± SD	24.7 ± 12.8	26.0 ± 14.0		
Week 12	Mean ± SD	19.8 ± 12.9	19.9 ± 13.7		
Change	Mean ± SD	–4.9 ± 8.7	–6.1 ± 9.4	1.26 (–0.77 to 3.28)	0.22
***N* – excluding outliers**[c]		**157**	**163**		
Week 0	Mean ± SD	24.7 ± 12.7	25.5 ± 12.8		
Week 12	Mean ± SD	19.3 ± 12.5	20.2 ± 13.8		
Change	**Mean ± SD**	**–5.4 ± 8.2**	**–5.3 ± 8.3**	**–0.11 (–1.93 to 1.70)**	**0.90**

a Based on all participants with missing data at week 0 replaced with maximum score from the other five areas and missing data at week 12 replaced by maximum SASSAD score at week 0 or week 4.
b Number of participants with evaluable data at week 0 and week 12, excluding participants where nurse became unblinded.
c Outliers were defined as change scores outside the range of ± 3 SD.

Planned subgroup analysis – filaggrin status

The laboratory screened for the two most common mutations in the filaggrin gene (loss-of-function mutations R501X and 2282del4); variants (mutations) were either heterozygous or homozygous affected. A sample size of 90 children with at least one mutation was required for this subgroup analysis (see *Chapter 2* for further details).

Of the 314 participants with test results, 94 (30%) had at least one mutation in the filaggrin gene. These were affected as follows:

- 11 wild type/heterozygous
- 71 heterozygous/heterozygous
- 12 wild type/homozygous affected.

The *p*-value for the interaction between the filaggrin status and the intervention was 0.87, indicating no evidence that the treatment effect varied between those with and without the mutation.

The analysis by filaggrin status is given in *Table 7*. The change in SASSAD score between baseline and week 12 in those in whom the mutation was absent was –5.1 in group A and –5.8 in group B. This represented a difference of 0.68 in favour of group B (95% CI –1.87 to 3.23, $p = 0.60$). The change in SASSAD score between baseline and week 12 in those in whom the mutation was present was –5.2 in group A and –6.3 in group B. This represented a difference of 1.05 in favour of group B (95% CI –2.36 to 4.47, $p = 0.54$).

Secondary analyses

Categories of improvement in Six Area, Six Sign Atopic Dermatitis score

The SASSAD scores grouped into categories of improvement are shown in *Table 8*. There was no evidence of a difference between the groups ($p = 0.62$), which supported the primary ITT analysis.

Night-time movement

The percentage of the night spent moving was measured using accelerometers (*Table 9*). Both groups showed an increase in the percentage of the night spent moving: 3.5% in group A and 4.1% in group B. The difference between the two groups was –0.64 in favour of group A (95% CI –4.68 to 3.40) and was not statistically significant ($p = 0.76$). Both groups showed an increase in night-time movement during the trial. This is in contrast to the other reported outcomes, which all showed improvements over time in both groups. As a result an exploratory sensitivity analysis was conducted (see below). The correlation between the SASSAD score and the first three nights of usable data from the accelerometers at baseline was 0.11 ($p = 0.06$), suggesting weak evidence of a weak correlation. Comparing the change in SASSAD score from baseline to week 12 with the change in the percentage of the night spent moving from the accelerometer data gave a correlation of –0.02 ($p = 0.77$), suggesting no evidence of any correlation.

Sensitivity analyses

Owing to possible differences between the watches, a sensitivity analysis was performed restricted to those who wore the same watch at baseline and week 12 ($n = 160$). The difference between

TABLE 7 Change in SASSAD score – filaggrin status

Time assessed		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N*[a] – mutation absent**		**103**	**109**		
Week 0	Mean ± SD	23.2 ± 12.3	25.4 ± 14.2		
Week 12	Mean ± SD	18.1 ± 12.5	19.6 ± 13.9		
Change	**Mean ± SD**	**–5.1 ± 8.0**	**–5.8 ± 10.6**	**0.68 (–1.87 to 3.23)**	**0.60**
***N*[b] – mutation present**		**45**	**47**		
Week 0	Mean ± SD	27.2 ± 13.4	26.7 ± 13.4		
Week 12	Mean ± SD	22.0 ± 13.4	20.4 ± 13.9		
Change	**Mean ± SD**	**–5.2 ± 9.5**	**–6.3 ± 6.8**	**1.05 (–2.36 to 4.47)**	**0.54**

a Number of participants in whom the mutation was absent and had data at week 0 and week 12.
b Number of participants in whom the mutation was present and had data at week 0 and week 12.

TABLE 8 Categories of improvement in SASSAD score

Level of improvement	Group A (water softener + usual care)	Group B (usual care)	Total
Number randomised	**170**	**166**	**336**
***N* analysed**[a]	**159**	**164**	**323**
Same or worse (≤ 0%)	39 (25%)	42 (26%)	81 (25%)
Reasonable (> 0% and ≤ 20%)	37 (23%)	30 (18%)	67 (21%)
Good (> 20% and ≤ 50%)	53 (33%)	56 (34%)	109 (34%)
Excellent (> 50%)	30 (19%)	36 (22%)	66 (20%)

a Number of participants with evaluable data at both week 0 and week 12.

TABLE 9 Percentage of the night spent moving

Time assessed		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* analysed**[a]		**114**	**121**		
Week 0	Mean ± SD	21.2 ± 7.7	22.4 ± 9.7		
Week 12	Mean ± SD	24.7 ± 15.9	26.5 ± 17.9		
Change	**Mean ± SD**	**3.5 ± 14.5**	**4.1 ± 16.8**	**–0.64 (–4.68 to 3.40)**	**0.76**
***N*[b] – same watch at baseline and 12 weeks**		**75**	**85**		
Week 0	Mean ± SD	20.7 ± 7.8	22.8 ± 10.5		
Week 12	Mean ± SD	26.0 ± 17.2	26.8 ± 18.2		
Change	**Mean ± SD**	**5.3 ± 16.0**	**4.0 ± 16.2**	**1.30 (–3.73 to 6.34)**	**0.61**
***N*[c] – participants with > 5 sleep bouts and wearing watch all night (according to diaries)**		**94**	**104**		
Week 0	Mean ± SD	21.1 ± 7.3	22.1 ± 9.1		
Week 12	Mean ± SD	23.1 ± 12.1	25.7 ± 17.9		
Change	**Mean ± SD**	**2.0 ± 11.1**	**3.6 ± 17.1**	**–1.62 (–5.70 to 2.46)**	**0.44**

a Based on participants with at least three nights of evaluable data at each time point.
b Based on participants with at least three nights of evaluable data at each time point and who wore the same watch at both time points.
c Based on participants with at least three nights of evaluable data at each time point with fewer than five sleep bouts during analysis period and who wore the watch according to diary information.

the two groups was 1.30 (95% CI –3.73 to 6.34), and was not statistically significant ($p = 0.61$), which supported the main analysis. Given that the direction of change for this outcome was different to that of all other reported outcomes (i.e. participants moved more rather than less during the trial), a post hoc sensitivity analysis was conducted restricted to those for whom we had the most confidence in the accuracy of the data. This was restricted to those who had five or more sleep 'bouts' during the analysis period (which would suggest that the units had been worn correctly), and those whose parents indicated that the watch had been worn throughout the night (information taken from diaries, $n = 198$). This analysis continued to show an increase in movement during the trial and the difference between the groups remained non-significant (*Table 9*).

Amount of medication used

Group A used on average 58.4 g (SD = 96.8 g) of medication over the 12-week period and group B used on average 67.3 g (SD = 97.3 g, *Table 10*). The difference between the two groups was −8.90 g (95% CI −30.50 to 12.70 g) and was not statistically significant ($p = 0.42$).

Sensitivity analyses

Two further sensitivity analyses were performed based on strength of medication and confidence of the nurses in the measurements. Detailed information is given in *Appendix 8*. Both analyses supported the main findings.

Patient Oriented Eczema Measure scores

Group A showed a drop of 34% (5.7 points) from 16.8 at baseline to 11.1 at week 12 and group B showed a drop of 22% (3.6 points) from 16.6 at baseline to 13.0 at week 12 (*Table 11*). The difference between the two groups was −2.03 (95% CI −3.55 to −0.51) which was statistically significant ($p < 0.01$).

The difference between the two groups is shown visually in *Figure 9*.

TABLE 10 Total amount of medications used (grams)

Steroid strength		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* analysed**		**160**	**153**		
Mild steroids (g)	Mean ± SD	12.0 ± 29.9	18.2 ± 35.6		
Moderate steroids (g)	Mean ± SD	19.7 ± 69.3	25.3 ± 59.1		
Potent steroids (g)	Mean ± SD	21.5 ± 41.4	18.4 ± 39.7		
Very potent steroids (g)	Mean ± SD	2.2 ± 11.7	1.8 ± 20.7		
Mild calcineurin inhibitors (g)	Mean ± SD	1.9 ± 7.9	2.7± 12.0		
Moderate calcineurin inhibitors (g)	Mean ± SD	1.1 ± 9.1	1.0 ± 7.9		
Total medications (g)	**Mean ± SD**	**58.4 ± 96.8**	**67.3 ± 97.3**	**−8.9 (−30.50 to 12.70)**	**0.42**

g, grams.

TABLE 11 Difference in change in POEM scores

Time assessed		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* analysed**[a]		161	162		
Week 0	Mean ± SD	16.8 ± 6.0	16.6 ± 5.6		
Week 12	Mean ± SD	11.1 ± 7.1	13.0 ± 6.7		
Change	**Mean ± SD**	**−5.7 ± 7.2**	**−3.6 ± 6.7**	**−2.03 (−3.55 to −0.51)**	**< 0.001**

a Number of participants with POEM data at both week 0 and week 12.

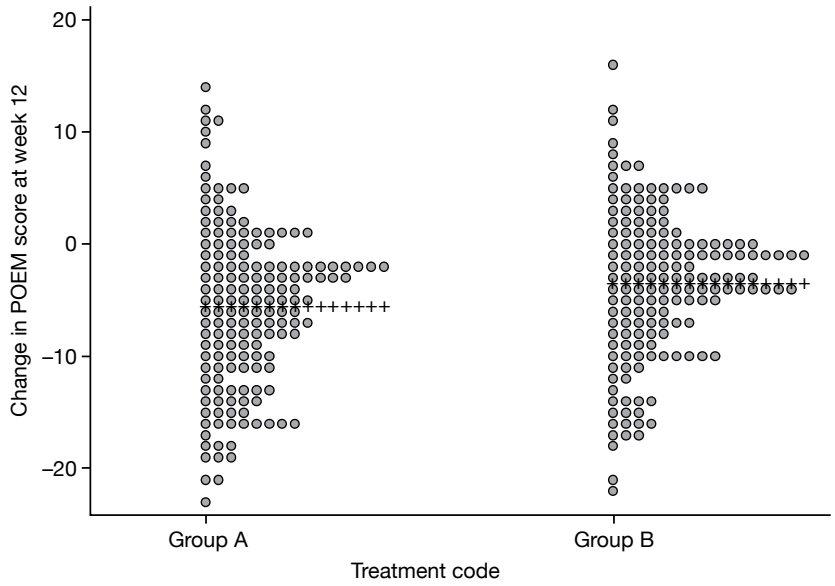


FIGURE 9 Change in POEM scores.

The POEM scores at week 4 also showed a difference in favour of group A, but this was not statistically significant. Group A showed a drop of 22% (3.8 points) from 16.9 at baseline to 13.1 at week 4, and group B showed a drop of 17% (2.8 points) from 16.8 at baseline to 13.9 at week 4. The difference between the two groups was −1.0 (95% CI −2.25 to 0.30), which was not statistically significant ($p = 0.13$).

Totally controlled weeks and well-controlled weeks

Group A had an average of 8.3 (SD 3.8) WCWs and group B had an average of 7.3 (SD 4.1) WCWs over the 12-week study period. The difference between the groups was 0.99 (95% CI 0.04 to 1.95). This difference of just under 1 week was statistically significant ($p = 0.04$).

The difference between the two groups can be seen in *Figure 10*.

This result was also reflected in the number of TCWs. Although the majority of participants had no weeks when the eczema was totally controlled (*Figure 11*), group A had an average of 2.9 (SD 3.5) TCWs compared with 1.7 (SD 2.8) in group B. This represented a difference of 1.19 (95% CI 0.43 to 1.95), which was statistically significant ($p < 0.01$).

Graphs showing the number of WCWs and TCWs for the entire 16-week trial period are shown in *Appendix 9*.

Dermatitis Family Impact questionnaire

Both groups showed a reduction in DFI score (*Table 12*). Scores in group A dropped by 32% (3.2 points) and in group B by 16% (1.8 points). This represented a difference of −1.33 points in favour of group A (95% CI −2.63 to −0.03), which just achieved statistical significance ($p = 0.05$).

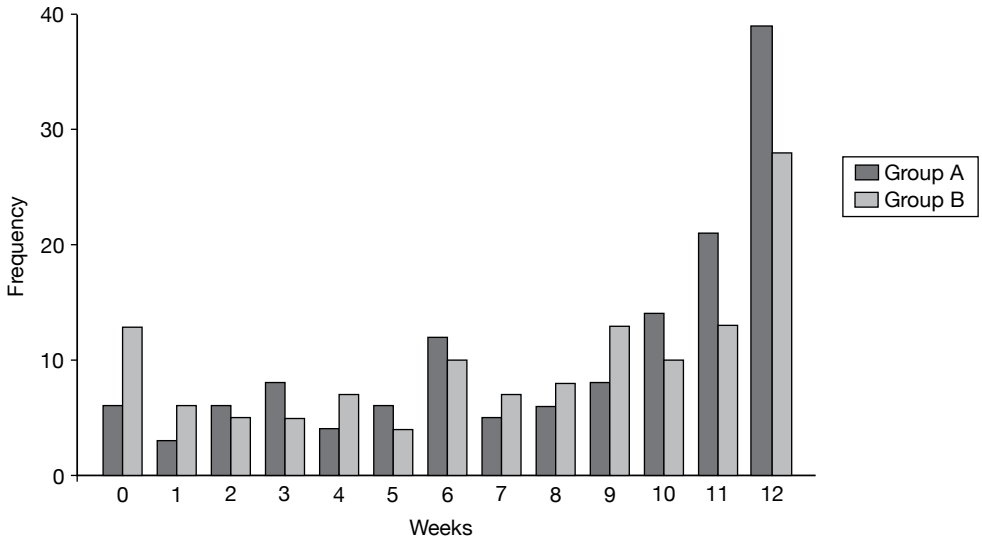


FIGURE 10 Number of well WCWs.

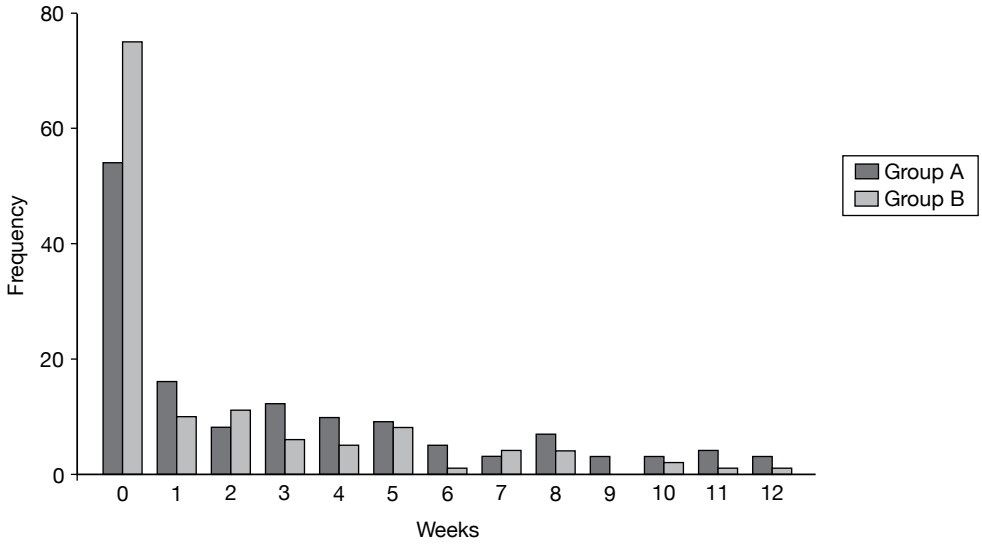


FIGURE 11 Number of TCWs.

TABLE 12 Difference in change in DFI score

Time assessed		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* analysed**[a]		**151**	**158**		
Week 0	Mean ± SD	10.0 ± 6.8	11.2 ± 7.3		
Week 12	Mean ± SD	6.8 ± 6.0	9.3 ± 7.1		
Change	**Mean ± SD**	**–3.2 ± 6.2**	**–1.8 ± 5.4**	**–1.33 (–2.63 to –0.03)**	**0.05**

a Number of participants with DFI data at both week 0 and week 12.

TABLE 13 Difference in change in EQ-5D score

Time assessed		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* analysed**[a]		**112**	**112**		
Week 0	Mean ± SD	0.690 ± 0.298	0.693 ± 0.274		
Week 12	Mean ± SD	0.810 ± 0.236	0.759 ± 0.245		
Change	**Mean ± SD**	**0.119 ± 0.269**	**0.066 ± 0.250**	**0.054 (–0.015 to 0.122)**	**0.12**

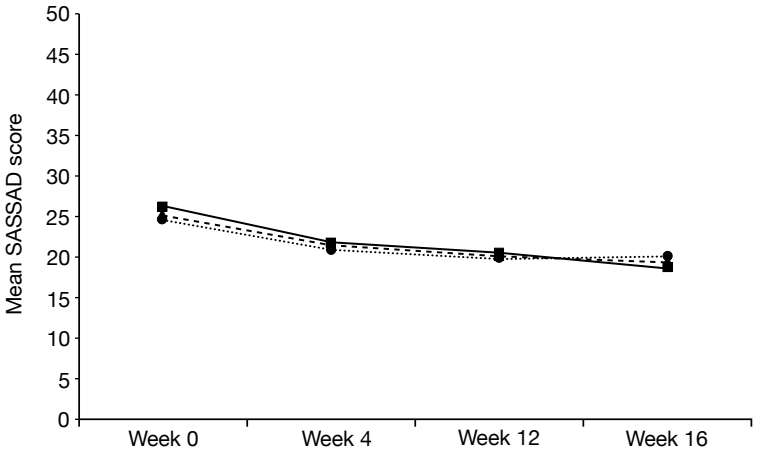
a Number of participants with EQ-5D data at both week 0 and week 12.

European Quality of Life-5 Dimensions

Both groups showed a small improvement in health-related quality of life. Scores in group A increased by 0.119 points and in group B by 0.066 points. The difference between the two groups was 0.054 (95% CI –0.015 to 0.122) and was not statistically significant ($p = 0.12$, *Table 13*).

Tertiary analyses

It was not appropriate to conduct analyses looking at possible duration of benefit or speed of onset of benefit, as there was no primary treatment effect. Nevertheless, the SASSAD scores collected between weeks 12 and 16 are shown for interest (when the softeners had been turned off for group A, and installed for group B) (*Figure 12*).



	Week 0	Week 4	Week 12	Week 16
Group A (water softener and usual care) *n* = 154	24.8	21.0	19.8	19.9
Group B (usual care) *n* = 160	26.1	21.7	20.4	18.8
Total *n* = 314	25.5	21.4	20.1	19.4

FIGURE 12 The SASSAD scores during trial period (weeks 0–16).

Purchase of water softener

Participants had the opportunity to purchase the water softener at the end of the study period. Water softeners were purchased by 55% of participants (179 purchases from 324 installations). Purchase rates in group A (93/168 installs; 55%) were the same as purchase rates in group B (86/156 installs; 55%), even though group A had an average 10.5-week installation period prior to deciding whether to purchase, whereas group B only had an average 3.5-week installation period.

Post hoc end of trial questionnaire

Participants were sent an end of trial follow-up questionnaire once all participants had completed the study. This sought information about current eczema status, whether they had a functioning water softener and, if so, their reasons for purchase. Non-responders were followed up by telephone.

Replies were received from 290/336 participants (86% return). Summarised results ($n = 290$) are given in *Table 14*, and collation of free text comments of relevance to SWET ($n = 165$) in *Table 15*.

A fuller discussion of willingness to pay (WTP) is given in *Chapter 5*.

Of the 290 participants who replied, 170 purchased the water softener (59%, including three purchases of non-SWET units) and 120 did not purchase the water softener (41%).

Of the 170 purchasers, 168 gave the reason for their purchase as either 'eczema improved on SWET' ($n = 111$, 66%) or 'because of wider benefits' ($n = 46$, 27%) or both reasons ($n = 11$, 7%).

TABLE 14 End of trial questionnaire

	How is child's eczema now? ($N^a = 281$)			
Purchase status	**Eczema clear**	**Eczema mild**	**Eczema quite bad**	**Eczema very bad**
Bought softener ($n = 164$)	18 (11%)	111 (68%)	27 (16%)	8 (5%)
Did not buy softener ($n = 117$)	10 (8%)	76 (65%)	23 (20%)	8 (7%)

a Number excluding nine who either ticked both 'mild' and 'quite bad'.

Three-Item Severity score and assessment of integrity of information bias

TABLE 15 Collated comments from parents

Reason(s) for buying water softener given by parents who purchased the water softener unit	*n*
Eczema improved on SWET (though hasn't disappeared) and believe water softener helps	43
Unsure at the time, but felt worth buying water softener in case it was beneficial in longer term	19
Eczema improved on SWET (though hasn't disappeared) and believe water softener helps and wider benefits of having a softener	15
Wider benefits not related to child's eczema	11
Eczema improved on SWET but have now found other factors more important than water softener e.g. avoiding certain foods; new skin care regime; avoiding stress	9
Eczema improved on SWET (and now clear or nearly gone) and believe due to water softener	8
Eczema improved on SWET but now unsure if improvement due to water softener or child growing out of it	3
Eczema improved on SWET but has relapsed and now can't see any benefit	3
Total	**111**
Comments from parents who did not buy the water softener	
Eczema did not improve on SWET, therefore did not wish to buy	23
Could not afford to buy the water softener but would have liked to	15
Eczema improved on SWET but not enough to warrant buying a water softener	7
Eczema improved on SWET and has continued clear without a water softener	3
Could not buy for practical/technical reasons/moving home	3
Needed a longer trial period to decide whether to buy or not	2
Eczema improved on SWET but did not believe this was due to water softener	1
Total	**54**

Nurses scored a representative site (target lesion) using the TIS score. Group A showed a mean reduction of 30% (1.2 points) from an average of 3.9 points at baseline to 2.7 points at week 12. Group B showed a reduction of 33% (1.3 points) from an average of 3.9 points at baseline to 2.5 points at week 12. The difference between the two groups based on the scores given by the nurses was 0.07 (95% CI –0.31 to 0.46) and was not statistically significant ($p = 0.71$, *Table 16*). This supports the primary outcome (SASSAD) data.

Given the clear and consistent difference between the blinded and the non-blinded outcomes in terms of treatment effect, it is likely that blinding in the trial was maintained. In order to confirm this, attempts were made to measure information bias using the digital images. However, during the course of the study a number of practical problems emerged: (i) the quality of digital images varied widely; (ii) not all uploaded photographs were taken of the target site; and (iii) some images were missing for one or more of the assessment visits. The TMG recommended that integrity of information bias be limited to examination of baseline and 12-week images. Images were recoded and sent in the first instance to Dr Emma Veysey, Consultant Dermatologist, for scoring using the TIS scale.

Feedback from SWET research nurses indicated that digital images poorly reflected in situ skin lesions. This was confirmed by the fact that Dr Veysey was able to fully score only 376/546 images (188/273 participants), owing to variable image quality. For this reason Professor Hywel Williams

TABLE 16 Change in TIS scores

Time assessed		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number enrolled		**170**	**166**		
***N*[a]**		**160**	**161**		
Week 0	Mean ± SD	3.9 ± 1.8	3.9 ± 1.7		
Week 12	Mean ± SD	2.7 ± 1.9	2.5 ± 1.8		
Change	**Mean ± SD**	**–1.2 ± 1.7**	**–1.3 ± 1.8**	**0.07 (–0.31 to 0.46)**	**0.71**

a Number of participants with TIS data at both week 0 and week 12.

also assessed a sample of 40 images, and these were compared with Dr Veysey's scores and the in situ scores obtained by the research nurses. This showed that there was reasonable agreement in the dermatologist's scoring of the digital images, but that the quality of the images meant that potential differences between the baseline and week 12 scores were lost. This was confirmed comparing the results of Dr Veysey's analysis with TIS scores recorded by the nurses in situ. In light of these findings, it was agreed that the assessment of information bias would be tested through sensitivity analysis in which participants were excluded if the research nurse reported that they had become unblinded before the primary outcome assessment ($n = 11$).

Adverse events

This trial involved the use of a commonly available domestic water softening unit with provision for mains drinking water during the time when the water-softening unit was installed. Therefore, the TMG did not anticipate any adverse events or adverse reactions of relevance to the trial. As a result, adverse event data were not routinely collected. Events of technical relevance such as plumbing difficulties, floods or difficulties with the units were logged at the co-ordinating centre and investigated by local water engineers as a matter of urgency.

The parents of two participants believed that their child's eczema had worsened as a direct result of installation of the water softener and asked to have the unit removed. They were instructed to switch off the unit, which was subsequently removed and their child withdrawn from the trial. The parents of a third participant expressed concern that the water softener appeared to be making their child's eczema worse, but the child continued to take part in the trial.

Chapter 5

Health economics

Introduction

Eczema has large cost implications for society and the individual families affected. In 1995–6 the total annual UK cost of eczema in children aged ≤ 5 years was estimated to be £47M (or £79.59 per child), of which 64% was accounted for by NHS health-care costs.[35] A further UK study looking at a broader age range estimated the total annual cost to be in the order of £465M, of which £125M was incurred by the NHS, £297M by the patients and £42M by society in terms of lost working days (price year not reported, but most likely to be 1994 or 1995 prices).[6] Childhood eczema has been shown to have a similar impact on health-related quality of life as other common childhood conditions such as asthma and diabetes.[36]

Current treatment consists predominantly of emollients, bath oils and topical corticosteroid creams, although some children may receive topical antibiotics, oral antibiotics, wet wraps, oral antihistamines and special dietary products. It was hypothesised at the outset of this trial that, should ion-exchange water softeners be effective, this may result in a reduction in the use of these products, and in the number of consultations, such that there might be potential cost savings for the NHS. Likewise, if effective, the costs incurred by families may also decline.

Ion-exchange water softeners are currently a private good in the UK; individual consumers are free to choose whether or not to purchase a unit out of their own disposable income. Before this trial, there was no scientific evidence about the clinical effectiveness or cost-effectiveness of ion-exchange water softeners for the treatment of eczema. As a result, the national health-care system in the UK does not currently fund this technology. One of the aims of the economic component of this trial was to assess whether the NHS should consider funding this technology.

Even though our RCT failed to find any objective evidence for the benefit of ion-exchange water softeners for improving eczema severity, an economic analysis is presented in this section because (i) it was part of the original research plan; (ii) it provides an indication of the potential costs if the intervention had been effective; (iii) while being highly prone to response bias, it is possible that the patient-generated utilities are measuring something important that physical signs alone do not capture; and (iv) the approaches and costs used may be useful for future health economic assessments of interventions for eczema or for other potential health benefits of water softeners.

Methods

Aim and perspective

The aim was to estimate the cost-effectiveness and cost–utility of ion-exchange water softeners for children with eczema, as compared with usual care. The study adopted an NHS perspective, in order to inform health policy relating to the use of ion-exchange water softeners for children with eczema.

Time frame

Costs and benefits were calculated for the 12-week study period only. As the trial has a short time frame, neither costs nor benefits were discounted.

Resource use and cost analysis

Resources collected during the trial are summarised in *Table 17*. The resources fall into two main categories: (i) those used to provide the intervention (consultation with a dermatologist, water softener device, installation, salt); and (ii) those that may change as a result of the intervention (NHS resource use, including number of visits to the GP, practice nurse, pharmacist, health visitor, specialist nurse, hospital admissions, hospital doctor and medication use).

The dermatology consultation was included in the intervention group in the base case because it was assumed that an additional clinic visit would be required in order to prescribe a water softener device. The impact of excluding this cost is further explored in sensitivity analysis.

TABLE 17 Resource use and unit costs (£ 2009)

Resource use item	Typical/mean	Minimum/best case	Maximum/worst case	Source
Annuity factor[a]	9.6633 based on $r=3.5\%$ and $n=12$ years	14.2124 based on $r=3.5\%$ and $n=20$ years	4.5151 based on $r=3.5\%$ and $n=5$ years	Drummond *et al.* 2005[37]
Purchase price (£)[d,e]	600	300	1800	Industry expert opinion
Annuitised 12-week purchase price[b]	14.33	4.87	92.00	
Installation cost (£) [d,f]	230	175	380	Industry expert opinion
Annuitised 12-week installation cost[b]	5.49	2.84	19.42	
Expected lifetime years	12	20	5	Industry expert opinion
Salt, cost per box (£)[d]	15.36	–	–	Direct Salt
Face-to-face consultant-led follow-up attendance, paediatric dermatology	151	0 (no visit assumed necessary)	228	*NHS reference costs 2008/9*[38]
Primary health care[c]				
GP (per surgery consultation)	31	27	35	PSSRU[39]
Practice nurse (per consultation)	9	9	11	PSSRU[39]
Health visitor (per visit home visit)	35	35	40	PSSRU[39]
Pharmacist (per visit)	42	34	85	PSSRU[39]
Specialist nurse (per hour)	74	29	88	PSSRU[39]
Secondary health care				
Hospital outpatients visit (per follow-up attendance, paediatric dermatology)	151	88	228	*NHS reference costs 2008/9*[38]
Hospital admission (non-elective inpatient stay (short stay)	493	329	588	PSSRU[39]
Medication and accessory costs				
Variety	–	–	–	BNF 58[40]

BNF, *British National Formulary*; PSSRU, Personal Social Services Research Unit.
a Annuity factor estimated as $\{1-[(1+r)^{-y}]\}/r$, where r = interest rate and y = lifespan in years of the product.
b Equivalent annual cost divided by 52 weeks and multiplied by 12, assuming an interest rate of 3.5% and lifespan of 12 years in base case.
c Costs exclude qualifications in base case.
d Prices include VAT at 17.5%.
e Purchase price range reflects source of purchase and type of softener unit.
f Minimum installation cost could be lower for DIY or by negotiation on purchase.

NHS resource use data were recorded by parents in a daily diary over the 12-week trial period. In addition, topical steroids and/or calcineurin inhibitors were weighed by trial nurses at baseline and the end of week 12. Several assumptions were required in order to cost the medication weights recorded:

- Where the medication weights were recorded but no medication name given, the average unit cost across medications in that potency category was assumed.
- Where no weights but some medication names were recorded it was assumed there had been no use of that medication over the 12-week study period. This applied to 25 cases (nine in group A, 16 in group B) where the nurses had rated their confidence in the assessment of weight as 'not sure' or 'not at all sure'. As slightly more of the missing values were in group B, the effect of this assumption would be conservative against the intervention.
- Where there were two medications within a single potency category it was assumed that half the weight had been used on each medication.
- Where there were more than two medications within a single potency category, the average unit cost across medications in that potency category was used.
- Where a medication did not have the strength or application types recorded, an assumption was made. For example, the most frequent omission was with respect to the strength of hydrocortisone. For cases where this was recorded, it was most frequently 1% strength and approximately 30 g had been used. As a result, a unit cost for those with missing information was assumed based on the cost of a 30-tube of 1% hydrocortisone.

It was assumed that all intervention households had one water softener device installed. This assumption was made despite knowing the exact number of devices installed into each home because in this study the devices were being installed into multiple homes for short periods of time. Therefore, although a minority of homes had to have replacement devices, we did not include the cost of these replacement machines because this is likely to be a consequence of the study design rather than some inherent failing of the devices, which have an expected average life span of 12 years. Salt consumption was assumed as a standard rate based on household size and the agreed amounts of salt engineers left at the time of installation (*Table 18*).

The unit costs for the resources were identified from published sources, or from expert opinion where necessary. The value and source of the proposed unit costs for each resource item are shown in *Table 17*. The unit cost for the actual water softener device and installation has been estimated as the appropriate proportion of the equivalent annual cost (i.e. estimated as an equivalent 12-week cost to accurately reflect the fact that the device has a typical lifespan of 12 years and depreciation has been assumed to be zero). This was done in order to express all costs on a 12-week basis. On this basis the average 12-week cost of the device and installation was £19.82. The cost analysis was undertaken using individual patient level data.

All costs are reported in UK pounds sterling for the year 2009. Mean resource use and costs per patient for group A and group B are presented along with mean difference in resource use and cost per patient and 95% CIs comparing the groups.

TABLE 18 Assumed salt usage

	SWET salt supply at installation		
Group	Number of residents	Salt boxes (six blocks/box)	Cost of salt for 12 weeks (£)
Group A (water softener + usual care)	≤ 3	2	30.72
	4–5	3	46.08
	≥ 6	4	61.44

Outcome measurement and valuation

Two cost-effectiveness analyses are presented using (i) the proportion of participants showing a 20% reduction in SASSAD score at week 12; and (ii) the proportion of participants showing a 50% reduction in SASSAD score at week 12. This enables health policy decision-makers to compare the cost-effectiveness of water softeners for the treatment of eczema with the cost-effectiveness of other eczema treatments.

An additional, cost–utility analysis is presented using health-related quality of life (EQ-5D). Data were captured using the children's version of the EQ-5D for children aged 7 years and over, or the proxy version of the EQ-5D for children aged 3–6 years.[30,31] A utility weight has been attached to the health state descriptions using the currently accepted UK adult tariff, calculated using the York A1 tariff.[32] Children under 36 months were excluded from this analysis, as the EQ-5D has not been designed for use in children aged < 3 years.

Quality-adjusted life-years (QALYs) for individual participants have been calculated using linear interpolation between the baseline and 12-week utility value (*Figure 13*). Using the area under the curve technique, the number of QALYs for the 12-week trial period was estimated for each participant as displayed in *Equation 1*.

$$[(UB+U12)\times 0.5\times 0.230769]-(UB\times 0.230769) \qquad \text{[Equation 1]}$$

where UB is utility at baseline, U12 is utility at 12 weeks, 0.5 reflects that we are measuring a triangle not a square and 0.230769 reflects the 12-week study period (12 weeks divided by 52 weeks).

The shaded area in *Figure 13* shows an example of the QALY area being measured for each individual participant, as the area between the linear interpolation line and a line drawn horizontally from the baseline value for the 12-week study period. *Figure 13* shows a gain in utility over time such that this individual would have gained a positive number of QALYs. If a loss of QALYs had occurred the diagonal line measuring utility over time would be reversed so that the line sloped downwards rather than upwards, and if there was no change in QALYs over the 12-week period then there would be no diagonal line indicating that utility had remained constant over time.

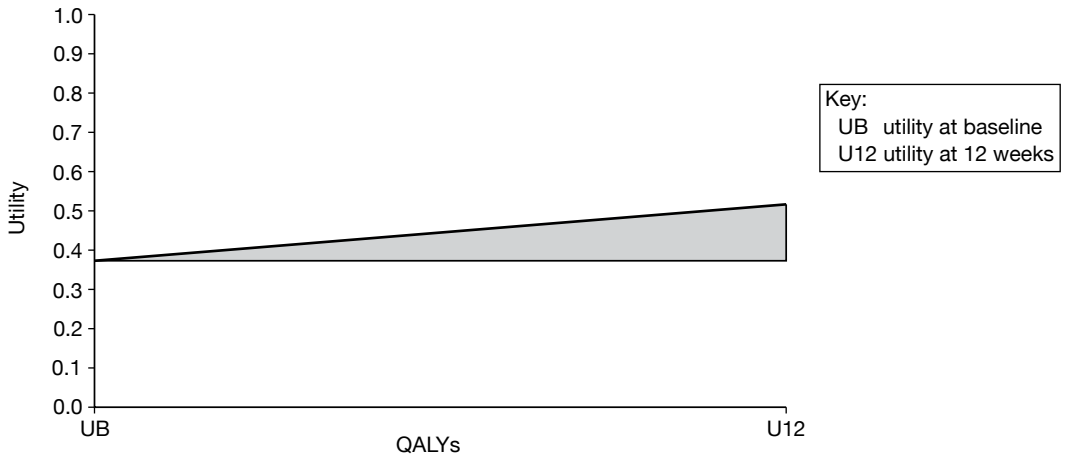


FIGURE 13 Quality-adjusted life-years.

Mean QALYs per patient for group A and group B are presented along with the mean difference in QALYs per patient and 95% CIs comparing the groups. This analysis allows health policy decision-makers to compare the value of water softeners for eczema with other health technologies in other areas of health.

Cost-effectiveness analysis and presentation of results

Where non-dominance occurs (that is where the intervention is more costly and more effective or less costly and less effective) an incremental cost-effectiveness ratio is presented as an incremental cost per patient achieving a 20% improvement in SASSAD score, an incremental cost per patient achieving a 50% improvement in SASSAD score and as an incremental cost per QALY. Additionally, cost-effectiveness acceptability curves are presented for the intervention and control group,[41,42] where the cost-effectiveness acceptability curve depicts the probability that an intervention is cost-effective at different levels of the cost-effectiveness threshold (that is for differing levels of WTP per QALY).

Sensitivity analysis

The base case is based on the typical, mean or most likely unit costs. As some of the unit costs are based on expert opinion, we have tested these assumptions by taking a best- and worst-case sensitivity analysis. All unit costs are varied firstly to their best case and then to the worst case to provide the range within which the true incremental cost-effectiveness ratio may lie (see *Table 17*). The broader this range, the greater our uncertainty in the base-case result.

For the cost–utility analysis, an additional sensitivity analysis was conducted including the children < 36 months by assuming a utility weight based on the child's severity of eczema (SASSAD score). Those with a SASSAD score of < 20 were assigned the mean utility weight of those aged ≥ 36 months with a SASSAD score of < 20, and those with a SASSAD score of ≥ 20 were assigned the mean utility weight of those aged ≥ 36 months with a SASSAD score of ≥ 20.

Secondary analyses

The base-case analysis makes best use of the data collected in the trial. However, it took a narrow perspective and short time frame. It had originally been planned to produce a model to explore the long-term effects of the water softeners. However, given the lack of treatment effect during the trial, this was no longer felt to be appropriate.

Contingent valuation study measuring willingness to pay

This study presented a unique opportunity to compare hypothetical WTP with actual WTP for a health intervention that is not currently available from the NHS. As a result, a WTP questionnaire was included in the assessments (see *Appendix 10*; it was designed based on previous contingent valuation questionnaires used by researchers at Nottingham University). We provided information to parents about the likely benefits for their home of having a water softener, and the uncertainty surrounding whether or not water softeners help to improve skin conditions, before asking the WTP question. Information was also provided on the lifespan and typical cost of the device. The WTP question was administered face to face at the baseline visit by the research nurse to all parents of participant children, and again by post at 12 weeks for a subsample of parents, to elicit the maximum WTP for an ion-exchange water softener device. Note: to avoid influencing data collected in the ex-ante WTP questionnaire, the actual reduced price (£437 including VAT) was not given to parents before their child's recruitment visit. From May 2007 to October 2008 this information was given out only after their child's 12-week assessment visit, once they had completed the second WTP questionnaire. Feedback indicated that a number of parents were unhappy with the short time between learning the reduced price and being asked to decide if they wished to purchase the water softener. Therefore, from

November 2008, parents were informed of the reduced price in the letter sent out immediately after their child's recruitment into the trial, and the second WTP questionnaire was abandoned.

Willingness to pay prior to using the water softener

Willingness to pay elicited prior to use of the ion-exchange water softener was measured at the baseline visit. Those giving zero bids were categorised as protestors (those who bid zero for moral or political reasons) or non-protestors (those who do not value water softeners at all).

Mean WTP was estimated and the distribution of WTP bids illustrated graphically (this represents the demand curve for water softeners for the treatment of childhood eczema).

A general linear regression analysis was undertaken to estimate how WTP for softeners before the trial varied according to a number of independent variables as defined in *Appendix 11*.

Actual willingness to pay

The number actually willing to pay for a water softener at the discounted price (or market price if they bought a non-trial device) was estimated as a proportion of those who were hypothetically willing to pay the actual asking price at baseline. The difference in hypothetical and actual WTP is reported.

A logistic regression analysis was undertaken to see which independent variables explained a parent's decision to purchase the water softener or not. The dependent variable was categorised into those who bought the device at the end of the trial (coded as 1) and those who did not buy the device (coded as 0). The independent variables included in the model are defined in *Appendix 11*.

This analysis enables a partial examination of the issue of hypothetical bias in contingent valuation in health care. However, it should be noted that as participants were offered a single price at the end of the trial, we are not able to estimate the actual maximum WTP for the water softener using this approach.

Results

Data from 323 participants (159 intervention and 164 control) were included in the base-case cost-effectiveness analysis and data from 228 participants (115 intervention and 113 control) were included in the base-case cost–utility analysis of participants aged 3 years and over. At baseline the groups were well matched (see *Table 2*).

Resource use and costs

Just 2.5% of weekly diaries were not completed, therefore data were not imputed for these entries. The mean total cost per patient in group A was £332 (SD £170) compared with £134 (SD £288) in group B (difference £198, 95% CI £146 to £250, $p < 0.001$). This significant cost difference was due to the cost of the intervention; all other resource categories (health professional visits, medications and other medical items) were not significantly different between groups (see *Table 19* for resource use and *Table 20* for resource costs).

Cost and resource-use data for children aged ≥ 3 years (as required for the cost–utility analysis) are included in *Appendix 12*.

TABLE 19 Mean (SD) resource use over the 12-week trial period

Resource use item	Group A (water softener + usual care) (*n* = 159)	Group B (usual care) (*n* = 164)	Mean difference (95% CI)
Intervention			
Ion-exchange water softener	1.00	0.00	1.00
Installation	1.00	0.00	1.00
Salt blocks	15.25 (7.42)	0.00 (0.00)	15.25 (14.08 to 16.41)
Face-to-face consultant-led follow-up attendance, paediatric dermatology	1.00	0.00	1.00
Secondary health care			
Hospital outpatients visit (follow-up attendance, paediatric dermatology)	0.26 (0.59)	0.35 (0.90)	–0.09 (–0.26 to 0.08)
Hospital admission [non-elective inpatient stay (short stay)]	0.00 (0.00)	0.01 (0.11)	–0.01 (–0.03 to 0.01)
Primary and community health care (consultation/visit)			
GP	0.52 (1.00)	0.49 (1.04)	0.03 (–0.20 to 0.25)
Practice nurse	0.04 (0.23)	0.15 (1.19)	–0.10 (–0.29 to 0.09)
Health visitor	0.01 (0.08)	0.02 (0.19)	–0.02 (–0.05 to 0.01)
Pharmacist	0.43 (1.27)	0.41 (1.19)	0.03 (–0.24 to 0.29)
Specialist nurse	0.21 (0.85)	0.27 (1.12)	–0.05 (–0.27 to 0.16)

TABLE 20 Mean health resource cost over the 12-week trial period (£ 2009)

Resource use item	Group A (water softener + usual care) (*n* = 159)	Group B (usual care) (*n* = 164)	Mean difference (95% CI)
Intervention	215.45 (7.88)	0.00 (0.00)	215.45 (214.22 to 216.69)
Ion-exchange water softener	14.33	0.00	14.33
Installation	5.49	0.00	5.49
Salt	44.63 (7.88)	0.00 (0.00)	44.63 (43.40 to 45.87)
Face-to-face consultant-led follow-up attendance, paediatric dermatology	151.00	0.00	151.00
Secondary health care	38.94 (88.63)	58.49 (167.24)	–19.56 (–48.77 to 9.65)
Hospital outpatients visit (follow-up attendance, paediatric dermatology)	38.94 (88.63)	52.48 (135.47)	–13.54 (–38.54 to 11.45)
Hospital admission [non-elective inpatient stay (short stay)]	0.00 (0.00)	6.01 (54.28)	–6.01 (–14.38 to 2.36)
Primary and community health care	72.12 (116.21)	78.68 (149.74)	–6.55 (–35.85 to 22.74)
GP	16.18 (30.97)	15.31 (32.30)	0.87 (–6.05 to 7.80)
Practice nurse	0.40 (2.11)	1.32 (10.75)	–0.92 (–2.63 to 0.77)
Health visitor	0.22 (2.78)	0.85 (6.66)	–0.63 (–1.75 to 0.48)
Pharmacist	18.23 (53.15)	17.16 (49.85)	1.07 (–10.22 to 12.36)
Specialist nurse	15.82 (63.06)	19.85 (82.82)	–4.03 (–20.12 to 12.06)
Medication and accessories	21.28 (31.99)	24.18 (41.15)	–2.91 (–10.97 to 5.15)
Total incremental cost	331.74 (169.95)	133.61 (288.33)	198.13 (146.47 to 249.80)

Family costs

Although the cost-effectiveness analysis adopted an NHS perspective, wider family costs were collected during the trial. Thirty-three per cent of families provided estimates of costs incurred as a result of their child having eczema over the trial period. For group A, mean family costs were £16.67 (SD £65.78, range £0–653) compared with a mean family cost of £20.82 (SD £92.29, range £0–1095) for group B, giving a difference of –£4.16 (independent samples test, $p < 0.641$). Items included medicinal products such as aqueous cream, E45 or supplements, travel and parking for appointments, special foods, cleaning products, clothing and bedding. It should be noted, however, that, although all participants were asked to report these data in the daily diary, it is not clear if non-reporting of these types of costs meant that they were not incurred or whether they were under-reported because in some instances it is hard to attach a monetary value. In a few cases respondents did not report a monetary value but did write a textual description of a resource item and so these items had to be excluded, for instance where respondents stated that their electricity bill or amount of clothes washing undertaken was higher. If mean costs are estimated across just those providing a cost estimate (48 participants in group A and 54 in group B), mean family costs for group A were £55.21 (SD £111.23, range £1.65–653) compared with a mean family cost of £63.24 (SD £153.17, range £1.19–1095) for group B, giving a difference of –£8.04 (independent samples test, $p < 0.761$). We did not collect non-monetary family costs, for instance time costs of accompanying children to visits, although the number of visits undertaken during the trial period tended to be quite small.

Cost-effectiveness analysis

The proportion of participants showing a 50% reduction in SASSAD score at week 12 compared with baseline was 18.87% (30/159 participants) in group A compared with 21.95% (36/164 participants) in group B, a difference of –3.08% ($p = 0.492$). The proportion of participants showing a 20% reduction in SASSAD score at week 12 compared with baseline was 48.43% (77/159 participants) in group A compared with 54.88% (90/164 participants) in group B, a difference of –6.45% ($p = 0.246$).

As the incremental mean cost is greater and incremental mean benefits lower for group A than for group B, it was not appropriate to estimate an incremental cost-effectiveness ratio because ion-exchange water softeners were dominated by usual care alone, i.e. they were both more expensive and no more effective than usual care, such that the NHS would not consider them a cost-effective use of NHS resources. The decision uncertainty is depicted in *Figures 14* and *15*. These cost-effectiveness acceptability curves show that there is around a 20% chance of the wrong decision being made if ion-exchange water softeners are not funded by the NHS.

Sensitivity analysis

For the best-case analysis dermatology consultation cost was removed from the intervention costs (as this may not be necessary in practice to obtain an ion-exchange water softener). The cost-effectiveness analysis based on the proportion of participants showing either a 50% or 20% reduction in SASSAD score at week 12 supported the base-case analysis. Costs in group A were greater than those in group B [mean cost £135.50 (SD £111.25) vs £94.13 (SD £179.51), incremental cost £41.37 (95% CI £8.76 to £73.98), $p = 0.013$], meaning that usual care was still both cheaper and slightly more effective than the use of an ion-exchange water softener in children with eczema. The associated cost-effectiveness acceptability curves (not shown) revealed that there is around a 35% chance of the wrong decision being made if ion-exchange water softeners are not funded by the NHS.

Worst-case analysis was not deemed to be necessary given that neither the base case nor the best case suggested cost-effectiveness for the NHS.

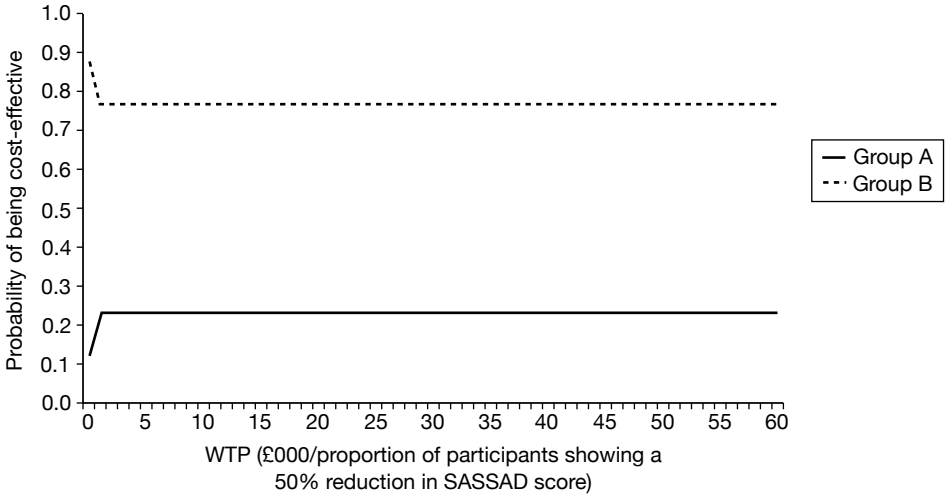


FIGURE 14 Decision uncertainty: plots of the cost-effectiveness acceptability curves for the proportion of participants showing a 50% reduction in eczema severity (SASSAD).

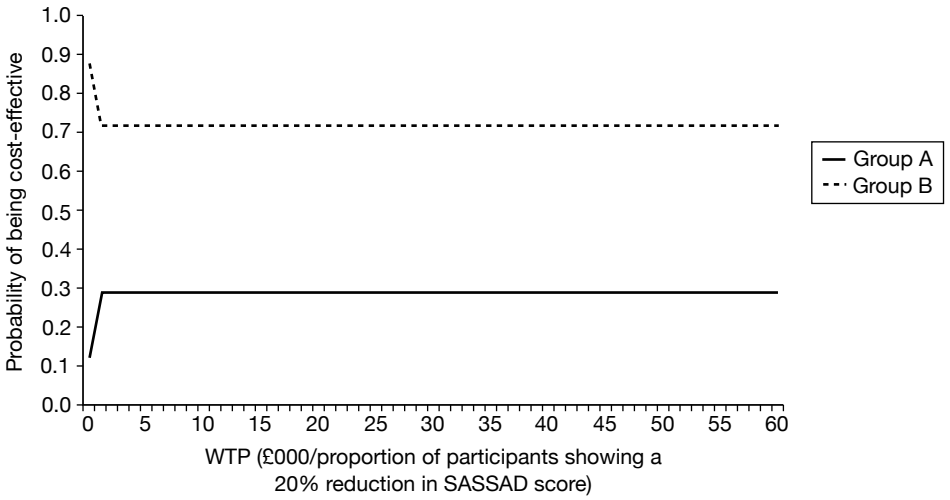


FIGURE 15 Decision uncertainty: plots of the cost-effectiveness acceptability curves for the proportion of participants showing a 20% reduction in eczema severity (SASSAD).

Cost–utility analysis

Group A gained a mean of 0.119 on the EQ-5D health-related quality of life scale and group B a mean of 0.066. The mean difference in EQ-5D was 0.054 (95% CI –0.015 to 0.122) (see *Table 13*).

The mean total cost per patient aged ≥ 3 years in group A was £315 (SD £64) compared with £143 (SD £343) in group B (difference £172, 95% CI £101 to £243, $p = 0<001$). (For full details, see *Appendix 12*.)

Group A gained a mean of 0.014 QALYs per patient and group B a mean of 0.008 QALYs per patient. The mean difference in QALYs per patient was 0.006 (95% CI –0.002 to 0.014, $p = 0.117$). Using the incremental mean cost reported in *Table 20,* the incremental cost per QALY was estimated as £28,002. *Figure 16* shows the cost-effectiveness acceptability curve for the 12-week study period. At all levels of WTP, usual care (group B) had a higher probability of being cost-effective.

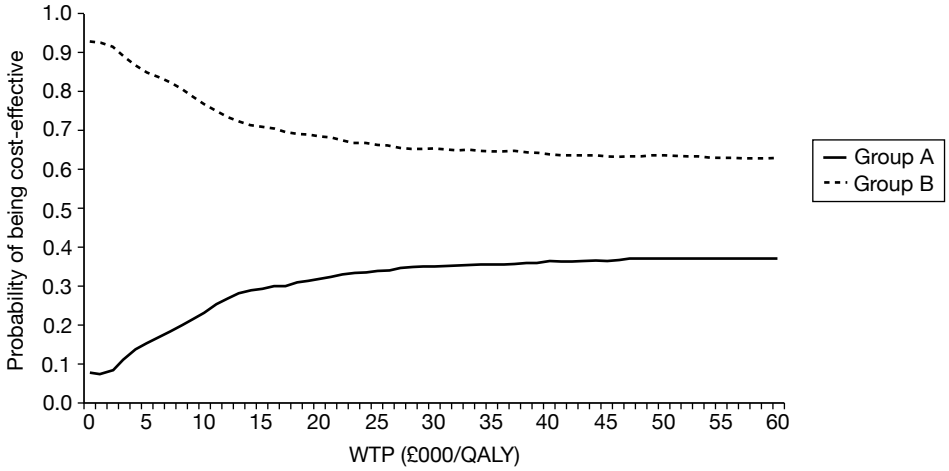


FIGURE 16 Decision uncertainty – plots of the cost-effectiveness acceptability curves for the base-case cost–utility analysis of year 3- to16- year-olds.

Sensitivity analysis

Sensitivity analysis including best-case costs and all participants (rather than just those aged ≥ 3 years who had EQ-5D scores) supported the main analysis. Possible incremental cost-effectiveness ratios ranged from £4548 (best case) to £53,957 (worst case).

Cost–utility sensitivity analyses for those aged ≥ 3 years are given in *Appendix 13*.

Secondary analyses

Modelling of long-term effects

As ion-exchange water softeners were not found to be clinically effective or cost-effective over the trial horizon, it was not felt to be appropriate to model the longer term cost-effectiveness of water softeners. However, an indication of the likely long-term cost of an ion-exchange water softener is helpful. For a typical family, the cost would be somewhere in the region of £3250. This assumes a 12-year lifespan for the device (covering initial purchase, installation and ongoing salt use) and a household of four or five people.

Contingent valuation study

Willingness to pay for water softeners before the trial

The majority of participants (333/336) provided an answer to the contingent valuation question, which asked parents to estimate the financial value of an ion-exchange water softener to them (the three not answering were all in group A). Given that water softeners are essentially private goods, it was felt that asking directly about participants' WTP for this product would be relatively intuitive. The mean (median/SD) WTP value was £506.68 (£500/£387.73) with a range from £0 to £3000 (see *Figure 17* for distribution of WTP responses). Just five (1.5%) participants (three in group A and two in group B) gave a value of zero and all were genuine zeros. Reasons given by these parents included not being willing to pay anything until proven to be of benefit for eczema, and the child's eczema not currently causing problems.

The results of the univariate general linear regression analysis in which hypothetical WTP was the dependent variable are reported in *Appendix 14*. The statistically significant variables

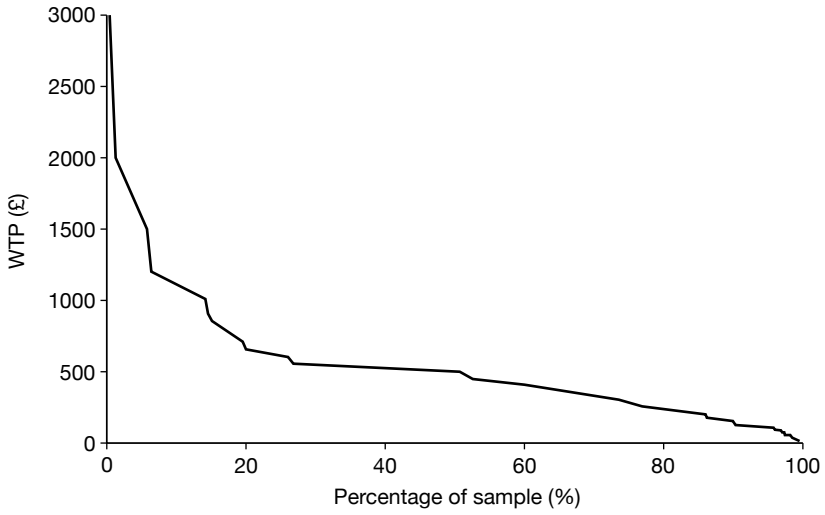


FIGURE 17 Willingness to pay for water softeners for children with eczema.

associated with a positive relationship with WTP included participants stating that their value reflected the anticipated benefits of the ion-exchange water softener (such participants were willing to pay on average £126.73 more than those not stating this reason); those households with an income of ≥ £50,000 (willing to pay £173.72 more on average than those not with this income); and number of nights at home (those with more nights at home willing to pay more). Participants who found the WTP task difficult, or who stated that their WTP reflected their ability to pay, reported significantly lower values of WTP.

The typical cost of an ion-exchange water softener is £600, but could range between £300 and £1800 (based on industry opinion). Using the mean WTP prior to using the water softener as a measure of benefit for the family, it can be inferred that families perceive the benefits of an ion-exchange water softener for their family to be a mean of £506.68. As the scenario provided to families included a description of the likely non-eczema-related cost savings (resulting from less lime scale and improved efficiency of household appliances leading to less fuel consumption and soap use for instance), this estimate of WTP can be taken to mean that families would find an ion-exchange water softeners to have a positive cost–benefit ratio for the family only at the lower price end of the market (i.e. where price is < £506.68). As shown above (see *Secondary analyses*), there were no significant cost savings for the families associated with costs incurred by the family as a result of their child's eczema, so these are not considered again here.

Willingness to pay for water softeners after the trial

At 12 weeks a subsample of 146 respondents (those recruited first to the study) were asked the same WTP question as at baseline to see if experience influenced valuations. Of these, only 97 (66%) provided a value (in addition two respondents stated 'priceless'). Not all 336 participants were asked this question because during the trial it became clear that parents wanted to have some idea of the actual price of the device they could buy at the end of the study in order to save for it. Once this information was divulged this question was felt to be inappropriate.

Mean (median/SD) WTP at the end of the trial was £375 (£300/£282) with a range from £0 to £1500 (*Figure 18*). Values for the same 97 participants prior to the trial were £475 (£400/£346 with a range from £0 to £1500). On average, experience of using the water softeners lowered their mean WTP by approximately £100. Overall, 26% gave higher WTP values at the end of the trial, 29% gave the same value and 44% gave a lower value.

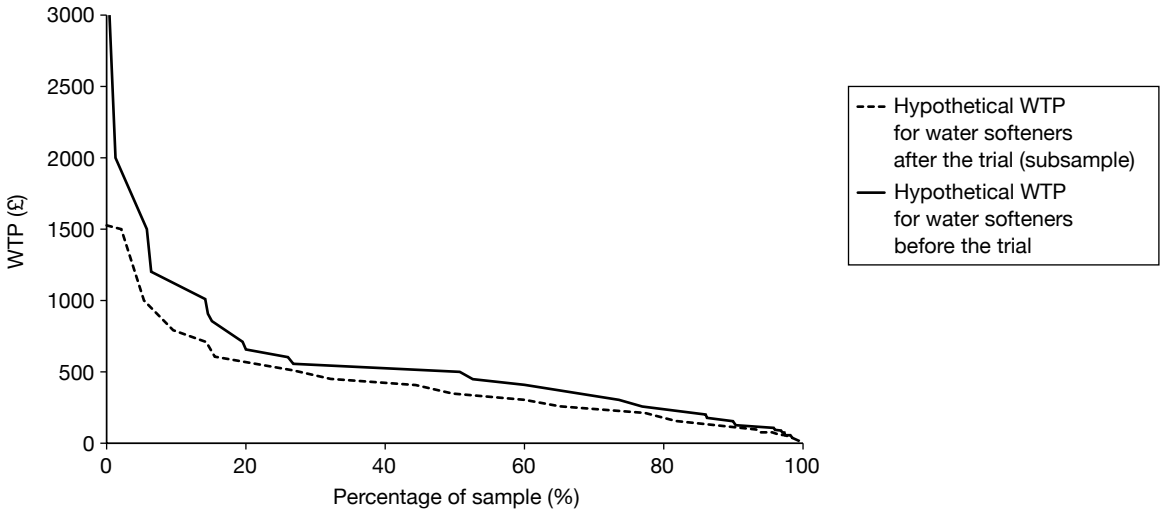


FIGURE 18 Demand curves for water softeners before and after participation in the trial.

The reasons given for WTP values before and after the trial are summarised in *Table 21* (respondents could give multiple responses).

Hypothetical versus real willingness to pay for an ion-exchange water softener

Table 22 shows the number (percentage) of participants who stated a hypothetical WTP value that was either above or below the actual discounted price they were offered at the end of the study (rows), and whether they actually chose to purchase the ion-exchange water softener (either a study device or private device – columns). Although the percentage who indicated a hypothetical WTP above the actual asking price and bought the device and those giving a WTP below the actual asking price and not buying the device account for over 50% of the relevant participants, clearly a large number changed their preferences during the trial, some changing in favour of buying the device and others choosing not to purchase, despite initially indicating that they thought the device might be worthwhile. The two groups account for a similar percentage of respondents.

To try to understand what influenced the decision to purchase or not, a binary logistic regression analysis was conducted. The results are shown in *Appendix 15*. Only the number of medications at baseline, water hardness at baseline and household income were significant determinants. An increase in the first two explanatory factors made it more likely that an ion-exchange water softener would be purchased; however, a household income of < £30,000 per annum made it less likely that an ion-exchange water softener would be purchased.

Discussion and conclusion

Main findings

The mean costs were consistently higher for the water softener group than for those receiving normal care as a result of the intervention costs. All other costs were similar between the groups and sensitivity analysis supported these findings. It is clear that on the basis of this trial, there is no evidence to suggest that ion-exchange water softeners provide a cost-effective treatment option for the treatment of children with eczema.

TABLE 21 Reasons for WTP for water softeners before and after the trial

Reason given	WTP reason before the trial[a] *n* (% of 336)	WTP reason after the trial[a] *n* (% of 99)	
This is a reasonable or fair amount for me to pay	136 (40)	41 (41)	
This is just a guess	109 (32)	26 (26)	
This amount reflects the benefits I think my child with eczema might get from the water softener	160 (48)	43 (43)	
This amount reflects the wider benefits of installing a water softener in my home	87 (26)	24 (24)	
This is how much I think a water softener would cost	84 (25)	24 (24)	
This is how much I can afford to pay	118 (35)	56 (57)	
Other reasons			
Pay more if proven to be effective but given unsure this is maximum WTP/wouldn't buy it for other benefits	24	No benefits experienced/not sure it is worth this amount	2
Based WTP value on family research into price of unit	6	Received benefits/but cannot afford it	2
If money no object would pay more/an amount that would not cause hardship to family	4	Undecided about whether there is a benefit but still useful to install	1
Considered running and service costs	2	Amount considered paying before trial	1
All I am prepared to pay	1	If helped eczema be priceless	1
Already decided to buy one at the end of the trial	1	Not popular with the rest of the family	1
Child's problems not so bad	1	Not had long enough to experience it	1
Total	**39**	Need to compare bills over same period	1
		The amount I am willing to pay to see if there is any benefit	1
		Total	**11**

a Participants could give more than one reason.

TABLE 22 Purchase decision by hypothetical WTP prior to start of the trial

Willingness to pay	Purchased water softener (%)	Did not purchase water softener	Total
WTP > purchase price	106 (59.2)	69 (43.9)	175 (52.1)
WTP < purchase price	73 (40.8)	88 (56.1)	161 (47.9)
Total	179 (53.3)	157 (46.7)	336 (100)
	Sensitivity 59%	Specificity 56%	

The results of the cost–utility analysis supported the cost-effectiveness analysis. Despite a slight (non-significant) improvement in the EQ-5D scores for those receiving the water softener, the cost–utility analysis estimated the use of water softeners to have an incremental cost per QALY of £28,018 in the base case. Sensitivity analyses revealed that this could range from £4548 per QALY (best case) to £53,957 per QALY (worst case).

For interventions with a cost per QALY > £20,000, the latest available National Institute for Health and Clinical Excellence (NICE) methods manual[43] states that decisions about whether

an intervention represents a good use of NHS resources will depend on a number of factors including the uncertainty surrounding the incremental cost-effectiveness ratio and whether the assessment of health-related quality of life was adequate or unlikely to have captured benefits of an innovative technology. Although, clearly, ion-exchange water softeners are a potentially innovative technology in the health-care context and this study used NICE's preferred measure of health-related quality of life (the EQ-5D, p. 38), this study found a large degree of uncertainty around estimates of the incremental cost per QALY, suggesting that this technology is unlikely to be viewed as offering the NHS value for money in treating the condition and age range considered.

Evidence from the contingent valuation study suggested that experience of using a water softener during the trial reduced the average WTP by approximately £100. This is possibly to be expected, given that people who believed in the value of water softeners would have been more likely to take part in the trial, and belief in the benefits of the water softeners was a significant factor in determining how much participants felt that they would be willing to pay prior to experiencing the intervention. However, the fact that many families opted to purchase the units despite little improvement in the eczema suggests that other factors were also important.

Strengths and weaknesses

This is the first economic evaluation of ion-exchange water softeners in the context of eczema care. The strengths of this economic evaluation are that it has been conducted alongside a RCT, which enabled comprehensive prospective data collection and suffered very few missing data. However, in line with all economic evaluations, it has had to employ some assumptions as detailed in *Chapter 2*. The uncertainty created by the most important of these was tested in sensitivity analyses, testing the extremes, but we did not include a probabilistic sensitivity analysis approach. It is a limitation of current health-related quality of life instruments as used in economic evaluations that they have not been developed or validated for very young children such that there is currently no best practice approach to valuing child health within a cost–utility framework. Although a child version of the EQ-5D has been tested in a survey of UK children aged 7–17 years,[31] which is completed by parental proxies,[44,45] and more recently, a revised youth version has been tested internationally,[46,47] there are still a number of methodological issues in this area of valuation, including questions about the relevance of included health dimensions and who, and from what perspective, the appropriate respondents are to attach a value to children's health states.[48,49] Consequently, we did not measure the health-related quality of life of those children aged < 3 years and these children were excluded from the cost–utility analysis. For those children aged > 3 years who had either a parental proxy or self-completed health-related quality of life score, a QALY was estimated for the trial period based on the utility weights of the York A1 tariff,[32] which were derived from non-institutionalised adults. Whether this is deemed acceptable depends on whether or not one believes voters'/taxpayers' perspectives are legitimate even when these perspective were elicited without specific reference to children's health status. Clearly, future research and consensus in this research area is needed. Given this context, the results of the cost–utility analyses reported above should be read with some caution.

Conclusion

Ion-exchange water softeners are unlikely to be a cost-effective intervention for children with eczema from an NHS perspective because of the lack of objective evidence of benefit and because they incur a cost. We find no basis for the NHS and other government bodies to consider funding ion-exchange water softeners for childhood eczema as they do not appear to work for this condition. The contingent valuation study taking a family perspective suggests that ion-exchange water softeners may be perceived as cost beneficial to certain individual families provided the cost of the device is at the lower end of the market price range.

Chapter 6

Discussion

Main findings

The primary outcome

This study is the only RCT to date assessing whether the installation of an ion-exchange water softener can help relieve the symptoms of eczema in children with moderate-to-severe eczema. The main findings based on a blinded evaluation of the primary end point of mean change in eczema severity at 12 weeks compared with baseline (as measured using the SASSAD) showed that installing water softeners was no better than usual care in relieving the symptoms of eczema. Furthermore, there was a narrow CI around that difference, excluding small but important clinical differences.

One possible reason for the discrepancy between our null trial findings and those of previous observational studies that found that increased prevalence of eczema in children living in hard water areas is that children in the observational studies ingested the water. In other words, it is possible that ingestion of hard water or a component to water that is related to water hardness actually induces skin inflammation directly or indirectly through inflammatory gene interactions, although we are not aware of any such mechanisms in the literature to date.

It is also possible that eczema represents a heterogeneous group of distinct genetic conditions, some of which will respond to water softeners and some of which will not. Previous research has suggested an association between the presence of eczema/dry skin and mutations of the filaggrin gene. A subgroup analysis based on the presence or absence of mutations of the filaggrin gene found no evidence that the treatment effect varied between those with and without the mutation.

We wish to stress that those who participated in the study were not formally tested for atopy by means of circulating specific IgE antibodies. They did, however, represent the sort of patients with eczema typically seen in clinical hospital practice. It is possible that a subgroup analysis of atopic versus non-atopic individuals might have shown that one group benefits while the other does not. Based on our previous observation that IgE responsiveness adds little information to our predictive ability about eczema,[50] added to our desire to minimise the number of subgroup analyses to avoid inappropriate post hoc findings, we chose not to measure atopic status in this pragmatic trial.

Other outcomes

In addition to our primary outcome measure, which was assessed blindly, we had a number of secondary outcomes, some of which were assessed blindly (proportion showing reasonable, good or excellent improvement, night-time movement, medication used) and some of which were assessed by parents who were not blinded (POEM, TCWs and WCWs, DFI, and EQ-5D).

For all of the blinded outcomes, there was no difference between the treatment groups. Of the unblinded secondary outcomes, all but one showed small, but statistically significant, differences in favour of the water softener group. However, the magnitude of improvement seen in these outcomes was small and unlikely to be clinically meaningful. It is also possible that our emphasis on objective outcomes meant that some important potential benefits were not captured in

the primary analysis. Other factors, such as improvements in quality of life or a reduction in symptoms (e.g. dry skin), may be important drivers in determining whether or not parents perceived a benefit.

Strengths and weaknesses

The main strengths of our study was its internal validity (concealment randomisation, blinding of research nurses and investigators to allocation, minimal data attrition) and the use of an objective validated primary outcome measure. Additionally, the study recruited the required number of participants according to the initial power calculation.

The 95% CIs for the primary outcome were extremely narrow, making it unlikely that a clinically significant benefit had been excluded by chance. Indeed, performing a per-protocol analysis based on those with maximum exposure to the water softener and excluding those who had changed their usual eczema treatments during the trial did not change the overall interpretation of these results.

Although the unblinded secondary outcomes (with the exception of EQ-5D) showed small statistically significant differences in favour of the water softener group, it is most likely that these were due to observer bias.

It is also possible that treatment effects were masked by the usual eczema care that the children received. We do not consider this to be the case and, in fact, we noted that total amount of medications used was lower than expected in this patient grouping.

A potential weakness could be that the relatively short duration of the trial was insufficient to capture any treatment effect. Anecdotal reports from patients with eczema suggested that any benefit from moving to a soft water area or installing a water softener would be apparent within a few days or within 2 weeks. This led us to anticipate that, if a treatment response existed, it was likely to occur more quickly than 12 weeks. It is still possible that water softeners could have a slowly evolving and subtle benefit that would be apparent only after 1 year or more. However, both treatment groups improved in disease severity during the trial, and there was no hint that the intervention group was starting to show more improvement than the control group towards the end of the 12-week period.

The continued use of soap and soap products during the trial may have limited the observed benefits if families were using too much soap in conjunction with the water softener. However, this was a pragmatic study that aimed to capture the effects of water softeners according to standard advice. Evidence of how much soap was actually used was not collected, as we did not want to change participants' behaviour by intensive monitoring.

Generalisability

This study has good external validity as it was designed as a pragmatic study. Participants were recruited from eight UK centres across the primary and secondary care setting, and included families of diverse socioeconomic backgrounds. Every effort was made to include participants who lived in rented accommodation as well as home owners, and participants were able to continue with their usual eczema care. Nevertheless, the results are applicable only to children

with moderate-to-severe eczema. The baseline characteristics of the sample are typical of children seen in clinics with moderate-to-severe eczema. We are not able to comment on the impact of other types of water-softening devices [e.g. physical water devices; or the impact of softened water in adults and other skin conditions (including dry skin)].

Implication for health care

The results of this study are clear, and do not support the use of ion-exchange water softeners for the treatment of eczema in children. Whether or not the wider benefits of installing a water softener in the home are sufficient to justify the purchase of a softener is something for individual householders to consider on a case-by-case basis.

Implication for future research

High Priority

Assessment of other non-pharmacological therapies

This trial demonstrated overwhelming demand for non-pharmacological interventions for the treatment of eczema, and this is something that should be considered when prioritising future research in the field, especially in relation to emerging genetic subtypes. Specific non-pharmacological interventions that could be tested include specialised clothing such as silk garments[51] or antibacterial garments impregnated with silver,[52] or the effects of occlusive bandaging in controlling eczema flares.[53] The evaluation of educational interventions for eczema, such as nurse education, is also ripe for evaluation in a UK setting.[54]

Core outcome measures

The profusion of poorly developed and validated outcome measures is also cause for concern and eczema research would benefit from harmonisation of a set of core outcomes for all clinical trials, as has been achieved by the Outcome Measures in Rheumatology (OMERACT) initiative and currently taken forward by the Core Outcome Measures in Trials (COMET) initiative. Some early work on prioritising key domains has started.[55]

Medium priority

Flare factors

While this trial has shown no benefit of water softeners for the treatment of eczema, there is still a need to explore and understand the effects of the environment on the incidence and prevalence of eczema, especially a more scientific understanding of what environmental factors may be associated with flares in people with established eczema. Some research has already pointed to the possibility that multiple exposures are acting together in a complex way before a flare occurs.[56,57]

Objective outcome measures

Further work is also required in the development of objective outcome measures for the assessment of eczema. The SWET trial neatly demonstrated the importance of using objective outcome measures in trials in which it is not possible to blind participants to treatment allocation. While the Actiwatches™ used in this trial showed great promise in this regard, it is concerning that data relating to the proportion of the night spent moving were poorly correlated with all of the other outcome measures. Further work is clearly required in order to understand why this might have been the case.

Low priority

Water softeners/conditioners

While we do not recommend a repeat of this study in the UK, it is always useful to see if the results can be replicated in other studies performed by different teams in other countries. Our research study evaluated only ion-exchange water softeners because they soften the water so dramatically. It is possible that other types of domestic water devices called 'physical water conditioners', which reduce limescale build-up by altering the physical properties of calcium and magnesium ions, could have an effect on the skin which could be explored in preliminary laboratory experiments that evaluate their effect on skin barrier parameters such as transepidermal water loss.[15] We cannot recommend either of these suggestions as priorities.

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Contributions of authors

Kim Thomas (Associate Professor of Dermatology, non-clinical) contributed to the conception and design of the study, trial management and oversight (as Lead Investigator) interpretation of data and writing of the report.

Karin Koller (Trial Manager) contributed to trial management and oversight, data collection, analysis and interpretation of data and writing of the report.

Tara Dean (Professor of Health Sciences) contributed to the conception and design of the study, recruitment to Isle of Wight and Portsmouth study centres (as Principal Investigator), trial management and oversight, interpretation of data and writing of the report.

Caroline O'Leary (Statistician) carried out all statistical analyses and contributed to analysis and interpretation of data and writing of the report.

Tracey Sach (Senior Lecturer in Health Economics) contributed to the conception and design of the study, carried out all health economics analyses and contributed to analysis and interpretation of data and writing of the report.

Anthony Frost (Director of Aqua Focus Ltd; UKTWA representative on TMG) contributed to the conception and design of the study, trial management and oversight, and writing of the report.

Ian Pallett (British Water Technical Consultant) contributed to the conception and design of the study, trial oversight and writing of the report.

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Hywel Williams (Professor of Dermato-epidemiology) contributed to the conception and design of the study, trial management and oversight (as Chief Investigator and Principal Investigator of Nottingham study centre), interpretation of data and writing of the report.

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Appendix 1

Information sources search strategies

Literature search strategy for RCTs:

The following databases were searched:

- The Cochrane Skin Group Specialised Trials Register (up to 13 January 2010)
- The Cochrane Library 2009, issue 4
- MEDLINE (2000 to end of 2009)
- EMBASE (2000 to end of 2009)
- CHINAL (inception to end of 2009)
- AHMED (inception to end of 2009).

Details of MEDLINE search

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomised.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 6 or 3 or 7 or 2 or 8 or 1 or 4 or 5
10. (animals not (human and animals)).sh.
11. 9 not 10
12. Exp Dermatitis, Atopic/
13. atopic dermatitis.mp.
14. atopic eczema.mp.
15. exp NEURODERMATITIS/
16. neurodermatitis.mp.
17. infantile eczema.mp.
18. childhood eczema.mp.
19. Besniers' Prurigo.mp.
20. Exp Eczema/or eczema.mp.
21. 17 or 12 or 20 or 15 or 14 or 18 or 13 or 16 or 19
22. 11 and 21
23. Limit 22 to yr = '2000 to 2009'

Appendix 2

Pre-recruitment screening

Telephone screen checklist carried out by research nurse

	Questions	YES	NO	Comments
1	**Is your child between the ages of 6 months and 16 years?**			Dates relate to age at baseline visit, not today's date. i.e. child must be at least 6 months old at baseline, or not have 17th birthday before baseline visit. It is ok to become 17 years old during the 16-week study period. If the family have more than one child with eczema it is important that they decide which child will be the 'index case' for the study.
2	**Do you live near one of the study centres / in a hard water area?**			Establish willingness to travel for clinic visits. If Nottingham/Notts check hardness from post-code on Severn Trent website www.stwater.co.uk
3	**Do you live in a property which is less than 5 storeys high?**			If high rise block of flats, family must live on first 4 floors to be eligible
4	**Do you already have a plumbed-in water softener device? (Not a drinking water filter). This includes ion-exchange softeners, polyphosphate dosing units, physical conditioners or any other treatment system aimed at reducing scale?**			If the home clearly has an ion-exchange water softener or any other "softening" device they are ineligible to enter the trial. If they're not sure if they have a water softener device or not, the study will send a water engineer to check the home. [NOTE: some modern boilers have water softeners attached to them e.g. the Combi-mate is a polyphosphate dosing unit. There is also a physical conditioner device called the Salamander]
5	**Do you have any plans to refit or modify your kitchen over the next 6 months?**			It is important that the kitchen plumbing and layout doesn't change between the original home screen and the date for installation, otherwise we might find an installation isn't technically possible after the participant has been randomised to the study.
6	**Does your child mainly live and sleep at this address?**			To ensure adequate exposure to the intervention, maximum time child can be away over next 4/5 months = 21 days. Ask about holidays planned over the next few months.
7	**Has your child** **i) started a new treatment regimen for their eczema within the last 4 weeks?** **ii) Taken oral steroids within the last 4 weeks?** **iii) Taken systemic medication for their eczema within the last 3 months? (e.g. cyclosporine A, methotrexate)** **iv) had UV therapy for their eczema in the last 3 months?**			If any of these are answered YES, this does not immediately exclude the child because these time frames relate to the date of the baseline visit, which could be scheduled for a date when all answers will be NO.

	Other topics to go though:	
8	**Do you live in your own home, or is it rented?** If rented, a letter will need to be sent to their landlord, or property owner, to ask permission for a water softener to be installed. We can supply a standard letter for them to send. Permission must be obtained BEFORE anything else can happen. If it is a council property, check if permission has been obtained from the relevant local council for softener installations	
9	**Have you read the Parents Information Sheet / FAQ about the study?** If no, send a copy of PIS plus age-related copies and FAQ (latest version), or give them study website address if they have access to the internet www.swet-trial.co.uk	
10	**Do you know how the water softener is installed?** Explain that the water softener unit will usually be installed underneath the kitchen sink, but, for practical reasons this may not always be possible e.g. it could end up being installed in a nearby cupboard. Explain there are four connections: inlet, outlet, drain and overflow, and that the overflow is a ½" (12 mm) pipe which needs to be run through an outside wall (as a safety device to alert the householder if a fault develops). Explain as a routine part of the installation they will be provided with an extra tap at the side of the kitchen sink (usually faucet-style) to provide mains (non-softened) water for drinking. This involves drilling a small 3/8" (10mm) hole in the kitchen worktop. At the end of the study the drinking tap will be removed and the hole capped off, or the tap can be left in place if they want to keep it e.g. to use it to supply water from a drinking water filter. They can opt-out of having the separate tap if they want to. Discuss different options: drinking softened water / buying bottled water / un-softened water through a kitchen 3-way tap (if they have this) or a tap on the front of an American-style fridge.	
11	**What happens next?** If all of the above is OK, parents will be contacted by John Kyle from the SWET Engineering Team (or MG Heating on Isle of Wight) to arrange for one of their water engineers to carry out a Home Screening Visit to check the **water hardness level** and whether the home is suitable for installation of the water softener. This will take about 30 minutes. To be eligible for the trial your water hardness needs to ≥ 200 mg calcium carbonate/litre (>80 mg/l calcium).	
12	**Suitable days/dates/times for engineer visit?** Explain that the SWET engineers are really busy guys, working not just on our study - and often travelling long distances to cover our SWET homes. So it is really helpful for the study if the parent can be (i) as flexible as possible when agreeing with an engineer a time/date and (ii) be aware that if they change the appointment at the last minute, it may be up to 2 weeks before the engineer can find another slot. As our study has a relatively short study period (just 16 weeks) an unexpected delay of 2 weeks can cause significant problems for us.	

Home screening carried out by water engineer

This site survey is to determine the suitability of the site for inclusion in the trial and whether there are any special requirements for installation.

PART ONE – please tick. If any grey boxes are ticked, property is **EXCLUDED** from study. Advise occupier.

	Exclusion/Inclusion Criteria	**YES**	**NO**
1.	Is the property less than 5 storeys high or is the residence on the 5th floor or below?		
2.	Does the property have a water treatment device installed, including ion-exchange softeners, polyphosphate dosing units, physical conditioners or any other treatment system aimed at reducing scale? If YES: please describe type of unit and record water hardness level of the HOT water: Unit: _____ hot water hardness _____ mg/l		

PART TWO – please tick. If any grey boxes are ticked, let occupier know that the result of the home screen will be advised as soon as possible.

		YES	**NO**
1.	Is the mains cold water hardness level greater than 200 mg/l calcium carbonate?		
2.	Can you install a water softener in the home? If the answer is NO please give reasons in box below:		

PART THREE - The following is a **checklist** which should be completed in full for each potential installation site to ensure that all aspects of installation are considered.

1.	Floor level of kitchen	G/1 / 2 / 3 / 4
2.	Location of internal stop valve	
3.	Is stop valve operable?	Yes / No
4.	If answer to 3 is No: is there an external isolation point?	Yes / No
5.	With stop valve fully closed does it isolate the supply? (Check at kitchen tap)	Yes / No
6.	With stop valve fully closed, are ALL cold supplies in the home isolated [or if they continue to flow, they do so under lower pressure i.e. from head tank?]	Yes / No
7.	Water hardness using Hach test kit	mg/l

8.	Water supply pressure at outside tap or washing machine connection (Ensure no other usage while taking the reading, e.g. washing machine, toilet, etc.)	psi
9.	Is the pipework to the washing machine clearly and visibly directly supplied from the expected location of the water softener?	Yes / No
10.	Identify location for softener downstream from the stop valve, and agree with occupier	(sketch overleaf)
11.	Is the cabinet floor structure adequate to carry the weight of the softener?	Yes / No
12.	Is it remote from sources of heat? (dishwasher, washing m/c, hot water pipes)	Yes / No
13.	Is there adequate access for salt replacement?	Yes / No
14.	Is the incoming main sufficiently close for the softener flexible connections?	Yes / No
15.	Is the incoming main sufficiently accessible to make the break-in?	Yes / No
16.	Pipe size at point of break-in	mm
17.	Pipe material: copper / galvanised / steel / plastic	
18.	Can the overflow be directed through a suitable outside wall?	Yes / No
19.	Identify location for overflow and check occupier agrees to hole being drilled for overflow pipe	(sketch overleaf)
20.	The study requires installation of a bypass (hardwater) mains drinking faucet by the kitchen sink, if technically possible. Is this technically possible?	Yes/ No
21.	Identify route for hard water drinking tap to kitchen sink	(sketch overleaf)
22.	Does occupier agree to drilling countertop for bypass (hardwater) mains drinking tap?	Yes / No N/A
23.	Is there an outside tap?	Yes / No
24.	If so, will softener be installed downstream of outside tap?	Yes / No
25.	If not, will occupier accept softened water at outside tap (advise how softener can be put into bypass mode)	Yes / No
26.	Is there adequate storage for salt (agree with occupier)?	Yes / No
27.	Hot water system	vented / unvented
28.	Number of residents living in the residence	
29.	Estimated man hours for installation	
30.	Have photos been taken?	Yes / No

On the chart below, sketch out the location of: incoming water main; stop valve; proposed location for softener; hot and cold pipes; outside tap; drain; cooker; washing machine; sink; outside walls; interior walls which obstruct proposed pipe runs.

Appendix 3

Outcome measures

Six Area, Six Sign Atopic Dermatitis score/Three-Item Severity score

Six Area, Six Sign Severity Score (SASSAD)

To be completed by Research Nurse

Head & neck	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Subject number

Subject Initials

Visit

Date

Centre

Trunk	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Hands (including wrists)	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Score

0 = absent

1 = mild

2 = mod

3 = severe

Feet (including ankles)	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Arms	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Representative site (photographed area) for TISS (Three Item Severity Score):	
Erythema	
Excoriation	
Oedema / papulation	
TOTAL TISS score	
(Not to be included in SASSAD score)	

Legs	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Total body score =

Location of representative site: _____

Photograph taken? Yes / No (circle)

Patient-Orientated Eczema Measure

Eczema Questionnaire - POEM

To be completed by parent/guardian

Please circle your answer for each question

1. Over the **last week**, on how many days has your child's skin been **itchy** because of the eczema?

   No days 1-2 days 3-4 days 5-6 days Every Day

2. Over the **last week**, on how many nights has your child's **sleep** been disturbed because of the eczema?

   No days 1-2 days 3-4 days 5-6 days Every Day

3. Over the **last week**, on how many days has your child's skin been **bleeding** because of the eczema?

   No days 1-2 days 3-4 days 5-6 days Every Day

4. Over the **last week**, on how many days has your child's skin been **weeping or oozing clear fluid** because of the eczema?

   No days 1-2 days 3-4 days 5-6 days Every Day

5. Over the **last week**, on how many days has your child's skin been **cracked** because of the eczema?

   No days 1-2 days 3-4 days 5-6 days Every Day

6. Over the **last week**, on how many days has your child's skin been **flaking off** because of the eczema?

   No days 1-2 days 3-4 days 5-6 days Every Day

7. Over the **last week**, on how many days has your child's skin felt **dry or rough** because of the eczema?

   No days 1-2 days 3-4 days 5-6 days Every Day

Dermatitis Family Impact

Family impact of childhood eczema

[To be completed by parent/guardian]

What is your relationship with the child? (e.g. mother/father): _____

How old are you? Less than 25 yrs ☐ 25 to 35 yrs ☐
36 to 45 yrs ☐ Older than 45 yrs ☐

The aim of this questionnaire is to measure how much your child's skin problem has affected you and your family OVER THE LAST WEEK. Please tick √ one box for each question.

1. Over the last week, how much effect has your child having eczema had on housework, e.g. washing and cleaning?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐
2. Over the last week, how much effect has your child having eczema had on food preparation and feeding?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐
3. Over the last week, how much effect has your child having eczema had on the sleep of others in your family?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐
4. Over the last week, how much effect has your child having eczema had on family leisure activities e.g. swimming?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐
5. Over the last week, how much effect has your child having eczema had on time spent on shopping for the family?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐
6. Over the last week, how much effect has your child having eczema had on your expenditure, e.g. costs related to treatment, clothes etc?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐
7. Over the last week, how much effect has your child having eczema had on causing tiredness or exhaustion in your child's parents / carers.
   Very much ☐ A lot ☐ A little ☐ Not at all ☐
8. Over the last week, how much effect has your child having eczema had on causing emotional distress such as depression, frustration or guilt in your child's parents / carers?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐

9. Over the last week, how much effect has your child having eczema had on relationships between the main carer and partner or between the main carer and other children in the family?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
10. Over the last week, how much effect has helping with your child's treatment had on the main carer's life?	Very much A lot A little Not at all	☐ ☐ ☐ ☐

Please check that you have answered EVERY question.

European Quality of Life-5 Dimensions

Health-related quality of life questionnaire (EQ-5D)
To be completed by parent/guardian if child aged 3-6 years

By placing a tick in one box in each group below, please indicate which statement best describes your child's health state today.

Mobility

S/he has no problems in walking about	❑
S/he has some problems in walking about	❑
S/he is confined to bed	❑

Self-Care

S/he has no problems with self-care	❑
S/he has some problems washing or dressing her/himself	❑
S/he is unable to wash or dress her/himself	❑

Usual Activities

S/he has no problems with performing her/his usual activities	❑
S/he has some problems with performing her/his usual activities	❑
S/he is unable to perform her/his usual activities	❑

Pain/Discomfort

S/he has no pain or discomfort	❑
S/he has moderate pain or discomfort	❑
S/he has extreme pain or discomfort	❑

Anxiety/Depression

S/he is not anxious or depressed	❑
S/he is moderately anxious or depressed	❑
S/he is extremely anxious or depressed	❑

Compared with her/his general level of health over the past 12 months, her/his health today is:

Better	❑
Much the same	❑
Worse	❑

Describing your health TODAY (EQ-5D) (EuroQol 5 dimension)

To be completed by child if aged 7 or over

Please tick ONE box in each section which best described your health TODAY.

Mobility

- I have no problems walking about ❑
- I have some problems walking about ❑
- I have a lot of problems walking about ❑

Looking after myself

- I have no problems washing or dressing myself ❑
- I have some problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

Usual Activities (e.g. going to school, hobbies, sports, playing)

- I have no problems doing my usual activities ❑
- I have some problems doing my usual activities ❑
- I am unable to do my usual activities ❑

Pain/Discomfort

- I have no pain or discomfort ❑
- I have some pain or discomfort ❑
- I have a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

- I am not worried, sad or unhappy ❑
- I am a bit worried, sad or unhappy ❑
- I am very worried, sad or unhappy ❑

During the last 12 months how has your health been in general?
Would you say it has been:

- Very Good ❑
- Good ❑
- Fair ❑
- Poor ❑
- Very poor ❑

Willingness-to-pay questionnaire

Health Economics Questionnaire

To be completed by parent/guardian

As part of this study we are interested to see how much people might value water softeners for their child with eczema. One way of measuring this is to ask how much you would be willing to pay in order to get a water softener, that is, what you would be prepared to give up in order to receive one.

You are NOT being asked to pay anything for the water softener that will be installed in your home as part of the SWET study - we are just interested in your views about the value of water softeners.

The likely benefits of installing a water softener in your home are:

- Your heating system (boiler) will work better and use less fuel.
- Your appliances, such as your washing machine, will not fur up.
- You will be able to use less washing powder and soap.
- You will not get scum or lime scale deposits on your bath, sinks and shower.
- It is also possible that using a water softener may improve your child's eczema – although obviously we are not sure of this, and this is why we are doing the study.

At the moment, water softening devices are only available if you buy one yourself. These units usually last for 10 to 20 years, and can be moved from one house to another. The devices typically cost anywhere in the region of £350 to £1500 (excluding installation costs and the recurrent costs of salt).

If you were to buy a water softener today, what is the maximum you would be willing to pay for it? (This value can be anything you like, including zero).

Remember: You will not be asked to pay this amount, but it should represent the amount that you would be willing to pay for the machine itself (excluding installation costs). Providing a money value is just a way of showing us how important (or unimportant) you think water softening devices are.

The most I would be willing to pay for a water softener is: **£.....**

Appendix 4

Protocol and statistical analysis plan

Softened Water Eczema Trial (SWET)

A multi-centre randomised controlled trial of ion-exchange water softeners for the treatment of eczema in children

Protocol

Version 6.0
12 October 2009

ISRCTN number: ISRCTN71423189
MREC Ref: 06/MRE08/77
Address of lead R&D:
University Hospitals Nottingham, Research and Development, E11 Currie Court, Nottingham NG7 2UH

Funded by: NHS Health Technology Assessment (HTA) Programme

Sponsored by: University of Nottingham

Co-ordinating Centre:
Centre of Evidence Based Dermatology, University of Nottingham, King's Meadow Campus, Lenton Lane, Nottingham. NG7 2NR

Abbreviations

GCP	Good Clinical Practice
CI	Chief Investigator
COREC	Central Office for Research Ethics Committees
CRF	Case Report Form
CTSU	Clinical Trials Support Unit
DFI	Dermatitis Family Impact (questionnaire)
Eczema	Atopic Eczema
EQ-5D	EuroQol 5 dimension (Quality of Life instrument)
HTA	Health Technology Assessment
ITT	Intention to Treat
MREC	Multi-centre Research Ethics Committee
MHRA	Medicines & Healthcare Products Regulatory Agency
PI	Principal Investigator
POEM	Patient-Oriented Eczema Measure
SASSAD	Six Area Six Signs Atopic Dermatitis Score
SOP	Standard Operating Procedure
TCW	Totally Controlled Weeks
TMG	Trial Management Group
TSC	Trial Steering Committee
WCW	Well Controlled Weeks

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2. BACKGROUND

2.1 Existing research

The NHS Health Technology Assessment (HTA) systematic review of atopic eczema treatments included a chapter on the evidence base for non-pharmacological interventions[1]. This failed to identify any trials evaluating the use of water softeners for patients with atopic eczema. The only trials of possible relevance were an inconclusive trial looking at the benefits of salt baths, and another that examined the use of biological versus non-biological washing powders. This search was updated in 2006 and no new references were found.

There is epidemiological evidence linking increasing water hardness with increasing atopic eczema prevalence. This was first demonstrated by the current research team in an ecological study published in *The Lancet* of 4141 randomly selected primary school children in the Nottingham area [2]. The 1-year period prevalence of eczema was 17.3% in the hardest water category and 12.0% in the lowest (odds ratio of 1.54, 1.19-1.99 after adjustment for confounders). Similar results have recently been found in Japan [3].

If the above associations are true, a number of plausible mechanisms can be forwarded to suggest why hard water could exacerbate eczema. Perhaps the most likely explanation is increased soap usage in hard water areas; the deposits of which can cause skin irritation in eczema sufferers. A direct chemical irritant effect from calcium and magnesium salts is also possible, or an indirect effect of enhanced allergen penetration from skin barrier disruption.

2.2 Hypothesis

- That the installation of an ion-exchange water softener will help to relieve the symptoms of eczema in children with moderate to severe eczema.
- That the installation of an ion-exchange water softener will result in cost implications to both patients and the NHS.

2.3 Benefit / risk assessment

This is very low risk trial as the intervention is non invasive with no known clinical side effects. Participants simply receive softened water for bathing and washing of clothes. Drinking water will remain unchanged.

The water softening units will be installed by a qualified water engineer according to the Code of Practice produced by British Water.

The unit to be used is a generic version of a commercially available unit which has been encased in a generic outer box in order to prevent commercial advantage for any individual water softener supplier. Ion-exchange technology is well understood and widely used throughout the world.

Possible benefits to trial participants, in addition to improvement in eczema symptoms, include reduced scaling of water appliances, reduced soap / cleaning product consumption and reduced energy consumption.

3. STUDY DESIGN

This is a single-blind, parallel group randomised controlled trial of 12-week duration, followed by a 4-week cross-over period (Figure 1). The study will be analysed as a parallel group study, but the final 4 week period will include exploratory analyses to explore within person effects. Specifically, these exploratory analyses will provide further information on (i) the speed of onset of benefit for the delayed treatment group, and (ii) on how quickly benefits are lost once treatment is removed in the active treatment group. Three hundred and ten children with moderate to severe eczema will each be enrolled into the study for a period of 16 weeks. Participants will be enrolled over a period of 18-20 months, starting in Spring 2007. The end of study is defined as being the final assessment visit of the last participant into the trial.

Figure 1: Study design

	STUDY PERIOD = 16 weeks		
	0 to 12 weeks	**12 to 16 weeks**	
Group A	Usual eczema care + water softener installed (n = 155)	Unit removed	Option to purchase unit at reduced cost
Group B	Usual eczema care + delayed installation (n = 155)	Unit installed	

4. OBJECTIVES

i. To assess whether the installation of an ion-exchange water softener improves eczema in children.
ii. If so, to establish the likely cost and cost-effectiveness of this intervention.

5. INTERVENTIONS

5.1 Treatments to be compared

Ion-exchange water softening units will be compared with usual care. Ion exchange water softening is a scientifically defined, understood and described process using a synthetic polystyrene resin in which primarily the divalent cations (positively charged), calcium and magnesium found in domestic water supplies, are replaced by the monovalent cation, sodium, from common salt. The water softener used in the study has two cylinders of resin which are used alternately. A control valve ensures that when the resin capacity of one cylinder is exhausted it automatically switches the water flow to the second cylinder and, using common salt, regenerates the first to be ready for use when the second is exhausted. Ion-exchange water softening units typically reduce the water hardness to practically zero[1].

All units will be installed in the child's principal residence and salt will be supplied for the duration of the trial. Standard procedure will be to soften all water in the home, and provide mains drinking water through an extra (faucet-style) tap installed at the side of the kitchen sink. Participants will be given the opportunity to opt out of having this

[1] By contrast, physical water conditioners affect the behaviour of calcium in water but they do not remove it. The process by which they have this effect is not fully understood scientifically and so their design is empirical. Whether or not Physical Water Conditioners have a beneficial effect on eczema is a question for future study once proof of principle has been tested using established ion-exchange technology.

separate, mains drinking water tap if they prefer.

Apart from having a unit installed in the home, participants will continue with their usual eczema treatments in the usual way and will be asked to bathe / wash their clothes according to their usual practice. The units will meet all necessary quality standards, and will be installed by a trained water engineer according to British Water's code of practice.

The water softeners to be used in this trial will be supplied and paid for by a consortium of representatives from the water treatment industry, co-ordinated through their Trade Association. The units will be encased in an unmarked box in order to prevent the possibility of commercial advantage to any particular company. Similarly, unmarked salt will be supplied for use during the trial.

Participants allocated to delayed installation will subsequently receive an active unit at week 12

During the pilot study, approval was sought from the Housing Departments of local Councils to install units in the homes of Council tenants. This was very successful and will be used again in the main trial in order to be as inclusive as possible with regards to trial participants. The relevant water companies will also be informed of the trial, and will be provided with details of the likely number of water softeners to be installed in each region.

5.2 Treatment adherence / loss to follow-up

Compliance with treatment does not represent a large problem for this trial as long as the participants are not absent from home for long periods of time. With the exception of a drinking water tap, the water is simply softened (or not) for the entire household. However, participants must remember to periodically replenish the salt (every few weeks) and it is possible that this may not be done. Evidence from the pilot study suggested that some families did use less salt than others.

In order to assess that the units are working correctly, water samples will be sent to the research team once a week. Any samples with a reading of > 20 mg/L calcium carbonate will be referred back to the engineer for investigation. Participants will also be reminded of the importance of replenishing the salt supply by telephone at 8 weeks. A weekly reminder will also be included in the child's symptom diary.

It is anticipated that loss to follow-up will be <15%. For the pilot study all of the children attended for their final appointment. Nevertheless, a previous 18-week study of treatments for children with atopic eczema run by the investigators resulted in a loss to follow-up of 15% [4] and we propose to adopt this as a more conservative estimate. At the end of the study all participants will be offered the chance to purchase the units at a reduced cost (£446.50 inclusive of VAT, installation and warranty; this is approximately half the full retail price).

5.3 Concomitant therapy

Participants will be allowed to use their usual eczema treatments as prescribed. However, children will be asked not to start any NEW treatments during the period of the study if medically possible. (*See also* exclusion criteria).

5.4 Rescue medication

Rescue medication will be defined by asking participants at the recruitment visit what they would do if they needed to "step-up" their treatment in response to a worsening of the eczema. The need to "step-up" treatment will then be recorded in the child's diary on a daily basis.

5.5 Starting and stopping treatment

Units will be installed in the participants' homes as soon as possible after being randomized to treatment (ideally within 10 working days).

If participants choose to withdraw from the study, any units that have been installed will be removed as soon as is practicably possible. Participants will be asked to complete an end of study questionnaire at this time and diaries will be collected.

If participants are away from the main residence for any reason, this information will be recorded in their treatment diaries. Absence from the home will be included in a predictors of response model and will be used as a measure of treatment adherence for the (secondary) per protocol analysis.

6. OUTCOME MEASURES

6.1 Primary outcomes

1. Difference between the active vs. standard treatment groups with regard to mean change in disease severity (Six Area Six Sign Atopic Dermatitis Score – SASSAD [5]) at 12 weeks compared to baseline. SASSAD is an objective severity scale that is completed by the research nurse during follow-up appointments. It does not involve input from the participant in any way.

6.2 Secondary outcomes

1. Difference between the groups in the proportion of time spent moving during the night[2]. Movement will be captured for periods of one week at week 1 and week 12, and will be measured using accelerometers (Actiwatch™). These units are worn by the child in the same way as a wrist watch

[2] This outcome has been included as an objective surrogate for sleep loss and itchiness (two of the defining features of eczema). Previous research has suggested that this is a suitable objective tool for assessing itch [6,7] and further pilot work is currently underway to assess its suitability for use within this trial (results available Dec 2006)

This outcome has been included as an objective surrogate for sleep loss and itchiness (two of the defining features of eczema). Previous research has suggested that this is a suitable objective tool for assessing itch [6,7] and further pilot work is currently underway to assess its suitability for use within this trial (results available in 2007).

2. Difference in proportion of children who report either good or excellent improvement in eczema severity at 12 weeks (using a 5-point Likert scale).

3. Difference in the amount of topical corticosteroid / calcineurin inhibitors used during the 12 week study period.

4. Difference in Patient Oriented Eczema Measure (POEM [8]) collected at baseline, weeks 4, 12 and 16. This scale is a well validated tool that has been developed to capture symptoms of importance to patients (rather than objective signs that are used in traditional severity scales, such as SASSAD).

5. Difference in the number of totally controlled weeks (TCW) and well controlled weeks (WCW) based on the number of days with eczema symptoms and the number of days that topical treatment is applied. This outcome is based on a recent systematic review conducted by the applicants looking at ways of assessing long-term control for chronic conditions such as atopic eczema, asthma and rheumatoid arthritis [9]. The terms TCW and WCW have been adopted for use by researchers in the field of asthma and appear to be a useful and intuitive means of capturing disease activity over time.

6. Difference in the mean change in the Dermatitis Family Impact (DFI) questionnaire at 12 weeks [10]. This scale was chosen as an appropriate quality of life scale for the study for two reasons:

    - *The intervention involves the entire household, so a quality of life scale appropriate to the family unit seems most appropriate.*

    - *It avoids the need to use two different age-specific dermatology quality of life scales (the Children's Dermatology Life Quality Index[11] and the Infants version of the same scale[12]).*

7. Mean change in health related Quality of Life at 12 weeks. This will be captured using a generic measure of health utility (the children's version of the EQ-5D for children aged 7 years and over, or the proxy version of the EQ-5D for children aged 3 to 6 years [13]).

6.3 Further exploratory analyses

In addition to the main outcomes listed above, further exploratory analyses are planned as follows

- Difference in mean change in disease severity (SASSAD) at 4 weeks compared to

baseline. This outcome is included in order to capture speed of onset of benefit.

- Further within person analyses will be conducted comparing outcomes collected during the final 4-week period (12 to 16 weeks), with those collected during the initial 4 weeks of the study (0 to 4 weeks). Data collected for the active treatment group will provide an indication of the likely carry-over effect of this intervention, which will be useful in planning the design of future trials in this area. Data collected for the delayed treatment group will inform the analysis regarding speed of onset of improvement.

- Predictors of response model – including baseline factors such as filaggrin status (see later section), baseline eczema severity, water hardness, swimming activity and time away from the home).

7. ELIGIBILITY CRITERIA

The intention is to keep entry criteria as broad as possible in order to improve the external validity of the trial and to boost recruitment.

7.1 Inclusion criteria

- Children aged 6 months to 16 years at baseline, with eczema as defined by the UK refinement of the Hanifin and Rajka diagnostic criteria [14].
- Eczema present at time of assessment (minimum SASSAD score of 10).
- Baseline water hardness of >200 mg/L of calcium carbonate.
- Home suitable for the installation of a water softening device (as assessed by water engineer)

Only one child will be enrolled per family. The choice as to which child becomes involved will be made by the parents and children involved, taking into account the inclusion criteria above.

7.2 Exclusion criteria

- Children who plan to be away from home for >21 days in total during the 16-week study period. This has been deemed necessary in order to ensure adequate exposure to the intervention. We will also aim to ensure children do not have a planned holiday in the 4 weeks prior to their 12 week assessment visit.
- Children who have taken systemic medication (e.g. Cyclosporin A, methotrexate) or UV light for their eczema within the last 3 months because of their long lasting effects.
- Children who have taken oral steroids within the last 4 weeks, or who, as a result of seeing a healthcare professional, have started a new treatment regimen for eczema within the last 4 weeks.
- Families who already have a water treatment device installed, including ion-exchange softeners, polyphosphate dosing units or physical conditioners.

8. SCREENING AND RECRUITMENT

8.1 Participants

Children aged 6 months to 16 years with atopic eczema will be enrolled into the study. A diagnosis of eczema will be standardised using the UK working party's diagnostic criteria for atopic eczema [14]. It is anticipated that participants will be recruited at a rate of 4-5 per centre per month and that recruitment will take place over 18 to 20 months.

8.2 Setting

Recruitment will take place in eight secondary care referral centres in the UK serving a variety of ethnic and social groups and including both urban and peri-urban dwellings. All have predominantly hard water (although water in the Nottingham area is mixed). Inclusion criteria assume baseline water hardness of >200 mg/L for entry into the trial. The eight recruiting centres will be i) Queen's Medical Centre, Nottingham; ii) Barnet & Chase Farm Hospital, London; iii) Addenbrookes Hospital, Cambridge; iv) The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight Healthcare Trust, Isle of Wight, v) University Hospital of Leicester NHS Trust, vi) St Mary;s Hospital, Portsmouth, vii) United Lincolnshire Hospitals NHS Trust and (viii) The Royal London Hospital. All centres hold designated paediatric clinics in which children with eczema are commonly seen.

Participants will be informed of the trial in various ways. In order to “kick start” recruitment during the initial phase, patients who have been referred to the recruiting centres over the previous 12-18 months will be sent letters and information sheets about the trial. On-going recruitment will also take place through outpatient clinics, although children who have recently seen a dermatologist (and have started on a new treatment regimen), will not be able to enter the trial for at least 4 weeks. In addition, R&D approval will be sought from Primary Care Trusts local to the seven recruiting centres, and letters and information sheets sent to patients under the dermatological care of their GP. In addition, primary schools will be informed of the trial and efforts will be made to advertise the study through direct advertising in the local media, and on relevant websites. Recruitment in Nottingham will be limited to those areas with a hard water supply based on postcode areas.

8.3 Randomisation and blinding

Participants will be entered into a web-based randomisation programme by the Trial Manager, or Research Nurse. This will randomise them to one of the 2 treatment arms based on a computer generated code, using random permuted blocks of randomly varying size. This will be created by the Nottingham Clinical Trials Support Unit (CTSU) in accordance with their standard operating procedure, and held on a secure server. The randomisation will be stratified by age, disease severity (baseline SASSAD ≤ 20, or SASSAD score >20) and recruiting centre. Access to the sequence will be confined to the CTSU Data Manager. Allocation to treatment arms will be in the ratio 1:1 and the Trial Manager will access the treatment allocation for each participant by means of a remote,

internet-based randomisation system developed and maintained by the Nottingham CTSU. The allocation group will be indicated to the Trial Manager only after baseline data have been irrevocably entered into the randomisation programme. The sequence of treatment allocations will be concealed until interventions have all been assigned and recruitment and data collection are complete.

The research nurses will be blinded to treatment allocation throughout the study period and the trial statistician will analyse the results based on treatment code, using an analysis plan finalised prior to revealing the coded allocation sequence. Only after the analysis is complete will the actual treatment arms corresponding to treatment codes be revealed. The only study personnel in direct contact with study participants will be the research nurses and water engineers. The trial manager and study support staff at the co-ordinating centre in Nottingham will have telephone contact with parents of participants. Trial participants will continue to see healthcare professionals for their usual eczema care.

Since participants will not be blinded to the study intervention, an objective primary outcome has been chosen in order to minimise response bias, The primary outcome of disease severity, measured using the Six Area Six Signs Atopic Dermatitis scale (SASSAD) will be assessed by the research nurses who are blind to treatment allocation. This scale is based purely on physical examination of the skin and does not require input from the participants themselves. Other secondary objective outcomes include nocturnal movement (measured using accelerometers) and the use of topical therapy.

Participants will be discouraged from discussing which treatment they have received with the research nurse. In order to reduce the opportunity for 'un-blinding', telephone contacts will be conducted by the (un-blinded) trial manager whenever possible and participants will be reminded not to mention their treatment allocation to the research nurse prior to their assessment visits. The importance of maintaining 'blinding' will also be highlighted in the participant information sheets.

Integrity of information bias will be assessed using clinical photographs of a target lesion. These images will be taken at each assessment visit and graded remotely by 2 independent dermatologists. These dermatologists will not be aware of the study design, or of the assessment visit at which the image was taken. Should the two dermatologists score an image very differently, a 3rd dermatologist will be asked to adjudicate. This method of photo assessment worked well in the pilot study.

8.4 Screening

Screening for the trial will be a 3-stage process. Those who express a willingness to take part in the trial will be approached as follows (NOTE: the order of the contacts may vary depending on the recruitment route):

1. By telephone or postal questionnaire – participants will be sent a Participant Information Leaflet along with a screening checklist. This will be followed up by telephone to assess eligibility. Participants will give either written or verbal agreement at this time for the study's water engineer to visit their home.

2. Home visit by the engineer – the home will be assessed for suitability of installation of a water softening device.

3. Appointment with the research nurse - assessment of eligibility criteria and recruitment into the trial. This appointment will be carried out in outpatients or in the patient's home.

Consent will be taken by the research nurse prior to conducting the recruitment assessment. Five copies of the consent forms will be generated for: i) the participants; ii) the medical notes; iii) the child's GP; iv) the Trial Master File and v) the local Site File.

9. DATA COLLECTION

9.1 Data Collection Methods (summarised in Table 1)

9.1.1.Face-face interviews with the research nurse

These interviews will take place at baseline (recruitment visit), 4 weeks, 12 weeks and 16 weeks.

The visits will include the following:

i. check of eligibility criteria (recruitment visit only)
ii. baseline characteristics / demographics (recruitment visit only)
iii. examining the child for disease severity (using the Six Area, Six Sign Atopic Dermatitis score)
iv. eczema symptoms (POEM)
v. interviewing the family for quality of life – dermatitis family impact questionnaire and EQ-5D
vi. willingness to pay for an ion-exchange water softener (recruitment and by letter sent at 10 -12 weeks)
vii. digital image of nominated target lesion[3]
viii. weighing medications.

9.1.2. Treatment diaries

Diaries will be used to capture:

i. the number of days when active topical treatment (topical corticosteroids, tacrolimus or pimecolimus) is applied
ii. whether or not treatment has needed to be "stepped up" – if so, in what way and for how many days ("stepping up" treatment will be defined in advance by the parents in consultation with the research nurse)
iii. daily global assessment of disease activity by child and parents
iv. nights away from home

[3] Target lesion nominated by research nurse in discussion with the child/parents.

v. health service resource use
vi. personal costs associated with the eczema
vii. whether or not the accelerometers have been worn (weeks 1 and 12).

Items i) and ii) above will be used to calculate the number of totally controlled weeks (TCW) and well controlled weeks (WCW) during the study. Diaries will also be used to remind participants to check the salt levels in the machine and to return a sample of the water for testing in the laboratory every week.

9.2 Accelerometers

Night-time movement will be measured each night for a period of 1 week at the beginning of the study (week 1) and at the end of the 12-week study (week 12). Data will be stored on the Actiwatch™ units and downloaded onto a laptop computer at the subsequent assessment visits. Recordings will take place every night between the hours of 10pm and 6am, as used by other investigators[6].

9.3 Telephone support

Participants will be contacted by the trial manager at 8 weeks in order to provide advice and support about the study.

9.4 End of Trial Follow-up Questionnaire

Parents of participants will be sent an end of trial follow-up questionnaire once all participants have completed the study. This will seek information about current eczema status, and whether or not they have a functioning water softener.

Table 1: Summary of schedule of assessment visits

	BASELINE = Day ZERO	**Group A installation**	**"4 week" Appointment**	**"8 week" Reminder**	**"12 week" Appointment**	**Group A Un-installation Group B Installation**	**"16 week" Appointment**
Water Engineer Home screening visit	Research Nurse Recruitment Visit clinic appointment	Water Engineer At 0–2 weeks	Research Nurse Clinic appointment At 4–6 weeks	Trial Manager At 8 to 9 weeks	Research Nurse Clinic appointment At 12–14 weeks	Water Engineer At 12–14 weeks	Research Nurse Water Engineer At 16 to 18 weeks
◊ Home visit to assess suitability of residence for installation of softener ◊ Estimate salt requirements and assess availability of storage for salt supply ◊ Test water hardness	◊ Baseline characteristics ◊ Eligibility criteria checked ◊ SASSAD ◊ POEM ◊ Utility measures (DFI and EQ-5D) ◊ Weigh medications ◊ WTP questionnaire ◊ Digital photo of index site ◊ Saliva sample ◊ Explanation and issue of Diary 1 ◊ Explanation of accelerometer (Actiwatch™) ◊ Issue Water Softener Information sheet ◊ Randomisation	◊ Install unit (Group A) within 10 working days of DAY ZERO (date of recruitment visit) ◊ Advice given to reduce soap consumption etc. ◊ Issue water sampling containers + prepaid envelopes	◊ SASSAD ◊ POEM ◊ Digital photo of index site ◊ Saliva sample (if not obtained at baseline) ◊ Collection of week 1 Actiwatch™ data ◊ Weigh medications ◊ Collection of Diary 1 and Issue of new Diary 2	◊ Telephone support from Trial Manager ◊ Reminder to start collecting Actiwatch™ data again ◊ Reminder to add salt (group A) ◊ Reminder to continue taking weekly water samples for hardness testing (Group A)	◊ SASSAD ◊ POEM ◊ Utility measures ◊ Digital photo of index site ◊ Weigh medications ◊ Collection of Week 11-12 Actiwatch™ data and Actiwatch™ ◊ Collection of Diaries 2 ◊ Issue Diary 3 ◊ Explanation of cross-over phase	◊ Remove unit (Group A) within 10 working days of 12 week anniversary of installation ◊ Install unit (Group B) within 10 working days of 12 week appointment with RN; retest water hardness. ◊ Advice given to reduce soap consumption etc (Group B) ◊ Issue water sampling containers and pre-paid envelopes (Group B)	Clinic appointment with Research Nurse to carry out: ◊ SASSAD ◊ POEM ◊ Utility measure ◊ Digital photo of index site ◊ Collection of Diary 3 Visit by Water Engineer to: ◊ Remove unit (Group B), if they do not wish to purchase unit, within 10 working days of 4 week anniversary of installation ◊ Reinstall unit (Group A) if they wish to purchase unit at first convenient time after 16 week appointment with RN.

9.5 Engineer's visits

Engineers will conduct a screening visit for potential trial participants in order to assess the suitability of their home for the installation of a water softener. A standard checklist will be prepared for this purpose. Any households which are not able to have a unit installed (for whatever reason) will not be enrolled into the study. The pre-recruitment visit will also assess the likely salt requirements of the family, and test water hardness.

If randomised to Arm A, an installation visit will take place as soon as possible following randomisation to treatment (ideally within 10 working days).

For the active treatment group parents will be sent information about how to bypass the unit and asked to do this immediately they return home after their child's 12-week assessment visit. Units will subsequently be removed by the water engineer as soon as possible (ideally within 5 working days) to ensure that the units cannot be turned on again during the final 4-week non-intervention period. If the family chooses to purchase a unit at a reduced price (£446.50) a unit will be reinstalled after they have completed the final 4-week non-intervention period of the study. Families in the active treatment group will send samples of water for hardness testing on a weekly basis throughout the 12 week period when the unit is installed. Those allocated to delayed treatment will receive an active unit at 12 weeks. This will then be removed after week 16 unless the family decides to purchase the unit. Families in the delayed treatment group will send samples of water for hardness testing on a weekly basis from weeks 13 to 16 inclusive.

10. STATISTICS

10.1 Statistical design

Analyses have been planned in order to place emphasis on objective outcomes that are less likely to be influenced by the potential bias inherent in a single-blind study. Nevertheless, a variety of additional tools are to be used that reflect more closely the disease process throughout the study period. Some of these are relatively objective indicators of disease activity (such as nocturnal movement and treatment application), whilst others reflect subjective concepts (such as self-reported symptoms in the POEM), in order to capture the many health-related dimensions affected by eczema.

The planned analyses should answer the following questions:

1. Does exposure to softened water for 12 weeks improve the symptoms and severity of eczema, compared to standard care?

2. Does softened water improve quality of life for patients and their carers?

3. Are water softeners a cost-effective treatment for children with atopic eczema?

In addition, tertiary analyses will explore the following parameters:

4. How quickly the benefits of softened water become evident.

5. How quickly the benefits of softened water are lost once treatment is stopped.

The main intention-to-treat analysis will be conducted at 12 weeks. An additional per protocol analysis will also be conducted for the primary outcome in order to test the proof of concept.

A sub-group analysis will also be conducted based on the presence or absence of mutations on the gene filaggrin (*see* section 12). Mutations on the filaggrin gene have been associated with dry skin and may therefore be a useful predictor of treatment response.

10.2 Sample Size estimate

Sample size estimates are based on other published data relating to the use of SASSAD in patients recruited in secondary care[15], [5]. Based on a minimum clinically relevant difference of 20% in the change in SASSAD score between the 2 groups, and assuming a mean baseline SASSAD score of 20 with a standard deviation in change scores of 10 [15], a sample size of 310 children will provide 90% power, assuming a significance level of 5% and attrition rate of 15% (see planned interventions section). Sample size estimates based on the results of the pilot study, support this sample size estimate.

10.3 Primary analyses

◊ Change in disease severity (SASSAD) at 12 weeks compared to baseline, will be assessed using Student's t-test. An adjusted analysis will also be conducted including the stratification variables of eczema severity, age and recruiting centre.

In order to aid the clinical interpretation of these data, the number needed to treat (NNT) assuming a range of improvements in SASSAD scores will also be presented (≥20%, ≥50% and ≥75% improvement).

10.4 Secondary analyses

◊ The proportion of time spent moving during the night will be compared using Student's t-test.

◊ The proportion of participants reporting either good or excellent improvement in disease severity on the global assessment scale will be analysed using a chi-squared analysis.

◊ A Student's t-test will be used to assess the difference in the number of grams of topical treatment applied.

◊ POEM scores will be compared at 12 weeks using Student's t-test.

◊ A Student's t-test will be used to assess differences in the number of Totally Controlled Weeks and Well Controlled Weeks throughout the study period.

◊ Mean scores on the Dermatitis Family Impact Scale and Quality of Life scores will be compared using a Student's t-test.

◊ Predictors of response model. Factors to be included in the model will be pre-specified prior to analysis, but will include baseline eczema severity, previous treatment history, water hardness at baseline, prior belief relating to the benefits of softened water, demographic variables and filaggrin status (*see* Section 12).

10.5 Tertiary analyses

◊ Changes in SASSAD at 4 weeks will be assessed using Student's t-test.

◊ For the within group analyses, mean change in disease severity (SASSAD) at week 4 (relative to baseline) compared to mean change in disease severity at week 16 (relative to week 12) will be analysed using a paired samples t-test. These analyses will be used to explore speed of onset and possible carry-over effects.

11. COST-EFFECTIVENESS ANALYSIS

11.1 Objective:

- To assess the cost-effectiveness of installing a water softening unit in the homes of families who have a child with eczema, when compared with usual care.

The cost analysis will compare the overall costs for the intervention to usual care, measuring resource use such as primary care contacts, medication prescribed, secondary care contacts and patient costs. Health and family resource use data will be measured using participant diaries. Resource use will be valued using published unit costs (e.g. Curtis and Netten [16], BNF 2005, and NHS reference costs (http://www.dh.gov.uk/PolicyAndGuidance/OrganisationPolicy/FinanceAndPlanning/NHSReferenceCosts/fs/en)), and patient reported estimates. The costs to the NHS and patient will be reported separately as well as in combination.

The primary measures of effectiveness for cost analyses purposes will be the number of participants who show a ≥50% improvement in SASSAD at 12 weeks compared to baseline. Secondary analyses will be conducted using continuous data from the SASSAD scale; the Dermatitis Family Impact Scale; and the generic measure of health utility as measured on the child version of the EQ-5D (for children aged 3–6 years, the proxy version will be used).

If non-dominance occurs an incremental cost-effectiveness ratio will be produced. Sensitivity analysis will be undertaken to test the robustness of results in the face of any uncertainties or assumptions made in the analysis. In particular, assumptions about the time period over which the difference in costs and difference in benefits are likely to be sustained. Where appropriate the change in health-related quality of life measured on the

EQ-5D will be multiplied by the expected duration of benefits from water softening in order to calculate the Quality Adjusted Life Years (QALYs) of the intervention group compared to the usual care group.

In addition to the cost effectiveness analysis, contingent valuation (CV) methodology will be employed to measure parental willingness to pay for the water softener device as a measure of benefit. CV methodology is now more widely used as a measure of benefit in the health care field [17]. It is an important issue in the context of this study, since it is not clear at this stage who will, or should, pay for the device: the parent or the NHS. Willingness to pay will be asked pre-intervention at the recruitment visit to get an ex-ante hypothetical willingness to pay and again at week 12. At the end of the study, all participants will get the opportunity to purchase the device that they used in the study, thus giving us a measure of parental actual willingness to pay. This will enable us to test whether a hypothetical bias exists in health CV studies in this context.

12. ADDITIONAL GENETICS STUDY

12.1 The role of filaggrin gene mutations as a predictor of treatment response

Mutations in the gene encoding the skin barrier protein filaggrin have recently been shown to strongly predispose to eczema. Reduced filaggrin activity is associated with an abnormally dry skin and defective skin barrier. It is estimated that up to 50% of children with eczema may carry one or two mutations in the gene encoding filaggrin, which has the gene symbol *FLG* [18]. Individuals carrying one null-allele for filaggrin make only 50% of the normal amount of filaggrin. Often these individuals have a mild form of ichthyosis vulgaris (a very dry skin) and are at risk for eczema. Individuals who have two null-alleles make no filaggrin and have a more severe form of ichthyosis vulgaris and are at greater risk of eczema[19,20].

In light of this breakthrough in understanding eczema, we have formed collaborative links with the research team that first reported this association (lead by Professor Irwin McLean at the Human Genetics Unit, University of Dundee). We plan to include filaggrin status as a possible predictor of treatment response in the current study. The mechanism of action by which water softeners improve eczema is currently unclear. Nevertheless, it seems intuitive to consider the possibility that a gene associated with dry skin may play an important role in predicting why some people with eczema are more affected by hard water than others.

For the sub-group analysis, study participants will be categorised into two groups according to filaggrin status:
Group 1: *FLG* +/+ (wild type) – control cohort
Group 2: *FLG* +/- (heterozygous for *FLG* null allele) and *FLG* -/- (homozygous for *FLG* null alleles)

This work will refine the phenotypic characteristics of filaggrin-deficient eczema, and will assess whether filaggrin is an important predictive factor in determining treatment

success.

12.2 Methodology

To determine filaggrin status it will be necessary to obtain DNA from individuals entering the study. Following written informed consent, participants will be asked to provide a saliva sample at enrolment (or at their 4-week clinic appointment, if more practical). If children are unable to spit into the container, swabs taken from inside the cheek will be used to collect the sample.

Sample containers will be identified using the designated study number and date of birth only. Personal contact details will be kept by the Trial Manager and will not be transferred to the laboratory researchers.

The containers will be shipped to the Human Genetics Unit, University of Dundee. DNA will be extracted by standard techniques and *FLG* genotyping for the common null-alleles will be carried out according to published protocols [19]. Samples will be kept in Dundee for future testing for genes associated with atopic eczema if new techniques become available.

FLG genotype status will be recorded and returned to the Centre of Evidence Based Dermatology in Nottingham, again using the study number and date of birth.

12.3 Written informed consent

Parents and participants will be offered the possibility of opting out of this part of the study. No participant will be enrolled until informed consent has been gained.

12.4 Sample size

The sample size for the main trial is based on the ability to detect at least a 20% difference in disease severity between the two groups (water softener versus usual eczema care). In order to ensure that sufficient power is available for the planned sub group analysis, further sample size calculations have been performed.

Assuming that the presence of at least one mutation in the gene encoding filaggrin results in improved treatment response, a total of 90 children with at least one such mutation would be sufficient to detect a 30% difference between the treatment groups in the primary outcome (disease severity), with 80% power and a significance level of 5% (s.d = 10). Allowing for 20% drop out means that 120 (39% of the children recruited) would need to carry the gene mutation. For 90% power, this figure would be 145 (47%) children. This is in line with previous published findings which suggest that the gene may be present in up to 50% of eczema sufferers[19], although this varies according to ethnic group[21,22].

13. TRIAL ADMINISTRATION

13.1 Trial personnel

This study will employ a part-time trial manager (60% fte) and 4 part-time research nurses (60% fte). Two MCRN-funded research nurses are also working part-time on the study (London and Lincolnshire). All staff will be supervised by Dr Kim Thomas at the University of Nottingham, although the research nurses employed at the other recruiting centres will report directly to the Principal Investigators for those centres. Water engineering aspects have been sub-contracted by UK WTA to MG Heating, Newport for all installations on the Isle of Wight. Kinetico Ltd, Southampton, are working on behalf of UKWTA, facilitating installations and engineering support on the mainland. Each company has a dedicated water engineer co-ordinator (who is a member of the Trial Management Group) and who will arrange and supervise visits by their own water engineers to participants homes.

In addition, a consumer panel has been convened consisting of 5 service users with experience of living with eczema. Mr David Potter acts as the consumer panel representative on the Trial Steering Committee. Copies of the participant information sheets, symptom diaries and publicity material have been shown to the panel of service users prior to submission for ethical approval. The panel members shared these documents with children with eczema aged 4 and 13 years.

13.2 Roles & responsibilities

The Chief Investigator will have overall responsibility for the design, maintenance and delivery of the trial, and will serve as the study guarantor to sponsors, funders and journals.

The Trial Manager will be responsible for all aspects of the day-to-day running of the trial.

The research nurses will be responsible for identifying and recruiting suitable participants, for conducting skin assessments and liaising with the local engineers over visit dates and times (prior to randomisation). Since research nurses are responsible for conducting the blinded outcome assessments, contact after the initial recruitment interview will be kept to a minimum. Subsequent telephone follow-up will be conducted by the trial manager or study support staff at the co-ordinating centre in Nottingham.

The Clinical Trials Support Unit (University of Nottingham) will provide data management for the trial. This will include a web-based randomisation service (with telephone backup), database design, data entry and central data monitoring.

Professor Andrew Nunn at the MRC Clinical Trials Unit in London will prepare an analysis plan prior to analysis.

13.3 Conflicts of interest

None.

13.4 Trial Organisation & administration

The trial is funded by the NHS Health Technology Assessment Programme. It is sponsored by the University of Nottingham, and will be managed and co-ordinated from the Centre of Evidence Based Dermatology in Nottingham. Data management will be conducted through the Nottingham Clinical Trials Support Unit. Statistical analysis will be over-seen by Professor Andrew Nunn at the MRC Clinical Trials Unit in London, and conducted by a junior statistician employed at the same trials unit.

Membership of the Trial Steering Committee (TSC) and Trial Management Group (TMG) have been documented at the beginning of this document.

The Trial Steering Committee will meet at least once a year and will provide overall supervision of the trial on behalf of the trial sponsor.

The Trial Management Group will meet more frequently and will be responsible for the day-to-day management of the trial. Members of the TMG will report to the TSC at their meetings.

Since this trial involves the use of a commonly available domestic water softening unit (and does not involve a medicinal product) we do not anticipate the need for a Data Monitoring Committee.

13.5 Trial Timetable and Milestones

	6 months	26 months	4 months	3 months	4 months
	1 Sep 06 to 28 Feb 07	1 Mar 07 to 31 May 09	1 Jun 09 to 30 Sep 09	1 Oct 09 to 31 Dec 09	1 Jan 10 to 31 Apr 10
Trial set-up*					
Training**					
Recruitment					
Follow-up					
Data checking					
Database locked				31 Dec 09	
Analysis / write up					

MREC, LREC and R&D approval

* Trial set-up will include the establishment of sponsorship agreement; preparation of trial procedures and CRF's; application for ethics and R&D approvals; purchasing equipment and publishing the protocol. Research nurses employed at each site and the study engineers will be identified during the 6-month set-up period.

** Training of Principal Investigators, Water Engineers and Research Nurses, including awareness of GCP.

13.6 Unblinding of participants

This is a single-blind study, in which unblinding of the study participants is not relevant. However, attempts will be made to ensure the continued blinding of the research nurses and the trial statistician. If any of the research nurses feel that blinding may have been compromised at any time, this will be logged accordingly.

14. ETHICS

14.1 Statement of confidentiality

Any data collected as a result of this trial will be treated as confidential. Participants will be identified by unique reference number and initials wherever possible. It is necessary for participants' name and contact details to be released to the co-ordinating centre, but this will not happen until fully informed consent has been taken.

14.2 Data protection

Data will be stored in accordance with the Data Protection Act. Investigators will retain patient records and CRFs in easily retrievable but secure form.

The Chief/Principal investigator will ensure that CRFs and other study documentation relating to their participants are kept in a locked departmental filing cabinet. Completion of, and access to the CRFs will be restricted to those personnel approved by the

Chief/Principal investigator.

15. ADVERSE EVENT REPORTING

This trial involves the use of a commonly available domestic water softening unit with provision for mains drinking water during the time when the water softening unit is installed. This being the case, we do not anticipate any adverse events or adverse reactions of any relevance to the trial. As a result adverse event data will not be routinely collected. Events of particular relevance such as plumbing difficulties, floods or difficulties with the units will be logged and reported to the MREC and relevant R&D departments annually.

16. TRIAL INSURANCE AND INDEMNITY

16.1 Negligent Harm

The usual NHS indemnity arrangements for negligent harm will apply.

16.2 Research Liabilities

The sponsor (University of Nottingham) has third-party liability insurance cover in accordance with all local legal requirements.

As a precautionary measure, the investigator, the persons instructed by him and the hospital are included in such cover in respect of work done by them in carrying out this study to the extent that the claims are not covered by their own professional indemnity insurance.

In addition, the study engineers will carry their own 3rd party liability insurance should the installation of the water softening devices result in flood or damage to property.

16.3 Non negligent harm

The devices to be used in the study will be covered by product warranty. Other than this, no compensation exists for non-negligent harm.

17. PUBLICATION POLICY

During the period of the trial, press releases will be issued from the Centre of Evidence Based Dermatology and will be approved by either the Chief Investigator (Hywel Williams) or the Lead Applicant (Kim Thomas). No party will be entitled to submit any publicity material without prior approval from the co-ordinating centre.

Trial publications and conference presentations will be submitted to the HTA for approval prior to submission to the event organisers or the editors. All publications will acknowledge the support of the HTA in funding this trial, and the support of the water industry.

Neutral or negative results will not constitute a reasonable justification to delay publication.

18. TRIAL FINANCES

This trial is funded by the NHS HTA Programme. Appropriate contracts will be established between the University of Nottingham and each of the recruiting sites; with the MRC Clinical Trials Unit, and with the consortium of water treatment companies.

In addition to the monies provided by the NHS HTA programme, representatives from the water industry have agreed to cover the following costs:

- Design, testing and supply of the water softening units.
- Salt supplies
- Testing of the water samples
- Supervision of water engineers

Trial participants will not be paid for taking part in the study, although a standard inconvenience allowance of £5 per visit will be given in the form of gift vouchers. If travel costs are greater than this, trial participants will be given gift vouchers up to a maximum of £10 per clinic visit.

SIGNATURE PAGE

Chief Investigator: **Professor Hywel Williams**

Signature: _____ **Date: _____**

RECRUITING CENTRE

I confirm that I have read this protocol and agree to conduct the study accordingly.

Principal Investigator: _____

Recruiting Centre: _____

Signature: _____ **Date:** _____

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APPENDIX 1: Recruiting centres

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The David Hide Asthma and Allergy Research Centre St Mary's Hospital Isle of Wight Healthcare Trust Newport Isle of Wight PO30 5TG Also: St Mary's Hospital Milton Road Portsmouth PO3 6AD	**Principal Investigator** Professor Tara Dean Reader in Epidemiology/ Director of Research / Associate Head School of Health Sciences and Social Work James Watson Building West 2 King Richard I Road University of Portsmouth; Portsmouth, PO1 2FR Tel: (023) 9284 4405; Fax: (023) 9284 5200
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Softened Water Eczema Trial (SWET)

Statistical Analysis Plan

Author: Caroline Gilbert

ABBREVIATIONS

CTSU	Clinical Trials Support Unit
CV	Contingent Valuation
DFI	Dematitis Family Impact
HTA	Health Technology Assessment
ITT	Intention To Treat
NIHR	National Institute for Health Research
POEM	Patient Oriented Eczema Measure
QALY	Quality Adjusted Life Years
SASSAD	Six Area Six Sign Atopic Dermatitis Score
SWET	Softened Water Eczema Trial
TCW	Totally Controlled Weeks
TMG	Trial Management Group
TSC	Trial Steering Commitee
WCW	Well Controlled Weeks

1. INTRODUCTION

This analysis plan details the planned statistical analyses for the Softened Water Eczema Trial (SWET).

This is a single-blind, parallel group, randomised controlled trial of 12-week duration, followed by a 4-week cross-over period. The objective is to assess whether the installation of an ion-exchange water softener improves eczema in children, and if so to establish the likely cost and cost-effectiveness of the intervention.

Participants are randomised to one of two groups on a 1:1 basis. The first group have a water softener installed the first 12 weeks of the trial followed by a 4 week washout period. The second group, the delayed treatment group, have the water softener installed for four weeks from week 12 onwards.

	STUDY PERIOD = 16 weeks	
	0 to 12 weeks	**12 to 16 weeks**
Group A	Usual eczema care + water softener installed (n = 155)	Unit removed
Group B	Usual eczema care + delayed installation (n = 155)	Unit installed

Throughout this document Group A will be referred to as the immediate installation group, and Group B as the delayed treatment group.

The analyses described in this document will be performed by the designated statistician at the MRC Clinical Trials Unit. All data will be analysed using Stata Version 10.1.

2. TRIAL OBJECTIVES

There are two key objectives for the trial:

1. To assess whether the installation of an ion-exchange water softener improves eczema in children
2. If so, to establish the likely cost and cost-effectiveness of this intervention

3. ENDPOINTS

Due to the nature of the intervention this study is being conducted as a single blind trial. For this reason objective, and validated outcome measures have been used (Schmitt, 2007).

3.1. Primary Endpoint

Participants with moderate to severe eczema will be randomised to one of the two groups described previously.

The primary endpoint is the difference between the immediate installation and delayed intervention groups with regard to mean change in disease severity (Six Area Six Sign Atopic Dermatitis Score – SASSAD) at 12 weeks compared to baseline.

3.2. Secondary Endpoints

1. The difference between baseline and week 12 of the proportion of time spent moving during the night. Movement will be captured for periods of one week at weeks 1 and 12, and will be measured using accelerometers (Actiwatch). These units are worn by the child in the same way as a wrist watch. Due to possible differences between the units every effort was made to ensure the children always used the same unit and where this was not the case this has been documented. A sensitivity analysis will be performed excluding those who did not use the same unit throughout the trial.

2. Difference in the proportion of children who report either a good or excellent improvement in eczema severity at 12 weeks (using a 5-point Likert scale). As these data were not collected[1], responders will be grouped into three groups; those who report a reasonable (≤20%), good (>20% and ≤50%) or excellent (>50%) improvement in SASSAD score at 12 weeks.

3. Amount of topical corticosteroid / calcineurin inhibitors used during the 12 week study period. This information is captured by weighing the medication at each visit and then summarised according to steroid strength to give the total amount used from baseline to week 12. Nurses will also be providing an indication of the level of accuracy of any estimates. A sensitivity analysis will be performed excluding those for whom the nurse is not confident about the amount of medication used.

4. Difference in Patient Oriented Eczema Measure (POEM). This scale is a well validated tool that has been developed to capture symptoms of importance to patients (rather than objective signs that are used in traditional severity scales, such as SASSAD).

5. Difference in the number of totally controlled weeks (TCW) and well-controlled weeks (WCW) based on the number of days with eczema symptoms and the number of days that topical treatment is applied up to primary endpoint at 12 weeks. This will be derived from the symptom diaries.

6. Difference in the mean change from baseline in the Dermatitis Family Impact (DFI) questionnaire at 12 weeks.

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[1] Omitted from CRFs to avoid unblinding of research nurses, and also on reflection this measure would be too open to bias in a single-blind study. Therefore improvement based on improvement in SASSAD score is preferable.

3.3. Tertiary Endpoints

If a beneficial effect is found the following tertiary analyses will be performed.

1) Speed of onset of benefit will be analysed in three ways. Firstly, the difference in the mean change in disease severity (SASSAD) at 4 weeks compared to baseline. Secondly, the final 4 week period (weeks 12 to 16) will be examined for the delayed treatment group. Finally the daily bother scores will be examined for the first 4 weeks of the trial for both groups.

2) Likely carry over effect will be examined using the full 16 week trial period for the immediate installation group. This information will be useful in planning the design of future trials in this area.

3) Predictors of response model, including baseline factors (see section 6.2)

4. SAMPLE SIZE

Sample size estimates are based on other published data relating to the use of SASSAD in patients recruited in secondary care. Based on a minimum clinically relevant difference of 20% in the change in SASSAD score between the 2 groups, and assuming a mean baseline SASSAD score of 20 with a standard deviation in change scores of 10, a sample size of 310 children will provide 90% power, with a significance level of 5% allowing for an attrition rate of 15%.

5. ITT ANALYSIS AND MULTIPLICITY

The SWET trial will be analysed as intent-to-treat (ITT) at week 12.

The ITT population will consist of all randomised participants with evaluable data. This will be the primary population used for the main analysis, which will use the randomised treatment allocation rather than actual treatment received. An additional sensitivity analysis will be performed excluding outliers.

Primary inference will be based on the primary endpoint analysis of the ITT population. Significance will be at the 5% level.

A secondary, per protocol analysis of the primary endpoint will be performed excluding the following participants:

- Those who were randomised into the study, but who failed to receive their allocated treatment.
- Those who are deemed to be major protocol violators as determined by the Protocol Violators Group (including independent members) review of the protocol deviation log.

Criteria for protocol violators are as follows:

- Missing SASSAD score at week 12
- Group A: exposed to fully softened water for <75% of the time their home has an active water softener in place (i.e. sleeping at home + unit fully working for <75% of the time their home has an installation)

- Group A: Participant away from home or with partially functioning water softener of >2 days/week for each of the 4 weeks prior to the primary outcome measure
- Group B: Participant away from home for > 2 days/week for each of the 4 weeks prior to the primary outcome measure
- Unblinding of research nurse prior to primary outcome measurement
- Starting new treatment prior to primary outcome measurement will be examined on a case-by-case basis to determine if they comprise a protocol violator.

Baseline characteristics (as described in section 6.2) will be summarised and if any major imbalance exists the analyses will be adjusted to account for this.

Analyses of all secondary endpoints and adjusted analyses will be considered supportive to the primary analysis so no adjustments for multiple comparisons will be made.

6. STRATA AND COVARIATES

6.1. Stratification variables

Randomisation is stratified by the following:

- Disease severity (baseline SASSAD ≥10 to ≤ 20, or SASSAD score >20)
- Recruiting centre

6.2. Other covariates

In addition to the stratification variables, other covariates to be considered in a predictors of response model are:

- Age (continuous)
- Previous treatment history (see section 8.3)
- Water hardness at baseline (WHO classification, continuous).
- Sex
- Ethnicity
- Filaggrin status
- Income
- Time away from home (based on a cut off of >21 days).

In addition, the following baseline characteristics will be summarised:

- Washing powder

- Fabric softener
- Bathing/showering frequency
- Swimming frequency
- Home ownership
- Allergy

7. PLANNED SUBGROUP ANALYSES

A sub-group analysis will be conducted based on the presence or absence of mutations on the filaggrin gene (collected using spit samples). Mutations on the filaggrin gene have been associated with dry skin and may therefore be a useful predictor of treatment success. The planned subgroup analysis will only be performed on the primary outcome of change in SASSAD score. The p-value for the interaction will be reported.

Assuming that the presence of at least one mutation in the gene encoding filaggrin results in improved treatment response, a total of 90 children with at least one such mutation would be sufficient to detect a 30% difference between the treatment groups in the primary outcome, with 80% power, 5% significance (2 sided) and a standard deviation of 10. Allowing for a 20% drop out means that 120 children would need to carry the gene mutation. For 90% power this figure would be 145.

8. DATA HANDLING

8.1. Missing data

The primary outcome is collected by nurses at study visits so missing items are not expected. Other missing data items such as age, sex, etc. will be queried so that there are no missing data for these variables.

Missing baseline water hardness score will be replaced with published water hardness data for that postcode.

For each endpoint the number with a missing outcome for each treatment group will be reported with reasons given where available.

If less than 5% of data are missing for the primary endpoint only participants with complete data will be included in the full ITT primary analysis. An additional sensitivity analysis will be conducted replacing missing data with the maximum value at baseline and week 4 (where this exists). If more than 5% of data are missing for the primary endpoint then more complex multiple imputation techniques will be used to handle the missing values. Secondary endpoint analyses will be analysed using a complete case analysis as these are only considered supportive of the primary endpoint analysis.

8.2. Partial dates

Missing months will be taken as June and missing days will be taken as the 15th day of the month.

8.3. Derived Variables

SASSAD scores will be computed prior to data entry. This will be checked using the individual components within the analysis files.

The proportion of time spent moving during the night will be obtained using accelerometers. The average of the first three nights of usable data at week 0 and the last three nights of usable data at week 12 will be used. Usable data is defined as values greater than 5% and less than 95% of the night spent moving to remove outliers. If there are less than three usable nights data, then this variable will be considered missing.

Patient Orientated Eczema Measure (POEM) scores will be calculated as a score between 0 and 28 based on seven symptoms. Parents are asked to state the number of days in the last week their child has been affected by each symptom. These are scored as follows; no days=0, 1-2 days=1, 3-4 days=2, 5-6 days=3 and everyday=4. The POEM score is the calculated as the sum of these 7 individual scores.

Totally Controlled Weeks (TCW) will be defined as zero days with an eczema bother score greater than 4 and zero days where “stepping up” of treatment was needed. Well-Controlled Weeks (WCW) will be defined as two days or less with an eczema bother score greater than 4 and two days or less days where “stepping up” of treatment was needed. The eczema score is recorded by the parent each day using a symptom diary and is based on how much bother the child’s eczema has been that day. The score is on a scale from 0 to 10 where 0 equals no bother at all and 10 equals the most bother you can imagine. The definition of “stepping up” varies from child to child and is documented in the symptom diary for the parent to refer to after discussion with the nurse at the beginning of the trial.

Dermatitis Family Impact (DFI) scores will be calculated as a score between 0 and 30 based on ten questions. Parents are asked to state how much the child’s skin problem has affected the family over the last week These are scored as follows; not at all=0, a little=1, a lot=2 and very much=3. The DFI score is the calculated as the sum of these 10 individual scores.

Age (in years and months) will be calculated at randomisation.

Previous treatment history will be assessed using treatment reported at enrolment. This will be grouped into low strength (mild and moderate topical steroids) and high strength (potent and very potent steroids and mild and moderate calcineurin inhibitors). Participants will be classed as a low strength user if they only use mild and moderate topical steroids, and a high strength user if the use potent or very potent topical steroids or mild or moderate calcineurin inhibitors (even if they also use mild or moderate topical steroids).

8.4. Bias

The research nurses are blinded to treatment allocation throughout the study period. If any of the nurses feel that this blinding may have been compromised, details are logged centrally with the Trial Manager. A Sensitivity analysis will be conducted excluding those participants for whom the research nurse became unblinded to treatment allocation

during the trial. Integrity of information bias will be assessed using clinical photographs of a target lesion.

8.5. Data quality

Data queries will be resolved at data entry using a query form. To minimise errors, all primary outcome data will be verified by a data entry clerk who did not originally enter the data. A 10% sample of all other data will be checked for accuracy.

9. PARTICIPANT CHARACTERISTICS AND COMPLIANCE

9.1. Demographic and Baseline Characteristics

Demographic, disease severity, filaggrin status and other baseline characteristics will be cross-tabulated against randomised treatment allocation to check for appropriate balance. If substantial imbalance exists an additional adjusted analysis will be performed.

9.2. Compliance

Absence from the home will be used as the measure of compliance (recorded on the symptom diary).

A log of all protocol deviations will be kept by the Trial Manager which will be reviewed by the protocol violations committee at the end of the trial in order to assign the events as major or minor protocol deviations. Participants with major deviations will be excluded from the per protocol analysis.

9.3. Withdrawals

If participants choose to withdraw from the study, any units that have been installed will be removed as soon as is practicably possible. Participants will be asked to complete an end of study questionnaire at this time and diaries collected.

The number of participants who withdraw from the study with the reasons for withdrawal will be summarised by randomised treatment allocation.

10. EFFICACY

10.1. Primary Efficacy Analyses

The primary analysis will be the comparison of the change from baseline in SASSAD scores at 12 weeks between the two intervention groups using a t-test, including a p-value and confidence interval. This will also be expressed as the number needed to treat for a 20% reduction in SASSAD score at week 12 and a 50% reduction.

10.2. Secondary Efficacy Analyses

1) The difference between baseline and week 12 of the proportion of time spent moving during the night will be compared across intervention groups using a t-test. The average of the first three nights of evaluable data at week 0, and the last three nights at week 12 will be used.

2) The proportion of children who report a reasonable (≤20%), good (>20% and ≤50%) or excellent (>50%) improvement in SASSAD score at 12 weeks, will be compared using a chi-squared test.

3) Amount of topical corticosteroid / calcineurin inhibitors used during the 12 week study period. This will be captured by weighing the medication at each visit. This will then be summarised by the nurses at week 12, including a measure of the degree of accuracy of any estimates. These will be spilt into two groups, low strength consisting of mild and moderate topical steroids, and high strength consisting of potent and very potent topical steroids and mild and moderate calcineurin inhibitors. The difference in the amount (in grams) of each of the two groups will be assessed using t-tests.

4) The difference in the change from baseline to week 4 and baseline to week 12 Patient Oriented Eczema Measure (POEM) scores will be compared using t-tests.

5) Difference in the number of well controlled weeks (WCW) as defined in section 8.3, will be analysed using a t-test. The number of totally controlled weeks (which are a subset of the WCW), will also be summarised.

6) Difference in the mean change from baseline in the Dermatitis Family Impact (DFI) questionnaire at 12 weeks, will be analysed using a t-test.

10.3. Tertiary efficacy analyses

1) Speed of onset of benefit will be analysed in three ways. Firstly, the difference in the mean change in disease severity (SASSAD) at 4 weeks compared to baseline will be analysed using a t-test. Secondly, the final 4 week period (weeks 12 to 16) will be examined for the delayed treatment group using a single sample t-test. Finally daily bother scores from the daily symptom diaries for the first 4 weeks of the trial will be plotted for both groups.

2) Likely carry over effect will be examined graphically using the daily bother scores during the 16 week trial period for the immediate installation group. This information will be useful in planning the design of future trials in this area.

3) A responder will be defined as a 20% or 50% decrease in SASSAD score. Two logistic regression models will be used to investigate predictors of response as listed in section 6.2.

11. ADDITIONAL ANALYSES

Descriptive statistics will be used to summarise the data from the end-of-trial questionnaire added part way through the trial.

12. REFERENCES

Schmitt J, Langan S, Williams H. What are the best outcome measurements for atopic eczema? A systematic review. *J Allergy Clin Immunol* 2007, 120:1389-1398

13. SIGNATURE PAGE

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Signature: _____ **Date:** _____

Designated Statistician: Caroline O'Leary

Signature: _____ **Date:** _____

Trial Steering Committee Chair: Dr David Paige

Signature: _____ **Date:** _____

Lead Applicant: Dr Kim Thomas

Signature: _____ **Date:** _____

Appendix 5

Committee membership

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Appendix 6

Home screening outcomes

Home screen pass rate

Homes on the mainland were initially assessed by water engineers employed through European Water Care Ltd, but in October 2007 this company withdrew from their contract with the trial following concern about the lower than expected number of homes found suitable for installation of an ion-exchange water softener (61% of the 150 mainland homes screened from May to October 2007) and issues over quality of workmanship. The original budget was based on a home screening pass rate and subsequent installation of units in 85% of homes. From November 2007, co-ordination of water engineers on the mainland was undertaken by John Kyle at Kinetico UK Ltd and home screens (and installation of water softeners) were carried out by a number of local independent water engineering subcontractors for the remainder of the trial. There was a noticeable improvement in the rate of homes deemed suitable (79% of the 150 mainland homes screened from November 2007 to July 2008). The final per cent of all screened homes deemed suitable for straightforward installation of an ion-exchange water softener was 72%.

TABLE 23 Home screen pass rates by SWET centre/area

Centre/area	Passed/total screened	Pass rate (%)
London (east)[a]	4/14	29
Nottinghamshire	39/63	62
Lincolnshire	11/77	65
London (north/north-east)	98/144	68
Isle of Wight	58/85	68
Cambridgeshire	125/162	77
Hampshire (Portsmouth)	49/61	80
Leicestershire	66/77	86

a Low pass rate due to older housing in this area of London and inaccessible mains stop valves.

Appendix 7

Further baseline characteristics

TABLE 24 Demographics

Baseline characteristics	Group A (water softener + usual care)	Group B (usual care)	Total
Number randomised	**170**	**166**	**336**
Age,* N *(%)			
Mean age (SD)	5.8 (4.2)	5.0 (4.0)	5.4 (4.1)
< 3 years old	46 (27)	52 (31)	98 (29)
3–6 years old	56 (33)	67 (40)	123 (37)
≥ 7 years old	68 (40)	47 (28)	115 (34)
Sex,* N *(%)			
Male	95 (56)	98 (59)	193 (57)
Female	75 (44)	68 (41)	143 (43)
Ethnicity,* N *(%)			
White	133 (78)	127 (77)	260 (77)
Asian	16 (9)	17 (10)	33 (10)
Black	6 (4)	4 (2)	10 (3)
Mixed	10 (6)	9 (5)	19 (6)
Other	4 (2)	8 (5)	12 (4)
Not stated/unknown	1 (1)	1 (1)	2 (1)

TABLE 25 Selected clinical characteristics at enrolment

Baseline characteristics	Group A (water softener + usual care)	Group B (usual care)	Total
Number randomised	**170**	**166**	**336**
Previous treatment history,* N *(%)			
High	97 (57)	81 (49)	178 (53)
Low	59 (35)	74 (45)	133 (40)
None	14 (8)	11 (7)	25 (7)
Filaggrin status,* N *(%)			
Presence of mutation	47 (28)	47 (28)	94 (28)
Absence of mutation	108 (64)	110 (66)	218 (65)
Unknown	15 (9)	9 (5)	24 (7)
***Food allergy,* N *(%)*[a]**			
No	105 (63)	103 (64)	208 (63)
Yes	61 (37)	59 (36)	120 (37)
***Baseline SASSAD,* N *(%)*[b]**			
Mean (SD)	25.3 (13.4)	26.0 (13.9)	25.6 (13.6)
10–19	75 (44)	68 (41)	143 (43)
>20	94 (56)	98 (59)	192 (57)

a There were eight missing values for the food allergy variable.
b There was one missing value for SASSAD at baseline.

TABLE 26 Income and homeownership at enrolment

Baseline characteristics	Group A (water softener + usual care)	Group B (usual care)	Total
Number randomised	**170**	**166**	**336**
***Income,* N *(%)*[a]**			
<£10,000	7 (4)	9 (5)	16 (5)
£10,000–20,000	12 (7)	20 (12)	32 (10)
£20,000–30000	26 (16)	36 (22)	62 (19)
£30,000–50,000	54 (33)	49 (30)	103 (31)
≥£50,000	43 (26)	38 (23)	81 (25)
Do not know	22 (13)	12 (7)	34 (10)
***Home ownership,* N *(%)*[b]**			
Do not know	0 (0)	1 (1)	1 (<0.5)
Owned by you outright	16 (9)	16 (10)	32 (10)
Being brought with the help of a mortgage or loan	118 (70)	119 (72)	237 (71)
Part-rented and part-mortgaged (shared ownership)	4 (2)	1 (1)	5 (1)
Rented privately	10 (6)	12 (7)	22 (7)
Rented from the council or a housing association	19 (11)	16 (10)	35 (10)
Rent-free (e.g. in a relative or a friend's property)	2 (1)	1 (1)	3 (1)

a There were eight missing values for the income variable.
b There was one missing value for the home ownership variable.

TABLE 27 Bathing and swimming frequency at enrolment

Baseline characteristics	Group A (water softener + usual care)	Group B (usual care)	Total
Number randomised	**170**	**166**	**336**
Bathing frequency at home, times per week[a]			
N	169	166	335
Mean (SD)	4.8 (2.4)	5.0 (2.4)	4.9 (2.4)
Median (IQR)	4 (3–7)	4 (3–7)	4 (3–7)
Bathing frequency away from home, times per week[b]			
N	163	161	324
Mean (SD)	0.4 (1.0)	0.4 (1.5)	0.4 (1.2)
Median (IQR)	0 (0–1)	0 (0–0)	0 (0–0)
Swimming frequency, *N* (%)[c]			
Never	62 (37)	67 (40)	129 (39)
Less than once a month	56 (33)	52 (31)	108 (32)
More than once a month	51 (30)	47 (28)	98 (29)

IQR, interquartile range.
a There was one missing value for the bathing at home frequency variable.
b There were 12 missing values for the bathing away from home frequency variable.
c There was one missing value for the swimming frequency variable.

TABLE 28 Water hardness and washing powder and softener use at enrolment

Baseline characteristics	Group A (water softener + usual care)	Group B (usual care)	Total
Number randomised	**170**	**166**	**336**
Water hardness,* N *(%)			
Mean (SD)	307.6 (50.2)	309.5 (58.0)	308.6 (54.1)
Median (IQR)	306 (274–342)	300 (270–340)	305.5 (273.5–340.0)
200–299 mg/l	72 (42)	66 (40)	138 (41)
300–399 mg/l	90 (53)	84 (51)	174 (52)
400–499 mg/l	8 (5)	15 (9)	23 (7)
≥ 500 mg/l	0 (0)	1 (1)	1 (< 0.5)
Washing powder,* N *(%)[a]			
Biological	21 (13)	12 (7)	33 (10)
Non-biological	145 (87)	151 (92)	296 (89)
Both	1 (1)	2 (1)	3 (1)
Fabric softener,* N *(%)[2]			
No	92 (55)	84 (51)	176 (53)
Yes	75 (45)	82 (49)	157 (47)

IQR, interquartile range.
a There were four missing values for the washing powder variable.
b There were three missing values for the softener variable.

Appendix 8

Medication sensitivity analyses

In addition to examining the difference in the total amount of medication used, this was also split into low-strength and high-strength medication. Low-strength medication consisted of mild and moderate steroids, and high-strength medication consisted of potent steroids, very potent steroids and all calcineurin inhibitors.

The difference in the amount of low-strength medication used was –11.66 g (95% CI –28.92 to 5.59 g), meaning group A used on average 1 gram (g) less a week of low-strength medications than group B (*Table 29*). However, this difference was not statistically significant ($p = 0.18$). The difference in the amount of high-strength medication used over the 12-week period was 2.82 g (95% CI –8.46 to 14.11 g), with group A using slightly more high-strength medication than group B (*Table 30*).

Where medications were not available for weighing at the clinic visits the nurses estimated the amount of medication used. At the end of the 12-week period they recorded the total amount

TABLE 29 Total amount (in grams) of low-strength[a] medication used between baseline and week 12

Steroid strength		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* analysed**		**160**	**154**		
Mild steroids	Mean ± SD	12.0 ± 29.9	18.1 ± 35.5		
Moderate steroids	Mean ± SD	19.7 ± 69.3	25.3 ± 58.9		
Total low-strength medication (g)[a]	**Mean ± SD**	**31.7 ± 83.5**	**43.4 ± 71.1**	**–11.66 (–28.92 to 5.59)**	**0.18**

a Low-strength medication consists of mild and moderate topical steroids.

TABLE 30 Total amount (in grams) of high-strength[a] medication used between baseline and week 12

Steroid strength		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* analysed**		**160**	**153**		
Potent steroids	Mean ± SD	21.5 ± 41.4	18.4 ± 39.7		
Very potent steroids	Mean ± SD	2.2 ± 11.7	1.8 ± 20.7		
Mild calcineurin inhibitors	Mean ± SD	1.9 ± 7.9	2.7 ± 12.0		
Moderate calcineurin inhibitors	Mean ± SD	1.1 ± 9.1	1.0 ± 7.9		
Total high-strength medication (g)	**Mean ± SD**	**26.6 ± 45.9**	**23.8 ± 55.3**	**2.82 (–8.46 to 14.11)**	**0.62**

a High-strength medication consists of potent and very potent topical steroids and mild and moderate calcineurin inhibitors.

of medication used along with an indication of the accuracy of these figures. The above analyses were repeated using measurements that the nurse was sure or very sure were accurate, but this made no difference to the conclusions (*Table 31*).

The difference in the total amount of medication used was –2.80 g (95% CI –25.78 to 20.18 g) and was not statistically significant ($p = 0.81$). The difference in the amount of low-strength mediation used was –9.50 g (95% CI –28.41 to 9.42 g) and this difference was not statistically significant ($p = 0.32$). The difference in the amount of high-strength medication used was 6.70 g (95% CI –5.11 to 18.51 g) was not statistically significant ($p = 0.27$). All three analyses supported the main analysis above.

TABLE 31 Total amount (in grams) of all medication used between baseline and week 12 restricted to those where the nurse was sure or very sure of the weights given

Steroid strength		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* analysed**		115	113		
Mild steroids	Mean ± SD	11.7 ± 32.7	16.6 ± 33.4		
Moderate steroids	Mean ± SD	16.9 ± 53.0	21.5 ± 55.5		
Potent steroids	Mean ± SD	20.7 ± 43.1	16.0 ± 39.0		
Very potent steroids	Mean ± SD	1.9 ± 10.6	0.1 ± 1.1		
Mild calcineurin inhibitors	Mean ± SD	2.1 ± 8.8	1.4 ± 5.4		
Moderate calcineurin inhibitors	Mean ± SD	0.5 ± 3.3	0.8 ± 8.3		
Total medication (g)	Mean ± SD	**53.7 ± 91.9**	**56.5 ± 83.9**	**2.80 (–25.78 to 20.18)**	**0.81**

TABLE 32 Total amount (in grams) of low-strength[a] medication used between baseline and week 12 restricted to those where the nurse was sure or very sure of the weights given

Steroid strength		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	*p*-value
Number randomised		**170**	**166**		
***N* analysed**		**115**	**113**		
Mild steroids	Mean ± SD	11.7 ± 32.7	16.6 ± 33.4		
Moderate steroids	Mean ± SD	16.9 ± 53.0	21.5 ± 55.5		
Total low-strength medication (g)	**Mean ± SD**	**28.6 ± 76.4**	**38.1 ± 68.3**	**–9.50 (–28.41 to 9.42)**	**0.32**

a Low-strength medication consists of mild and moderate topical steroids.

TABLE 33 Total amount (in grams) of high-strength[a] medication used between baseline and week 12 restricted to those where the nurse was sure or very sure of the weights given

Steroid strength		Group A (water softener + usual care)	Group B (usual care)	Difference and 95% CI (A–B)	p-value
Number randomised		**170**	**166**		
***N* analysed**		**115**	**113**		
Potent steroids	Mean ± SD	20.7 ± 43.1	16.0 ± 39.0		
Very potent steroids	Mean ± SD	1.9 ± 10.6	0.1 ± 1.1		
Mild calcineurin inhibitors	Mean ± SD	2.1 ± 8.8	1.4 ± 5.4		
Moderate calcineurin inhibitors	Mean ± SD	0.5 ± 3.3	0.8 ± 8.3		
Total high-strength medication (g)	Mean ± SD	**25.1 ± 47.5**	**18.4 ± 42.8**	**6.70 (–5.11 to 18.51)**	**0.27**

a High-strength medication consists of potent and very potent topical steroids and mild and moderate calcineurin inhibitors.

Appendix 9

Well-controlled weeks and totally-controlled weeks to 16 weeks

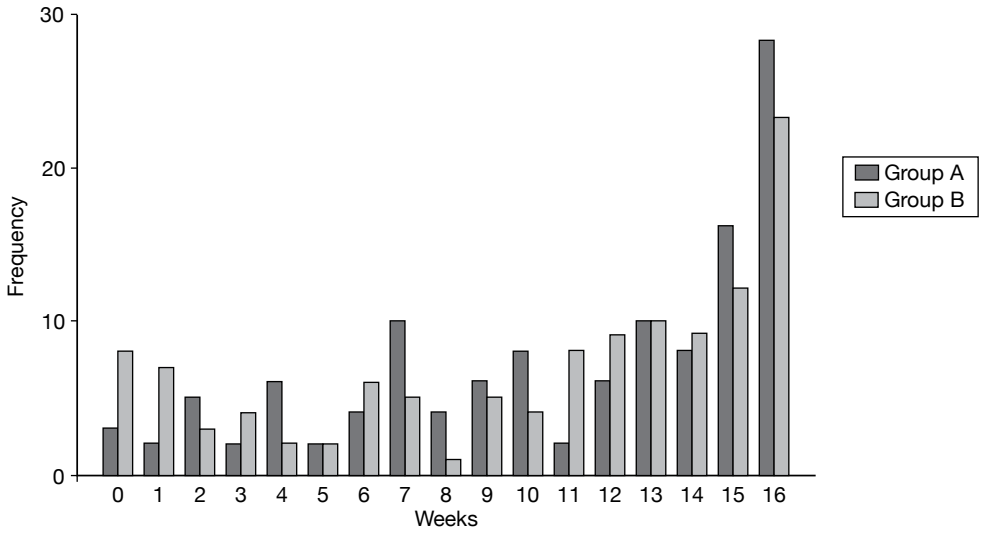


FIGURE 19 Well-controlled weeks for the whole 16-week study period.

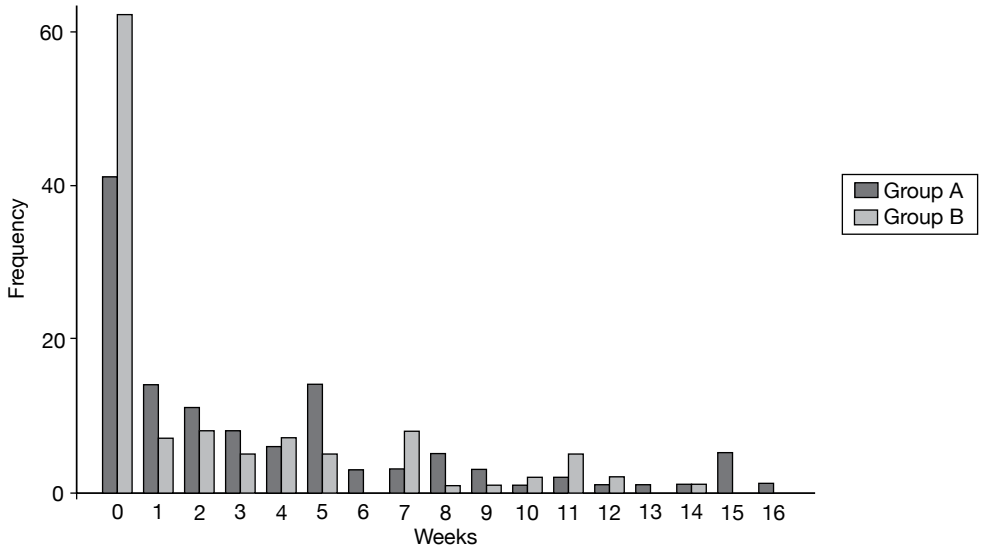


FIGURE 20 Totally-controlled weeks for the whole 16-week study period.

Appendix 10

Health economics questionnaire

To be completed by parent/guardian

As part of this study we are interested to see how much people might be willing to pay in order to get the potential benefits of a water softener.

You are NOT being asked to pay anything for the water softener that will be installed in your home as part of the SWET study - we are just interested in your views in order to guide the NHS in the future.

The likely benefits of installing a water softener in your home are:

- Your heating system (boiler) will work better and use less fuel.
- Your appliances, such as your washing machine and kettle, will not fur up.
- You will be able to use less washing powder and soap.
- You will not get scum or lime scale deposits on your bath, sinks and shower.
- It is also possible that using a water softener may improve your child's eczema – although obviously we are not sure of this, and this is why we are doing the study.

At the moment, water softening devices are only available if you buy one yourself. These units usually last for 10 to 20 years, and can be moved from one house to another. The devices typically cost anywhere in the region of £350 to £1500 (excluding installation costs and the recurrent costs of salt).

If you were to buy a water softener today, what is the maximum you would be willing to pay for it? (This value can be anything you like, including zero).

Remember: You will not be asked to pay this amount, but it should represent the amount that you would be willing to pay for the machine itself (excluding installation costs). Providing a money value is just a way of showing us how important (or un-important) you think water softening devices are.

Health Economics Questionnaire- continued

To be completed by parent/guardian

Which of the following best describe how you worked out your answer?

(Please tick all those that apply):

(a) This is a reasonable or fair amount for me to pay.

(b) This is just a guess.

(c) This amount reflects the benefits I think my child with eczema might get from the water softener.

(d) This amount reflects the wider benefits of installing a water softener in my home.

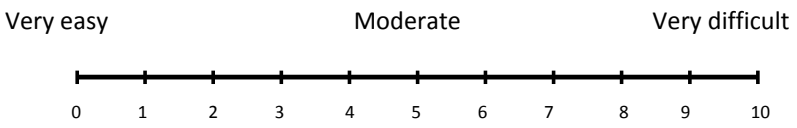
(e) This is how much I think a water softener device would cost.

(f) This is how much I can afford to pay.

(g) Other (please explain):

_____

(2) How difficult was it to estimate the money value for a water softening device. Please indicate by putting a cross on the scale below:



Appendix 11

Variable definitions used in the contingent valuation study

Variable	Definition (number in each response category) [non-responders/missing data]
WTP prior to trial	Mean £506.68 (SD £387.73; range 0–£3000), [3]
Purchase	0) not purchased (157) R; 1) purchased (179), [0]
Child age	1) < 3 years 98; 2) 3–7 years (123); 3) ≥ 7 years (115) R, [0]
Child gender	0) female (143) R; 1) male (193), [0]
Child baseline SASSAD score	Mean 25.73 (SD 13.71; range 10–94), [0]
Child experienced a 20% reduction in SASSAD score	0) no (146) R; 1) yes (177), [13]
Child filaggrin status	0) no or unknown status (242) R; 1) positive filaggrin status 94, [0]
Number of nights at home	Mean 73.61 (SD 11.36; range 4–84), [2]
Number of medications at baseline	Mean 4.91 (SD 2.12; range 0–13), [0]
Household income (per annum)	1) < £30,000 (109); 2) £30,000–50,000 (102); 3) ≤ £50,000 80 R, [45]
Intervention group	0) group B (166) R; 1) group A (170), [0]
Water hardness at baseline	Mean 308.55 mg/l calcium carbonate (SD 54.11; range 200–540), [0]
Number of residents at home	Mean 4.15 (SD: 0.96, range 2–8), [12]
Reason given: this is a reasonable or fair amount for me to pay	0) no (200) R; 1) yes (136), [0]
Reason given: this is just a guess	0) no (227) R; 1) yes (109), [0]
Reason given: this amount reflects the benefits I think my child with eczema might get from the water softener	0) no (176) R; 1) yes (160), [0]
Reason given: this amount reflects the wider benefits of installing a water softener in my home	0) no (249) R; 1) yes 87, [0]
Reason given: this is how much I think a water softener would cost	0) no (252) R; 1) yes 84, [0]
Reason given: this is how much I can afford to pay	0) no (218) R; 1) yes (118), [0]
Reason given: other reasons	0) no (297) R; 1) yes 39, [0]
Difficulty of WTP question	Mean 6.29 (SD: 2.52, range 0–10), [3]

R denotes that this group was used as the reference group when a categorical variable was included in the regression analysis.

Appendix 12

Cost and resource use data for ages 3 years plus

Just 2.2% of weekly diaries were not completed; therefore data were not imputed for these entries. The mean total cost per patient in group A was £315 (SD £164) compared with £143 (SD £343) in group B [difference £172, 95% confidence interval (CI) £101 to £243, $p = 0 < 001$]. This significant cost difference was due to cost of the intervention all other resource categories (health professional visits, medications and other medical items) were not significantly different between groups (see *Tables 34* and *35*).

In both age groups it is noticeable how little health-care resource both groups used over the 12-week study period. It is also clear to observe that no resource category other than total intervention costs were significantly different between group A and group B. Thus, group A had higher costs because of receiving the intervention and there were no significant differences in any other resource item or cost. The ion-exchange water softener did not result in cost savings for the NHS as there was no reduced use of medications or other health-care resource use in group A over group B in this trial.

TABLE 34 Mean (SD) resource use and mean difference in resource use per patient (95% CI) over the 12 months for groups A and B

Resource use item	Group A (water Softener + usual care) ($n = 115$)	Group B (usual care) ($n = 113$)	Mean difference (95% CI)
Intervention			
Ion-exchange water softener	1.00	0.00	1.00
Installation	1.00	0.00	1.00
Salt (blocks)	18.05 (2.69)	0.00 (0.00)	18.05 (17.55 to 18.55)
Face-to-face consultant-led follow-up attendance, paediatric dermatology	1.00	0.00	1.00
Secondary health care			
Hospital outpatients visit (per follow-up attendance, paediatric dermatology)	0.21 (0.55)	0.35 (0.99)	–0.14 (–0.35 to 0.07)
Hospital admission (non-elective inpatient stay (short stay)	0 (0.00)	0.02 (0.13)	–0.02 (–0.04 to 0.01)
Primary and community health care (per consultation/visit)			
GP	0.46 (0.93)	0.51 (1.13)	–0.05 (–0.32 to 0.22)
Practice nurse	0.03 (0.18)	0.19 (1.43)	–0.16 (–0.43 to 0.11)
Health visitor	0.00 (0.00)	0.01 (0.09)	–0.01 (–0.03 to 0.01)
Pharmacist	0.45 (1.135)	0.37 (1.20)	0.08 (–0.025 to 0.41)
Specialist nurse	0.17 (0.91)	0.32 (1.32)	–0.15 (–0.45 to 0.14)

TABLE 35 Mean (SD) cost and cost difference (95% CI) per patient over the 12 months for groups A and B (2009 £)

Resource use item	Group A (water Softener + usual care) (*n* = 115)	Group B (usual care) (*n* = 113)	Mean difference (95% CI)
Intervention	**217.03 (6.90)**	**0.00 (0.00)**	**217.03 (215.76 to 218.31)**
Ion-exchange water softener	14.33	0.00	14.33
Installation	5.49	0.00	5.49
Salt	46.21	0.00	46.21
Face-to-face consultant-led follow-up attendance, paediatric dermatology	151.00	0.00	151.00
Secondary health care	**31.51 (83.66)**	**60.84 (190.47)**	**–29.33 (–67.94 to 9.28)**
Hospital outpatients visit (per follow-up attendance, paediatric dermatology)	31.51 (83.66)	52.12 (149.33)	–20.60 (–52.31 to 11.11)
Hospital admission (non-elective inpatient short stay)	0.00 (0.00)	8.73 (65.29)	–8.73 (–20.90 to 3.44)
Primary and community health care	**54.26 (84.47)**	**58.28 (96.27)**	**–4.02 (–27.68 to 19.63)**
GP	14.29 (28.83)	15.91 (34.93)	–1.62 (–9.99 to 6.74)
Practice nurse	0.31 (1.66)	1.75 (12.89)	–1.44 (–3.86 to 0.98)
Health visitor	0.00 (0.00)	0.31 (3.29)	–0.31 (–0.92 to 0.30)
Pharmacist	18.99 (56.80)	15.61 (50.26)	3.38 (–10.61 to 17.37)
Specialist nurse	12.23 (67.15)	23.58 (97.53)	–11.35 (–33.25 to 10.55)
Medication and accessories	20.67 (31.44)	25.01 (41.72)	–4.34 (–14.00 to 5.32)
Incremental mean cost	**315.07 (163.99)**	**143.02 (343.31)**	**172.05 (101.45 to 242.62)**

Appendix 13

Cost–utility sensitivity analysis for ages 3 years plus

Best case

The best-case costs for the 3 years and over age group resulted in mean costs of £130.82 (SD £110.57) for group A and £102.88 (SD £225.02) for group B [mean difference £27.94, 95% confidence interval (CI) –£18.55 to £74.44, $p = 0.237$]. Combining this with the incremental quality-adjusted life-years (QALYs) presented above for 3- to 16- year-olds of 0.006, the incremental cost-effectiveness ratio was estimated as £4548 in the best-case scenario. *Figure 21* shows the cost-effectiveness acceptability curve (CEAC) for the 12-week study period. At a WTP of £30,000 per QALY there is a 39.0% chance of the ion-exchange water softener being cost-effective in this population.

Worst case

For worst-case costs, the mean cost for group A was £520.74 (SD £236.73) compared with £189.23 (SD £464.75) for group B, mean difference £331.51 (95% CI £234.81 to £428.21, $p < 0.001$). Combining the incremental cost with the incremental QALYs presented above for 3- to 16- year olds of 0.006, the incremental cost-effectiveness ratio was estimated as £53,957 in the worst-case scenario. *Figure 22* shows the CEAC for the 12-week study period. Again, at all levels of WTP, normal care (group B) was more likely to be cost-effective.

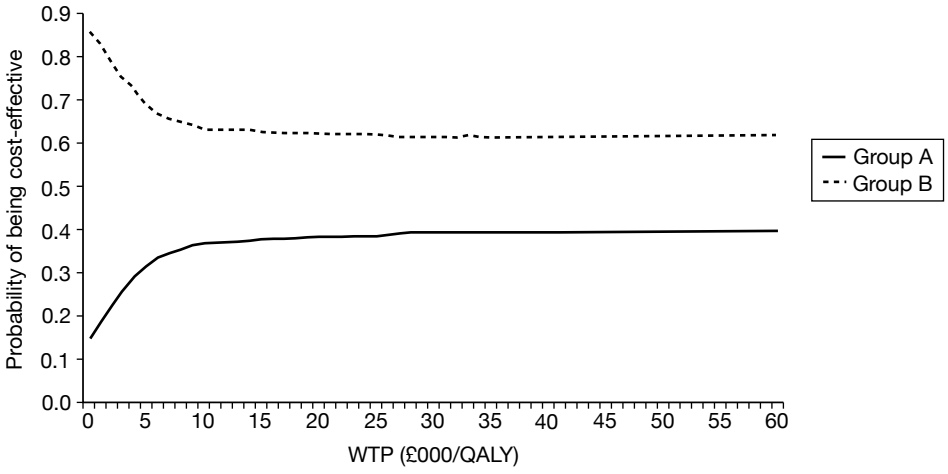


FIGURE 21 Decision uncertainty: plots of the CEACs for the sensitivity analysis best-case cost–utility analysis for ages ≥3 years.

Imputing missing values

Sensitivity analysis, including all trial participants, used imputed QALY scores for children < 3 years based on their baseline SASSAD scores. Group A gained a mean of 0.014 QALYs per patient and group B a mean of 0.007 QALYs per patient. The mean difference in QALYs per patient was 0.006 (95% CI 0.001 to 0.012, $p = 0.022$). Using the incremental mean cost reported in *Table 20*, the incremental cost-effectiveness ratio for group A was estimated as £31,018.

Figure 23 shows the CEAC for the 12-week study period. Using this model, the acceptability curves crossed in favour of water softeners at a WTP of approximately £45,000 per QALY.

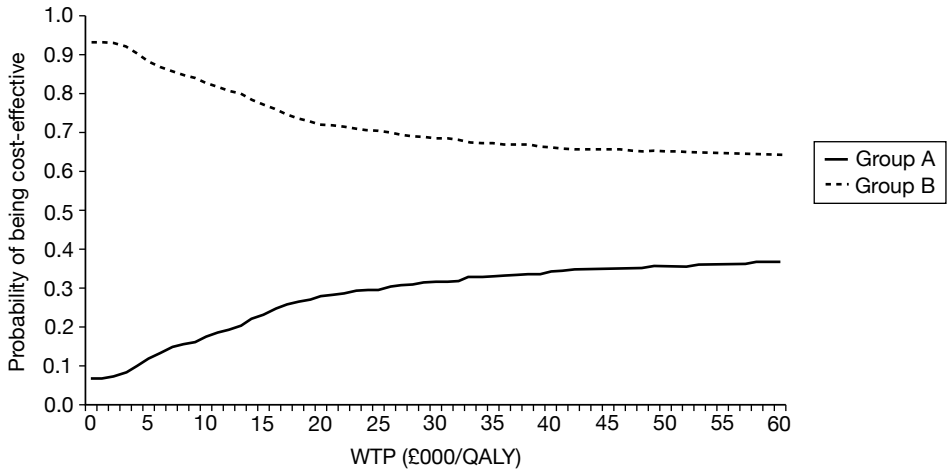


FIGURE 22 Decision uncertainty: plots of the cost-effectiveness acceptability curves for the sensitivity analysis worst-case cost–utility analysis for ages ≥ 3 years.

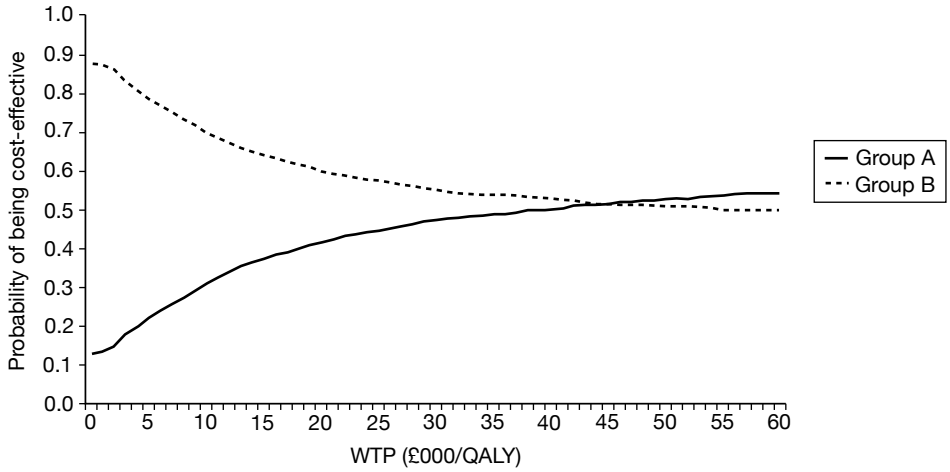


FIGURE 23 Decision uncertainty: plots of the CEACs for the sensitivity analysis cost–utility analysis for all ages.

Appendix 14

Parameter estimates of the general linear regression analysis to explain variation in willingness-to-pay values prior to the trial

Parameter estimates of the general linear regression performed to explain variation in WTP values prior to the trial, data for 278[a] participants were included in the analysis.

Explanatory variable	Estimate (95% CI)
Intercept	718.226 (177.753 to 1258.699)[c]
Child age	
< 3 years	–57.509 (–174.794 to 59.776)
3–7 years	–48.185 (–156.508 to 60.139)
Child gender	30.223 (–123.057 to 62.612)
Child baseline SASSAD score	–0.687 (–4.188 to 2.814)
Child-positive filaggrin status	92.146 (–6.162 to 190.454)
Number of nights at home	4.694 (0.349 to 9.039)[b]
Number of medications at baseline	7.148 (–16.247 to 30.543)
Household income (per annum)	
< £30,000	–173.720 (–291.605 to –55.835)[c]
£30,000–50,000	–155.102 (–274.014 to –36.190)[b]
Intervention group	–32.84 (–123.523 to 57.843)
Water hardness at baseline	–0.581 (–1.45 to 0.288)
Number of residents at home	–36.987 (–89.256 to 15.282)
Reason given: this is a reasonable or fair amount for me to pay	–103.56 (–200.008 to –7.111)[b]
Reason given: this is just a guess	–20.473 (–122.854 to 81.908)
Reason given: this amount reflects the benefits I think my child with eczema might get from the water softener	126.738 (31.852 to 221.623)[c]
Reason given: this amount reflects the wider benefits of installing a water softener in my home	20.491 (–86.644 to 127.625)
Reason given: this is how much I think a water softener would cost	86.917 (–19.37 to 193.204)
Reason given: this is how much I can afford to pay	–102.913 (–202.548 to –3.278)[b]
Reason given: other reasons	–99.292 (–239.652 to 41.068)
Difficulty of WTP question	–26.354 (–44.474 to –8.235)[c]

a This is based on a complete case analysis. Details of missing data are provided in *Appendix 11*.
b $p < 0.05$.
c $p < 0.01$.
Adjusted $R^2 = 0.142$.

Appendix 15

Binary logistic regression analysis to explain decision to purchase

Parameter estimates of the binary logistic regression performed to explain decision to purchase an ion-exchange water softener, data for 273[a] participants were included in the analysis.

Explanatory variable	OR (95% CI)
Constant	0.705
Child age	
< 3 years	1.207 (0.591 to 2.465)
3–7 years	1.185 (0.618 to 2.274)
Child gender	1.027 (0.584 to 1.804)
Child experienced a 20% reduction in SASSAD score	1.623 (0.929 to 2.835)
Child-positive filaggrin status	0.656 (0.361 to 1.192)
Number of nights at home	0.987 (0.958 to 1.018)
Number of medications at baseline	1.243 (1.078 to 1.434)[c]
Household income (per annum)	
< £30,000	0.345 (0.166 to 0.717)[c]
£30,000–50,000	0.582 (0.275 to 1.231)
Intervention group	1.040 (0.602 to 1.796)
Water hardness at baseline	1.007 (1.001 to 1.012)[b]
Number of residents at home	1.026 (0.750 to 1.403)
Reason given: this is a reasonable or fair amount for me to pay	1.052 (0.588 to 1.883)
Reason given: this is just a guess	1.094 (0.595 to 2.012)
Reason given: this amount reflects the benefits I think my child with eczema might get from the water softener	0.610 (0.341 to 1.091)
Reason given: this amount reflects the wider benefits of installing a water softener in my home	1.022 (0.533 to 1.963)
Reason given: this is how much I think a water softener would cost	0.847 (0.440 to 1.630)
Reason given: this is how much I can afford to pay	0.912 (0.499 to 1.668)
Reason given: other reasons	0.775 (0.321 to 1.874)
WTP prior to trial	1.000 (1.000 to 1.001)
Difficulty of WTP question	0.934 (0.834 to 1.045)

a This is based on a complete case analysis. Details of missing data are provided in *Appendix 11*.
b $p < 0.05$.
c $p < 0.01$.
d $p < 0.001$.
Adjusted $R^2 = 0.196$.

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