

# Randomised controlled trial of silk therapeutic garments for the management of atopic eczema in children: the CLOTHES trial

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## Scientific summary

### The CLOTHES trial

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# Scientific summary

## Background

Atopic eczema (AE) is a common childhood skin condition that causes itch, soreness and sleep loss. The treatment of AE typically includes the regular use of emollients and topical corticosteroids. Although effective, these treatments can be time-consuming and messy to apply, and patients often worry about side effects.

Many patients are keen to explore non-pharmacological interventions for the management of AE, and the use of silk garments has been advocated as an effective treatment. Such garments are available on prescription or for private purchase, but the evidence base for their use is limited. As a result, the National Institute for Health Research Health Technology Assessment programme commissioned the CLOTHing for the relief of Eczema Symptoms (CLOTHES) Trial.

## Objectives

### Primary objective

- To assess whether or not the addition of silk therapeutic garments to standard care reduces AE severity in children with moderate to severe disease over a period of 6 months.

### Secondary objectives

- To estimate the within-trial cost-effectiveness of silk therapeutic garments from a NHS and a family perspective.
- To explore parent/guardian and child views on and experiences of using silk garments, and factors that might influence the use of these garments in everyday life.
- To examine prescribers' and commissioners' views on the use of silk garments for the management of AE.

## Methods

### Study design

A multicentre, parallel-group, observer-blind, pragmatic randomised controlled trial (RCT) of 6 months' duration, followed by a 2-month observational period. Children were randomised (1 : 1) to receive silk garments plus standard care or standard care alone. The primary outcome was assessed by research nurses blinded to the treatment allocation at 2, 4 and 6 months.

The trial included a nested qualitative evaluation, a health economic analysis and a subgroup analysis based on the presence or absence of loss-of-function mutations in the gene encoding filaggrin (*FLG*).

### Recruitment

The trial took place in five UK centres. Participants were identified through secondary and primary care, and in response to local advertising.

### Eligibility criteria

Children with AE, aged 1–15 years, were enrolled. All had a score of  $\geq 9$  on the Nottingham Eczema Severity Score, denoting moderate to severe disease over the last 12 months. Participants had at least one area of active AE on a part of the body that would be covered by the garments.

Children were excluded if they had taken systemic medication (e.g. ciclosporin, oral corticosteroids) or had received light therapy for AE in the preceding 3 months, used wet/dry wraps more than five times in the last month, started a new medication or treatment regimen that may affect AE in the last month, were currently using silk garments for their AE and were unwilling to stop during the trial, and were currently taking part in another clinical trial. Only one child was enrolled per family.

### **Interventions**

For the intervention group, two brands of silk garments were used [DermaSilk™ (AlPreTec Srl, San Donà di Piave, Italy) and DreamSkin™ (DreamSkin Health Ltd, Hatfield, UK)], as these were the two brands available on prescription at the time of trial design. Both brands were made with antimicrobially protected, knitted, sericin-free 100% silk.

Participants received three sets of garments (long-sleeved vest and leggings, or body suits and leggings, depending on the age of the child), and were instructed to wear the garments as often as possible during the day and at night. Garments were replaced, as required, during the 6-month RCT (if they were worn out, were lost or no longer fitted).

All participants continued with their standard AE care including regular emollient use and topical corticosteroids (or calcineurin inhibitors) for controlling inflammation. The participants were asked not to change their standard AE treatment for the duration of the trial unless medically warranted. If a research nurse suspected that the AE had become infected, participants contacted their normal medical team for confirmation of diagnosis and subsequent treatment.

## **Outcomes**

### **Primary outcome**

Atopic eczema severity was assessed by research nurses at baseline, 2, 4 and 6 months using the Eczema Area and Severity Index (EASI). Baseline EASI was used as a covariate in the analysis model.

### **Secondary outcomes**

- Global assessment of AE by research nurses (Investigator Global Assessment) and by participants (Participant Global Assessment) at baseline, 2, 4 and 6 months.
- Participant-reported AE symptoms (Patient Oriented Eczema Measure) assessed weekly.
- Three-Item Severity scale at baseline, 2, 4 and 6 months, assessed by the research nurses.
- Use of AE treatments: proportion of days on which topical steroids, topical calcineurin inhibitors, emollients and wet/dry wrapping were used.
- Health-related quality of life at baseline and 6 months from the perspectives of the family (Dermatitis Family Impact), the main carer (EuroQoL-5 Dimensions-3 Levels) and the child (Atopic Dermatitis Quality of life preference-based index; Child Health Utility – 9 Dimensions in those aged  $\geq 5$  years).
- Durability of the garments and acceptability of use (at 6 months), and adherence (weekly).
- Within-trial cost-effectiveness from a NHS perspective.

### **Safety outcomes**

Skin infections requiring antibiotic or antiviral treatment and serious adverse events related to AE.

### **Sample size**

Three hundred participants provided 90% power, at the 5% significance level (two-tailed), to detect a difference of around 3 points between the groups in mean EASI scores. Sample size was based on a repeated-measures analysis of covariance, standard deviation (SD) 13, correlation between EASI scores at different time points of 0.6 and loss to follow-up of 10%.

### Randomisation and blinding

Randomisation was stratified by recruiting hospital and by participants' age: < 2 years, 2–5 years or > 5 years. A computer-generated pseudo-random code with random permuted blocks of randomly varying size (2, 4 or 6) was created by the Nottingham Clinical Trials Unit.

The sequence of treatment allocations remained concealed until the database was locked at the end of the study, when it was revealed to data analysts.

Participants in the intervention group were further randomised to one of the two silk garment brands. Branding labels and packaging were removed from the garments prior to distribution.

### FLG genotype analysis

Saliva samples were collected for deoxyribonucleic acid extraction. Those of white European ethnicity were tested for the four most prevalent *FLG* loss-of-function mutations in this population: R501X, 2282del4, R2447X and S3247X.

### Statistical methods

The main approach to analysis was modified intention to treat, that is, analysis according to randomised group regardless of adherence to allocation and including only participants who provided outcome data at follow-up. All regression models included the randomisation stratification variables of recruiting site and age as covariates, and also included baseline scores (if measured). Adjusted differences in means are presented for continuous outcomes, and adjusted risk differences and relative risks for binary outcomes.

The primary analysis used a multilevel model with observations at the 2-, 4- and 6-month follow-ups, nested within participants, and included participants in whom EASI was assessed at least once at follow-up. The EASI scores were right skewed at all follow-up time points. The score was log-transformed for analysis and the effect of the trial garments is presented as a ratio of geometric means. This ratio was back-transformed to the original EASI scale to facilitate the interpretation of findings.

Sensitivity analyses for the primary outcome were performed (1) to include adjustment for variables that had an observed imbalance at baseline, (2) using multiple imputation for missing outcomes and (3) to explore the impact of adherence in wearing the garments by estimating the complier average causal effect at 6 months using instrumental variable regression methods.

A planned subgroup analysis based on presence or absence of loss-of-function mutations in *FLG* was conducted for the primary outcome by adding an interaction term between allocated treatment and *FLG* genotype to the primary analysis model.

Participants were classified as being broadly adherent if they wore the trial garments for at least 50% of the days or 50% of the nights.

### Health economics

Within-trial economic analysis compared the costs and quality-adjusted life-years (QALYs) from the perspective of the UK NHS. QALYs were estimated using linear interpolation and area-under-the-curve analysis, adjusting for baseline values, age and study centre.

A regression-based approach was used for the statistical analysis. The level of uncertainty associated with the decision over which option was most cost-effective was explored using non-parametric bootstrapping to construct the cost-effectiveness acceptability curve.

### Qualitative study

A nested qualitative study examined parent and child experiences of using silk garments within the trial, and barriers and motivators to prescribing silk garments from the perspectives of prescribers and commissioners.

Ten face-to-face or telephone interviews with child participants and three focus group discussions (two with children aged 7–8 years and one with children aged 5–6 years) were conducted.

Semistructured telephone interviews and focus groups were conducted with 33 parents/guardians of children in the trial (four focus groups and 22 telephone interviews).

Telephone interviews were conducted with 21 health-care professionals including dermatology specialist nurses ( $n = 9$ ), dermatologists ( $n = 4$ ), general practitioners ( $n = 3$ ), pharmacists ( $n = 3$ ) and health-care commissioners ( $n = 2$ ).

The results were analysed thematically using the five-stage Framework Analysis process for the adult studies, and using the three methods of holistic, selective and detailed data analysis for data derived from child participants.

## Results

Three hundred children were randomised between 26 November 2013 and 5 May 2015 (151 to standard care and 149 to intervention), with 282 (94%) included in the primary analysis (141 in each group).

The participants had a mean age of 5 years; 42% were female and 79% were of white ethnicity. Demographics and AE characteristics were well balanced at baseline, apart from a slight imbalance in sex, baseline EASI, parent-reported history of asthma and food allergy. These were adjusted for in the sensitivity analysis.

Adherence was high: 82% of participants wore the garments for at least 50% of the time (median of 81% of nights and 34% of days). Acceptability assessed at 6 months suggested that 70% were satisfied or very satisfied with the garments and 74% of the children were either happy or very happy to wear them. Specific concerns were raised about poor durability and fit of the garments.

Research nurses remained blinded to treatment allocation for 96% of participants.

For the primary outcome of AE severity, there was no difference between the groups in the nurse-assessed EASI scores. Geometric mean EASI scores at baseline and at 2, 4 and 6 months were 8.4, 6.6, 6.0, 5.4, respectively, in the standard care group and 9.2, 6.4, 5.8, 5.4, respectively, in the intervention group. For EASI scores averaged over the 2-, 4- and 6-month follow-up visits, the ratio of geometric means was 0.95 [95% confidence interval (CI) 0.85 to 1.07;  $p = 0.43$ ]. This CI is equivalent to a difference between the intervention and the standard care groups over the study period ranging from a decrease of approximately 1.5 points on the EASI scale (indicating less severe AE in the intervention group) to an increase of 0.5 points (indicating more severe AE in the intervention group).

For the secondary outcomes, there were no between-group differences in nurse-assessed AE severity, quality of life or medication use. Some small differences were observed for two of the participant-reported secondary outcomes, most probably as a result of response bias and the collection of multiple outcomes.

The rate of skin infections was similar in the two groups, occurring in 39 out of 141 (28%) participants in the standard care group and in 36 out of 142 (25%) participants in the intervention group. Two participants in the standard care group and four participants in the silk garments group were hospitalised for AE during the study.

All sensitivity analyses for the primary outcome (adjusting for additional baseline factors, imputing missing values and exploring the impact of adherence in wearing the garments) were supportive of the primary analysis. There was no differential effect of the clothing on EASI eczema severity according to *FLG* subgroup ( $p$ -value for interaction effect 0.47).

The mean cost of silk garments, including initial and replacement garments, was £318.52 (SD £136.60) per participant in the base case. Sixty-one (45.5%) participants required at least one replacement garment over the 6-month period.

Combined with wider health resource use, the adjusted mean difference in cost per participant was £364.94 (95% CI £217.47 to £512.42;  $p < 0.001$ ). This difference reflects the cost of the intervention; wider NHS costs were not significantly different between the groups.

The adjusted mean difference in QALY per participant was 0.0064 (95% CI -0.0004 to 0.0133). The adjusted incremental cost per QALY was £56,811, suggesting that silk garments for AE are not cost-effective within currently accepted thresholds.

In the qualitative component of the CLOTHES trial, parents and children provided valuable insights that correlated closely with the quantitative trial results. On the whole, clinicians and commissioners had limited knowledge and experience and were reluctant to prescribe garments that they perceived as being costly and lacking in robust evidence of effectiveness.

## Conclusion

### *Implications for health care*

This trial found no evidence of clinical or economic benefit of using silk garments compared with standard care in children with moderate to severe AE.

There were no differences between the treatment groups for any of the blinded outcomes. Furthermore, the 95% CIs around the primary efficacy estimates were narrow, suggesting that a clinically important treatment effect is unlikely to have been missed.

At the time of commissioning this research (2011), £840,272 was spent on prescriptions for silk garments per annum in the UK (all indications). By 2015, this amount had more than doubled to more than £2M per annum, suggesting considerable uptake of silk garments in recent years.

This is the first large, independent trial to have evaluated silk garments for the management of AE and the nested economic evaluation suggests that use of these garments is unlikely to be cost-effective for health providers.

The CLOTHES trial was an adequately powered RCT, with high follow-up rates and good adherence to the trial interventions. The study has strong external validity as it was pragmatic in design to reflect normal practice and participants were broadly reflective of the types of patients who are likely to be prescribed silk garments for their AE. The trial placed special emphasis on objective outcome measures in order to minimise response bias.

These trial results provide health commissioners with a better evidence base on which to make informed decisions about silk garments for AE. Whether or not the small benefits identified in some of the secondary outcomes are sufficient to justify purchasing these garments is something for individual parents to consider on a case-by-case basis.

### *Recommendations for research*

The use of non-pharmacological interventions for the management of AE remains a priority area for research, particularly among patients.

Other non-pharmacological interventions that have been prioritised by patients and health-care professionals in a UK priority-setting partnership are:

1. role of food allergy testing in the management of AE
2. psychological treatments for itching/scratching
3. best ways to wash
4. best natural products to use on the skin
5. avoidance of irritants and allergens in the environment
6. role of diet (exclusion diets and nutritional supplements)
7. role of education programmes and multidisciplinary care.

Methodological challenges remain in comparing trials of the same interventions as a result of the different study designs and outcome measures used. Efforts to support global initiatives to improve trial design, such as the Harmonising Outcome Measures for Eczema initiative, should be encouraged and their recommendations adopted into future AE trials.

### **Trial registration**

This trial is registered as ISRCTN77261365.

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