Silk garments plus standard care compared with standard care for treating eczema in children: a randomised controlled, observer blind, pragmatic trial (CLOTHES Trial)

Short title:

Silk garments for treating eczema: CLOTHES Trial

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ABSTRACT

Background

The role of clothing in the management of eczema (syn. atopic dermatitis, atopic eczema) is poorly understood. This trial evaluated the effectiveness and cost-effectiveness of silk garments (in addition to standard care) for the management of eczema in children with moderate to severe disease.

Methods and findings

This was a parallel group randomised controlled, observer-blind trial. Children aged 1 to 15 years with moderate to severe eczema were recruited from secondary care and the community in five UK centres.

Participants were allocated using on-line randomisation (1:1) to standard care, or standard care plus silk garments; stratified by age and recruiting centre. Silk garments were worn for 6 months.

Primary outcome (eczema severity) was assessed at baseline, 2, 4 and 6 months, by nurses blinded to treatment allocation using the Eczema Area and Severity Index (EASI), which was log-transformed for analysis (intention-to-treat analysis). Safety outcome: number of skin infections.

Three hundred children were randomised (26th Nov 2013 to 5th May 2015): 42% girls, 79% white, mean age 5 years. Primary analysis included 282/300 (94%) children (n = 141 in each group). The garments were worn more often at night than in the day (median of 81% of nights (25th to 75th centile 57% to 96%) and 34% of days (25th to 75th centile 10% to 76%)). Geometric mean EASI scores at baseline, 2, 4 and 6 months were 9·2, 6·4, 5·8, 5·4 for silk clothing and 8·4, 6·6, 6·0, 5·4 for standard care. There was no evidence of any difference between the groups in EASI score averaged over all follow up visits adjusted for baseline EASI score, age and centre (adjusted ratio of geometric means: 0·95, 95% CI 0·85 to 1·07). This confidence interval is equivalent to a difference of -1·5 to 0·5 in the original EASI scale units which is not clinically important. Skin infections occurred in 36/142 (25%) and 39/141 (28%) for silk clothing and standard care respectively. Even if the small observed treatment effect was genuine, the incremental cost per QALY was £56,881 in the base case analysis from an NHS perspective, suggesting that silk garments are unlikely to be cost-effective within currently accepted thresholds. Main limitations: whilst minimising detection bias, use of an objective primary outcome may have underestimated treatment effects.

Conclusions

Silk clothing is unlikely to provide additional benefit over standard care in children with moderate to severe eczema.

AUTHOR SUMMARY

Why was the study done?

- Prior to this trial, evidence on the use of silk garments for the management of eczema was limited.
- Three, small randomised controlled trials (RCTs) had been conducted, but these were small (74 participants in total), and at risk of bias.
- The existing evidence was insufficient to guide clinical practice on the use of silk clothing in the management of eczema, and no cost-effectiveness analyses had been undertaken.

What did the researchers do and find?

- We conducted a pragmatic, observer-blind, randomised controlled trial that recruited 300 children with moderate to severe eczema and followed them for 6 months.
- Participants were randomised to receive standard eczema care plus silk clothing (100% sericin-free silk garments (DermaSilk or Dreamskin), versus standard care alone.
- After 6 months, there was no evidence of a difference between the groups in eczema severity (EASI scores) assessed by research nurses; the 95% confidence interval ranged from 1.5 points favouring silk clothing to 0.5 points favouring standard care), which is not a clinically important difference.
- Even if the potential small benefit of silk garments was genuine, our analysis suggests that they are unlikely to be cost-effective within currently accepted thresholds, with an incremental cost per quality adjusted life year of £56,881.

What do these findings mean?

- The CLOTHES trial is the first large, independent RCT to have evaluated silk garments for the management of eczema.
- Results of this trial suggest that silk garments are unlikely to provide additional clinical or economic benefits over standard care for children with moderate to severe eczema.
- These results provide robust evidence for health commissioners and prescribers to make informed clinical decisions.

INTRODUCTION

Eczema (syn. atopic dermatitis, atopic eczema) is a chronic, itchy, inflammatory skin condition that is common throughout the world [1]. Childhood eczema has a substantial impact on the quality of life of children and their families [2]. Many families are keen to identify new ways of managing the symptoms of eczema using non-pharmacological approaches [3].

Clothing may play a role in either soothing or exacerbating eczema symptoms, and patients are commonly advised to avoid wool because of its tendency to worsen itch, and to use cotton or fine weave materials next to the skin [4]. Specialist clothing is now available on prescription in a variety of forms including sericin-free silk, viscose, and silver-impregnated fabrics. These garments are claimed to be beneficial for the management of eczema as they can help to regulate the humidity and temperature of the surface of the skin, are smooth in texture, and they may reduce skin damage from scratching. Some products have anti-microbial properties that could help to reduce the bacterial load on the skin, which may be important in eczema [5].

To date, there have been just three small randomised controlled trials (RCTs) of silk clothing for the management of eczema [6-8]. These trials involved very few participants (n=22, 30 and 22 participants respectively), were of generally short duration, did not incorporate an economic evaluation, and were at risk of bias [9].

In view of the limited evidence for the use of silk clothing, the UK National Institute for Health Research Health Technology Assessment programme commissioned the CLOTHing for the relief of Eczema Symptoms trial (CLOTHES Trial). The trial had two main objectives: (i) to assess whether use of silk garments plus standard eczema treatment reduces severity in children with moderate to severe eczema compared with standard treatment alone, and (ii) if so, to establish the likely cost-effectiveness of silk garments.

METHODS

The protocol has been published [10] and the protocol (S1 Protocol) and statistical analysis plan are available (www.nottingham.ac.uk/CLOTHES). The study was approved by Health Research Authority East Midlands - Nottingham 1 Research Ethics Committee (13/EM/0255), and parents/guardians gave written informed consent (children gave assent as appropriate). The trial was registered on Current Controlled Trials prior to start of recruitment (ISRCTN77261365 11 Oct 2013). This study is reported as per CONSORT guidelines (S1 CONSORT checklist). A full trial report is available (http://www.journalslibrary.nihr.ac.uk/hta).

Study design

The CLOTHES trial was a multi-centre, parallel group, observer-blind, pragmatic RCT of 6 months' duration. Children aged 1 to 15 years were randomised (1:1) to receive silk garments plus standard eczema care, or standard eczema care alone. The primary outcome was assessed by research nurses blinded to the treatment allocation at baseline, 2, 4 and 6 months.

The trial included a nested qualitative evaluation and health economic analysis.

Changes to the protocol after start of participant recruitment included amendment of the number of *FLG* mutations to be included in the genetic analysis, and addition of details of the nested qualitative evaluation.

Recruitment

Recruitment took place in five UK centres: Nottingham University Hospitals NHS Trust; Royal Free London NHS Foundation Trust; Cambridge University Hospitals NHS Foundation Trust; Portsmouth Hospitals NHS Trust and Isle of Wight NHS Trust. Participants were identified through secondary care, primary care, or in response to local media advertising.

Children aged 1 to 15 years were enrolled. All had a diagnosis of eczema according to the UK Working Party's diagnostic criteria [11] and a score of nine or more on the Nottingham Eczema Severity Score (NESS); denoting moderate to severe eczema over the last 12 months [12]. All participants had at least one area of active eczema on 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 eczema in the preceding 3 months; used wet/dry wraps ≥5 times in the last month; started a new medication or treatment regimen that may affect eczema in the last month; were currently using silk clothing for their eczema and were unwilling to stop during the trial; and if they were currently taking part in another clinical trial. Only one child was enrolled per family.

Interventions

The silk garments used in the trial (Dermasil or Dreamskin) are licensed as a medical device with a CE mark for use in eczema , denoting that they comply with EU legislation and safety requirements. Two brands were included to improve the generalizability of the trial findings, to avoid commercial advantage to any one company, and to limit the financial commitment for the companies who donated the garments.

The garments are made with antimicrobially-protected, knitted, sericin-free silk (100%). Sericin is removed from the silk fibres during manufacture because it is a protein that coats the outside of silk fibres and has the potential to cause allergic reactions. 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 clothing as often as possible during the day and at night.

Standardised usage instructions were provided and participants were advised to allow topical medications to absorb into the skin prior to wearing the garments. Replacement garments were provided if they were worn out, lost, or no longer fitted during the 6-month period of the trial.

Participants in both the intervention and control group continued with their standard eczema care in line with National Institute for Health and Care Excellence (NICE) guidance [13], including regular emollient-use and topical corticosteroids (or calcineurin inhibitors) for controlling inflammation. Participants were asked not to change their standard eczema treatment for the duration of the trial unless medically warranted. If a skin infection was suspected, participants were advised to contact their normal medical team for confirmation of diagnosis and subsequent treatment.

Outcomes

Core outcomes as defined by the Harmonizing Outcomes Measures for Eczema (HOME) initiative [14,15] were included.

Primary outcome

Eczema severity captured using the Eczema Area and Severity Index (EASI) [16], was assessed by trained research nurses at baseline, 2, 4 and 6 months. Baseline EASI was used as a covariate in the analysis model. EASI is a validated scale recommended as the core outcome instrument for eczema signs [17]. EASI involves an evaluation of four eczema signs (erythema (redness), excoriation (scratching), oedema/papulation (swelling and fluid in the skin) and lichenification (thickening of the skin)), and an assessment of percentage area affected by eczema in four body regions (head and neck, upper limbs, trunk and lower limbs). Higher scores represent more severe disease.

Secondary outcomes

a) Global assessment of eczema by research nurses (Investigator Global Assessment: IGA) [18] and by participants (Participant Global Assessment: PGA) at baseline, 2, 4 and 6 months, using a 6-point scale (clear, almost clear, mild, moderate, severe, very severe).

b) Self-reported eczema symptoms using the recommended core outcome instrument, [14] the Patient Oriented Eczema measure (POEM) which captures frequency of itch, sleep loss, bleeding, weeping/oozing, cracking, flaking and dryness [19]. Higher scores represent more severe disease. POEM scores were collected weekly using an on-line questionnaire for 6 months.

c) Three Item Severity scale (TIS) [20] at baseline, 2, 4 and 6 months, assessed by the research nurses at a representative body site (defined as the most bothersome patch of eczema that was covered by the garments).

d) Use of eczema treatments: number of days of use of topical steroids, topical calcineurin inhibitors, emollients and wet / dry wrapping were assessed weekly using an on-line questionnaire. Research nurses assessed change in eczema treatment regimen at each visit and categorized as no change, neutral change, reduction, or escalation.

e) Health Related Quality of Life at baseline and at 6 months from the perspectives of the family (Dermatitis Family Impact (DFI)) [21], the main carer (EuroQol five dimension three level (EQ-5D-3L)) [22], and the child (Atopic Dermatitis Quality of life preference based index (ADQoL) [23]; Child Health Utility 9D (CHU-9D) [24] in those aged 5 years and over).

f) Durability of the garments and acceptability of use (at 6 months), and adherence (number of days/nights garments worn, assessed weekly).

g) Within trial cost-effectiveness from NHS perspective using the ADQoL to estimate Quality-Adjusted Life Years (QALYs). ADQoL is a preference-based utility instrument with four eczema-specific domains covering: ability to join in activities, mood, ability to be comforted and sleep-loss. The resulting 16 possible health states range in utility from 0·356 (worst state) to 0·841 (best state) [23].

Safety outcomes

a) Skin infections requiring antibiotic or antiviral treatment, and serious adverse events (SAEs) related to eczema.

Sample size

Three hundred participants provided 90% power at the 5% significance level (two-tailed) to detect a difference of 3 points between the groups in mean EASI scores. Although this between-group difference is approximately half the published minimum clinically important difference for EASI (suggested from one study in adults receiving systemic therapy) [25], we wanted to be sure that a clinically important difference was not missed. Sample size was based on 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 10%.

Randomisation and blinding

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

Research nurses accessed the randomisation website via unique user logins. 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.

Staff at the co-ordinating centre sent confirmation of treatment allocation to participants (along with the silk clothing as necessary). Whilst it was not possible to blind participants to their treatment allocation, efforts were made to minimise expectation bias by emphasising in the trial documents that the evidence supporting the use of silk garments for eczema was limited, and that it was not yet known if such clothing offered any benefit over standard care. Participant-facing study documents also avoided the use of value-laden terms such as "specialist" or "therapeutic" clothing.

In order to preserve blinding of the research nurses, participants were reminded in the study literature and in their clinic appointment letters/texts not to wear the clothing when they attended clinic, or to mention the clothing when talking to the research nurses. All questions relating to the acceptability and use of the clothing were completed by either postal or on-line questionnaires, and telephone and email contact with participants was made by staff from the co-ordinating centre whenever possible. If the research nurses became un-blinded, this was recorded.

FLG genotype analysis

Saliva samples were collected for DNA extraction and *FLG* genotyping. Only participants of white European ethnicity were included, because *FLG* mutations are ethnically specific. Results for the four most prevalent loss-of-function mutations in the white European population (R501X, 2282del4, R2447X and S3247X) were obtained for 217 individuals and were used to define genotype categories: *FLG* wild type (no mutations identified); *FLG* heterozygotes (one *FLG* null mutation); and *FLG* homozygotes or compound heterozygotes (two *FLG* null mutations).

Statistical methods

Analyses were carried out by LEB (trial statistician) using Stata/SE 13·1. The main approach to analysis was modified intention to treat, that is, analysis according to randomised group regardless of adherence to allocation and including participants who provided at least one follow-up. Estimates of the intervention effect are presented with 95% confidence intervals and p-values. All regression models included the randomisation stratification variables (recruiting site and age) as covariates, and baseline scores if measured. Adjusted differences in means for the intervention group compared to the standard care group are presented for continuous outcomes, and adjusted risk differences and relative risks for binary outcomes. For outcomes collected at the 2, 4 and 6 month visit, the effect of the trial garments on eczema severity changing over the study period was explored by including an interaction term between treatment group and time-point in the model. As there was no evidence of a differential effect over time for any outcomes, we report a single estimate per outcome that averages the treatment effect over all time-points.

The primary analysis used a multilevel model with observations at 2, 4 and 6 months nested within participants. The model used a random intercept and slope at the participant level with an unstructured covariance matrix for these random effects. The model assumed that missing EASI scores were missing at random given the observed data. EASI scores were right skewed at all time-points. Diagnostic plots indicated that the assumptions for the multilevel model on the original EASI scale were not met. The data were log transformed for analysis and the effect presented as a ratio of geometric means [26, 27]. This ratio was back transformed to the original EASI scale to facilitate interpretation of findings.

Sensitivity analyses for the primary outcome adjusted for variables that had an observed imbalance between the groups at baseline; used multiple imputation for missing outcome data; and explored the impact of adherence in

wearing the clothing by estimating the complier average causal effect (CACE) at 6 months using instrumental variable regression.

A planned sub-group analysis based on presence or absence of loss-of-function mutations in *FLG* (which is associated with impaired skin barrier function and more severe disease), was conducted for the primary outcome by adding an interaction term between allocated treatment and *FLG* genotype (none, one, or two *FLG* null mutations) to the primary analysis model.

The global assessment scores (IGA and PGA) were dichotomized into ‘clear, almost clear or mild eczema versus ‘moderate, severe or very severe eczema, and analysed using generalised estimating equations. The mean weekly POEM scores, percentage of days that topical steroids were used, and quality of life outcomes were analysed using linear models (weighted according to the number of questionnaires completed for the weekly POEM and topical steroid use). The TIS was analysed using the multilevel model framework as outlined above for the primary outcome (not transformed). Changes to treatment regimen were based on whether a participant had reported treatment escalation over the 6 month RCT period and analysed using a generalised linear model. Skin infections were analysed using negative binomial regression. SAEs, durability and acceptability of use of the garments were summarised descriptively.

Adherence in wearing the trial clothing was summarised using the percentage of days and nights that the study clothing was worn. Participants were classified as being broadly adherent if they wore the trial clothing for at least 50% of the days or 50% of the nights. This was done for participants where at least half (12/24) of the weekly questionnaires were completed, and sensitivity analysis explored the impact of different assumptions for those participants who completed less than 50% of the weekly questionnaires. Adherence with the trial clothing was explored descriptively according to age and baseline eczema severity using correlation coefficients.

Full details of the analysis are documented in the Statistical Analysis Plan, which was finalised prior to database lock and release of treatment allocation codes for analysis.

Following concerns that the baseline EASI scores appeared lower than might be expected for children with moderate to severe eczema , an additional post-hoc analysis was conducted to explore the interaction between baseline severity and treatment group, by adding an interaction term between allocated group and baseline EASI score (log transformed and continuous) to the primary analysis model.

Patient involvement

Public and patient involvement (PPI) was embedded throughout the CLOTHES trial. Various PPI methods such as online surveys, discussion groups and patient panels, were used to inform multiple aspects of the trial design including choice of comparator, eligibility criteria, potential barriers to participation and outcome measures. PPI members also contributed to the development of patient-facing study materials, and took part in media interviews to enhance recruitment, A PPI representative was a co-applicant on the grant and was involved in all stages from trial design through to data interpretation and write up, and another PPI representative was a member of the Trial Steering Committee.

The study results will be published on the CLOTHES website, and a written summary and child-friendly animated film will be sent to trial participants.

Health economics

Within-trial economic analysis (conducted by THS using Stata/SE 14·1) compared the costs and QALYs in the standard care and intervention groups from the perspective of the UK National Health Service (NHS). We attached published unit costs (UK£2014/15) [28-30] to individual level quantities of resource use (S1 Table), and estimated the mean cost per participant incorporating the cost of the intervention and wider healthcare resource use (primary care, secondary care and medications).

QALYs were estimated using linear interpolation and area under the curve analysis, adjusting for baseline values, age and study centre. A regression-based approach (seemingly unrelated regression equations) [31] 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 [32] to construct the cost-effectiveness acceptability curve (CEAC) [33]. Neither costs nor QALYs were discounted.

To test the impact of taking an alternative approach to costing the silk garments, sensitivity analysis included an estimate of the amount pharmacists are reimbursed for each item of clothing they prescribe. This was based on the NHS Business Services Authority formula to estimate the actual cost to the NHS. Using the March 2015 tariff data [34], where the average discount was 7.43% and the pharmacist's professional fee £0.90 per prescription item, the analysis was re-run.

RESULTS

Recruitment and retention

Three hundred children were randomised between 26th November 2013 and 5th May 2015 (last study visit 21st October 2015). The primary analysis included 141 participants in each group who had at least one primary outcome assessment after baseline (Fig 1). For all but four participants, outcome assessments were performed by the same nurse at all study visits.

Fig 1: Participant flow diagram

For the weekly on-line questionnaires (24 questionnaires over 6 months), 126/149 (85%) in the intervention group and 127/151 (84%) participants in the standard care group completed 12 questionnaires or more. The median number completed was 22 (25th to 75th centile 17 to 24) in both groups.

Baseline characteristics

Participants had a mean age of 5 years, 42% were girls and 79% were white. At recruitment, 72% had moderate or severe AE, as judged by the Investigator Global Assessment (Table 1). Demographic and clinical characteristics were well balanced at baseline apart from gender and parental reported history of asthma and food allergy (Table 1). The mean baseline EASI score was slightly higher in the intervention group as more children had a baseline EASI score of over 30 points (14 participants for intervention; 4 participants for standard care). However the median and inter-quartile ranges (IQR) were similar between the groups (Table 2).

Table 1: Baseline demographic and clinical characteristics

	Standard care (n = 151)	Intervention (n = 149)	Total (n = 300)
Demographics			
Age (years) Mean [sd]	5 [3·6]	5·1 [3·7]	5·1 [3·6]
Median [25th, 75th centile]	4 [2, 8]	4 [2, 7]	4 [2, 7·5]
Min, max	1, 14	1, 15	1, 15
Gender			
Boys	82 (54%)	92 (62%)	174 (58%)
Girls	69 (46%)	57 (38%)	126 (42%)
Ethnicity			
white	123 (81%)	114 (77%)	237 (79%)
Indian/Pakistani/Bangladeshi	8 (5%)	7 (5%)	15 (5%)
Black	6 (4%)	6 (4%)	12 (4%)
Chinese	1 (1%)	3 (2%)	4 (1%)
Other Asian (non-Chinese)	0 (0%)	4 (3%)	4 (1%)
Mixed Race	12 (8%)	13 (9%)	25 (8%)

Other	1 (1%)	2 (1%)	3 (1%)
Clinical characteristics			
History of atopy (self-reported)			
Asthma	57 (38%)	46 (31%)	103 (34%)
Allergic rhinitis	60 (40%)	56 (38%)	116 (39%)
Food allergy	80 (53%)	68 (46%)	148 (49%)
Anaphylaxis	23 (15%)	23 (15%)	46 (15%)
Type of eczema			
Discoid	19 (13%)	17 (11%)	36 (12%)
Flexural	144 (95%)	147 (99%)	291 (97%)
Location of eczema			
Head and neck	115 (76%)	120 (81%)	235 (78%)
Hands and wrists	116 (77%)	108 (72%)	224 (75%)
Feet and ankles	100 (66%)	96 (64%)	196 (65%)
Limbs	151 (100%)	149 (100%)	300 (100%)
Trunk	128 (85%)	122 (82%)	250 (83%)
Previous medical care			
General practitioner only	41 (27%)	40 (27%)	81 (27%)
General practitioner and secondary care	110 (73%)	109 (73%)	219 (73%)
Medication used in the month prior to randomisation			
Emollients	150 (99%)	146 (98%)	296 (99%)
Topical steroids	136 (90%)	130 (87%)	266 (89%)
Calcineurin Inhibitors	14 (9%)	15 (10%)	29 (10%)
Wet/dry wraps (1 to 4 times)	13 (9%)	14 (9%)	27 (9%)
Nottingham Eczema Severity Score (NESS)*			
Moderate eczema in last year (9-11)	28 (19%)	30 (20%)	58 (19%)
Severe eczema in last year (12-15)	123 (81%)	119 (80%)	242 (81%)
Investigator Global Assessment (IGA) on day randomised			
Almost clear	4 (3%)	2 (1%)	6 (2%)
Mild	39 (26%)	39 (26%)	78 (26%)
Moderate	77 (51%)	67 (45%)	144 (48%)
Severe	30 (20%)	36 (24%)	66 (22%)
Very severe	1 (1%)	5 (3%)	6 (2%)
Patient orientated eczema measure (POEM)*			
Mean [sd]	16·6 [4·8]	17·3 [5·8]	17 [5·4]
FLG genotype[$] (using mutations R501X, 2282del4, R2447X , S3247X) for white ethnicities only (n)	(123)	(114)	(237)
no mutations	72 (59%)	71 (62%)	143 (60%)
one *FLG* null mutation	31 (25%)	20 (18%)	51 (22%)
two *FLG* null mutations	12 (10%)	11 (10%)	23 (10%)
Not known	8 (7%)	12 (11%)	20 (8%)
Health Care Resource use (UK£2014/15) (4 weeks pre-trial) mean[SD]	£34.82 (69.14)	£35.60 (69.46)	£35.20 (69.17))

Data are n (%) unless otherwise specified.

Categories for history of eczema, type of eczema and location of eczema are not mutually exclusive.

* Higher values represent more severe AE

[$] For children, where informed consent for genetic study was given and the saliva sample was taken. Data are presented for white European ethnicities only as *FLG* mutations are population-specific and mutations tested are prevalent in white European individuals.

Table 2: Outcomes assessed during clinic visits

Outcome and allocated group	Baseline	2 month	4 months	6 months	Adjusted intervention effect*Intervention - standard care (95% CI)	
BLINDED OUTCOMES						
Eczema area and severity index (primary outcome)						
Standard care						
n	151	137	133	139		
Median [25th, 75th centile]	7·3 [4·2, 12]	5·3 [2·5, 10·5]	4·3 [2·1, 10]	4·2 [2, 9·2]		
Geometric mean	8·4	6·6	6·0	5·4		
Intervention					Ratio of geometric means 0·95 (0·85, 1·07), p = 0·43	
n	149	139	135	133		
Median [25th, 75th centile]	7 [4·1, 15·4]	4·9 [2·2, 9·9]	4·1 [2·2, 9·4]	4 [1·9, 7·9]		
Geometric mean	9·2	6·4	5·8	5·4		
Three item severity scale (TIS) – mean [sd] (n)					Difference in means 0·09 (-0·22, 0·40), p = 0·57	
Standard care	4·9 [1·8] (n = 151)	4·0 [1·9] (n = 137)	4·1 [2·2] (n = 133)	3·7 [1·9] (n = 139)		
Intervention	4·9 [1·8] (n = 149)	4·1 [2·0] (n = 139)	4·1 [2·1] (n = 136)	3·7 [2·0] (n = 134)		
Investigator global assessment (IGA) of moderate, severe or very severe eczema – n (%)					Risk difference -0·1% (-9·3%, 6·3%), p = 0·70	Relative risk 0.98 (0.82, 1.12), p = 0.63
Standard care	108/151 (72%)	72/137 (53%)	63/133 (47%)	56/139 (40%)		
Intervention	108/149 (72%)	71/139 (51%)	60/136 (44%)	58/134 (43%)		
UNBLINDED OUTCOMES						
Participant global assessment (PGA) of moderate, severe or very severe eczema – n (%)					Risk difference -10·1%, (-18·3%, -2·0%), p = 0·01	Relative risk 0.83 (0.70, 0.98), p = 0.03
Standard care	113/151 (75%)	82/137 (60%)	72/133 (54%)	60/139 (43%)		
Intervention	98/149 (66%)	62/139 (45%)	56/135 (41%)	51/134 (38%)		

Treatment escalation since previous visit – n (%)					Risk difference (any escalation[$]) -5·3% (-16·3%, 5·7%), p = 0·34	Relative risk (any escalation[$]) 0.87 (0.62, 1.22), p = 0.43
Standard care	-	34/137 (25%)	16/133 (12%)	16/139 (12%)		
Intervention	-	15/139 (11%)	16/136 (12%)	16/134 (12%)		
Quality of life outcomes[#]						
Dermatitis Family Impact Questionnaire (DFI) mean [SD] (n)					Difference in means -0·8 (-2·1, 0·4), p = 0·18	
Standard care	12·0 [6·3] (n= 151)	N/A	N/A	8·6 [6·8] (n = 138)		
Intervention	12·4 [6·6] (n= 149)	N/A	N/A	7·6 [6·1] (n = 133)		
Atopic Dermatitis Quality of Life (ADQoL) # mean [SD] (n)						
Standard care	0·6952 [0·1300] (151)	N/A	N/A	0·7292 [0·1308](139)	Difference in means 0·0260 (-0·0018, 0·0539), p = 0·07	
Intervention	0·6883 [0·1409] (149)	N/A	N/A	0·7515 [0·1273](134)		
CHU-9D# (5years and over only) mean [SD] (n)						
Standard care	0·8292 [0·1263] (n=64)	N/A	N/A	0·8828 [0·1059](67)	Difference in means -0·0243 (-0·0584, 0·0098), p= 0·16	
Intervention	0·8386 [0·1115] (n=70)	N/A	N/A	0·8677 [0·1114](65)		
EQ-5D-3L index# for parents HRQL mean [SD] (n)						
Standard care	0·8983 [0·1612] (151)	N/A	N/A	0·9107 [0·1529] (138)	Difference in means 0·0115 (-0·0185, 0·0415), p = 0·45	
Intervention	0.9018 [0.1710] (147)	N/A	N/A	0.9184 [0.1564] (134)		

* - 282 participants were included in the analysis model for the EASI (n = 141 each group, note one participant in the intervention group attended 2 follow-up visits but EASI was not fully assessed at either of these visits as the child and parent did not want lower limbs assessed). 283 participants were included in the analysis models for the global assessments and TIS (n = 141 standard care, n = 142 intervention). 271 participants were included in the analysis model for DFI (n = 138 standard care, n = 133 intervention). All analyses were adjusted for site, age, and baseline value of the outcome if it was measured.

$ - Treatment escalation analysed as any treatment escalation between baseline and 6 months: 50/140 participants (36%) in the standard care group and 42/138 (30%) in the intervention group. Participants who missed visits were included if they had an escalation at any of the visits they attended or if they attended the 6 month visit and there was neutral or no change or a reduction in treatment.

Ranges for quality life scores: DFI (0 to 30); ADQoL (0.356 to 0.841); CHU-9D (0.33 and 1); EQ-5D-3L (-0.594 to 1)

Adherence, contamination and blinding

Adherence in wearing the garments was good. The garments were worn more often at night than in the day (median of 81% of nights (25th to 75th centile 57% to 96%) and 34% of days (25th to 75th centile 10% to 76%)) (Fig 2 and S2 Table). Adherence in wearing the garments was not associated with age or eczema severity at baseline (S2 Table). Contamination of the standard care group was low; six participants reported wearing silk clothing during the trial (including one participant who was allocated to the standard care group but was sent the silk clothing in error. This participant was included in the analysis according to randomised allocation).

Fig 2: Mean number of days/nights trial garments worn each week

The percentage of participants that escalated their eczema treatment during the 6-month trial was similar in the two groups (Table 2).

Acceptability of the garments assessed at 6 months suggested that 85/121 (70%) were satisfied or very satisfied with the clothing (95% CI 61% to 78%), and 89/121 (74%) of participants were either happy or very happy to wear the garments (95% CI 64% to 81%). Some participants raised concerns about the garments including poor durability and fit.

Research nurses remained blinded to treatment allocation for 289/300 (96%) of participants. Unblinding occurred for three participants in the standard care group and eight in the intervention group.

Primary outcome

For the primary outcome of eczema severity, there was no difference between the groups in the nurse-assessed EASI scores. For EASI scores averaged over the 2, 4 and 6-month follow-up visits, the adjusted ratio of geometric means was 0·95 (95% CI 0·85 to 1·07; p = 0·43) (Table 2 and Fig 3). This confidence interval equates to a difference of approximately -1·5 to 0·5 points in the original EASI scale units.

Fig 3: Primary outcome: Geometric mean nurse-assessed eczema severity (EASI scores) with 95% confidence intervals

All sensitivity analyses for the primary outcome (adjusting for additional baseline factors, imputing missing values and exploration of the impact of adherence (CACE analysis)) were supportive of the primary analysis (S3 Table). There was no differential effect of the clothing on EASI eczema severity according to *FLG* subgroup (S4 Table) or severity of eczema at baseline (S5 Table).

Secondary outcomes

For the secondary outcomes, there were no between group differences in nurse-assessed eczema severity (IGA, TIS), quality of life (DFI, EQ-5D-3L, CHU-9D), or medication use (percentage of days eczema medications used, or escalation of eczema treatments) (Tables 2 and 3). However, small differences were observed for two of the participant-reported secondary outcomes of eczema severity (PGA, POEM) (Tables 2 and 3; Fig 4).

Table 3: Secondary outcomes assessed on weekly questionnaires

	Standard care(n = 147)	Intervention(n = 145)	Adjusted difference in means Intervention – standard care(95% CI)
Participant mean of weekly POEM score during the 6 month RCT [#]			
Mean [SD]	14·2 [5·5]	11·6 [5·6]	-2·8 (-3·9, -1·8), p < 0·001
Percentage of days topical steroids used[$]			
Mean [SD]	44·1 [28·2]	39·3 [27·8]	-3·7 (-9·6, 2·3), p = 0·23
*Percentage of days emollients used**mean [SD]	88·4 [20·1]	86·0 [22·1]	
Percentage of days calcineurin inhibitors used^			
Mean [SD]	5·8 [15·9]	5·7 [16·3]	
Percentage of days wet/dry wraps used^			
Mean [SD]	5·2 [17·1]	3·1 [12·5]	

Table shows data for participants who completed at least one questionnaire
Summary statistics and analyses reported are weighted according to the number of questionnaires completed.

Difference in means adjusted for baseline POEM score and stratification variables age and site

$ Difference in means adjusted for topical steroid use at baseline (yes/no) and stratification variables age and site.

* Between group analysis not done as assumptions for model not met, as most participants were using these most of the time.

^ Assumptions were not met due to the large number of participants that weren't using these treatments.

Fig 4: Mean weekly patient-reported symptoms (POEM scores) with 95% confidence intervals

Safety outcomes (number of skin infections and hospitalizations due to eczema) were similar in the two groups (Table 4).

Table 4: Safety outcomes

	Standard care(n = 141)	Intervention(n = 142)	Adjusted relative risk Intervention - standard care (95% CI)
Any skin infection during 6-month RCT – n (%)[#]	39 (28%)	36 (25%)	0·89 (0·54, 1·47), p = 0·66
Number of skin infections per participant			
Median [25th, 75th centile]	1 [1, 2]	1 [1, 2]	
Min, max	1, 5	1, 8	
n	39	36	
Number of inpatient stays per participant due to eczema – n (%)			
0	139 (99%)	138 (97%)	
1	1 (1%)	2 (1%)	
2	1 (1%)	2 (1%)	
3 or more	0	0	

Relative risk for skin infections adjusted for stratification variables age and site.
Table shows data for participants who attended at least one follow-up visit
Percentages for any skin infection and inpatient stay use the number of participants attending at least one follow-up visit as the denominator.
Skin infections were reported by the parent/main carer and defined as any skin infections that required treatment with antivirals or antibiotics.
Inpatient hospital stays for eczema (for any reason) were reported by the parent/main carer.

Cost-effectiveness

The economic evaluation included all participants with complete resource use and ADQoL data at baseline and 6 months (n=273). The cost of a single set of tops and leggings ranged from £66.02 to £155.49, depending on the size of the child. The mean cost of silk garments for 6 months, including initial and replacement garments, was £318.52 (SD: £136.60) per participant in the base case (Table 5). The mean number of sets of garments (tops and leggings) per participant in the base case was 4·15 (SD 1.56). Sixty-one (45.54%) intervention participants received replacement garments over the 6 months. Combined with wider health resource use, the adjusted mean difference in cost per participant was £364.94 (95% CI £217.47 to £512.42: $p < 0·001$) for those who received silk garments compared to those who did not in the base case (Table 5). The difference in total costs between groups reflects the cost of the intervention, wider NHS costs were not significantly different between groups (£48.57

higher per participant on average in the intervention group, 95% CI -105.92, 203.05: p=0·537). For resource use and costs for all resource items see S6 Table and S7 Table.

The adjusted mean difference in QALY per participant was 0.0064 (95% CI -0.0004, 0.0133: p = 0·07) (Table 5). The adjusted incremental cost per QALY was £56,811, suggesting that silk garments for AE are not cost-effective within currently accepted thresholds. At a willingness to pay of £30,000 per QALY the probability of silk garments being cost effective was 12.13%. This conclusion did not change in sensitivity analysis testing an alternative approach to costing the silk garments. Although the cost of silk garments reduced, at £53,989 per QALY, the estimated incremental cost per QALY was still over the accepted NICE threshold value (see S8 Table).

Table 5: Key findings from the base case economic evaluation (UK£2014/15)

Outcome	Standard caren=139 Mean (SD)	Intervention n=134 Mean (SD)	Unadjusted (**Adjusted**) mean difference intervention – standard care (95% CI)
HEALTH OUTCOMES			
Utility (ADQoL)			
Baseline	0·6959 (0·1288)	0·6879 (0·1418)	-0·0081 (-0·0404, 0·0241)
6 months	0·7292 (0·1308)	0·7515 (0·1273)	0·0224 (-0·0084, 0·0531)
QALYs			
Over 6 months	0·3563 (0·0562)	0·3598 (0·0561)	0·0036 (-0·0098, 0·0169),(**0·0064 (-0·0004, 0·0133))**
COSTS			
Garments	0·00 (0·00)	318.52 (136.60)	318.52 (295.71, 341.33)
Primary care visits	47·01 (73·71)	36·52 (57·74)	-10·49 (-26·30, 5·33)
Secondary care visits	153·00 (327·13)	213·09 (604·47)	60·09 (-55·16, 175·34)
Prescriptions	120.86 (243.81)	119.82 (244.67)	-1.04 (-59.25, 57.18)
Total healthcare costs, excluding garments	320.86 (446.13)	369.43 (805.88)	48.57 (-105.92, 203.05)
Total healthcare costs, including garments	320.86 (446.13)	687.96 (809.27)	367.09 (212.12, 522.07) (**364.94 (217.47,512.42)**)

Incremental Costs Effectiveness Ratio (ICER) = £56,811per QALY

DISCUSSION

Main findings

This trial found little evidence of clinical or economic benefit of using silk garments in addition to standard care, compared with standard care alone in children with moderate to severe eczema. There were no differences between the treatment groups for any of the outcomes that were assessed by research nurses who were unaware of participants' treatment allocation, and the percentage of days on which topical corticosteroids or calcineurin inhibitors were used did not differ between the groups. The 95% confidence intervals around the primary efficacy estimates were narrow, suggesting that a clinically important treatment effect is unlikely to have been missed, and sensitivity analyses (imputing missing values, adjusting for baseline imbalances and exploring the impact of adherence in wearing the garments) supported the primary analysis.

Sub-group analysis based on *FLG* genotype showed no evidence of differential treatment response in children with an inherited impairment in skin barrier function, and a post-hoc analysis exploring the impact of baseline severity on the primary outcome showed no effect; suggesting that children with more severe disease were no more likely to benefit from silk clothing than those with milder disease.

The trial garments are marketed as possessing antimicrobial properties, but this study found no evidence to suggest a reduction in the number of skin infections in those using the clothing compared to those randomised to standard care alone.

Of the seven unblinded secondary outcomes, two (POEM and PGA) showed small differences in favour of the silk garments, most noticeably in the first 3-months of the trial. Whilst these small differences could have been genuine, they are most likely due to an expectation bias that declined with time. Our nested qualitative study (to be reported separately), highlighted the hopes that both children and parents placed on the silk clothing. A previous eczema trial has reported differences between blinded and unblinded outcomes when expectation in the benefits of the trial intervention is high [35].

Relevance to other studies

There have been no further RCTs on the effectiveness of silk garments for eczema since the CLOTHES trial began (search updated 14th March 2016), and meta-analysis of the available silk clothing trials is

not possible due to heterogeneity of designs. Additional brands of silk garments have since become available for use in eczema (e.g. Skinnies™), but these have not been formally evaluated in RCTs. At the time of commissioning this research (2011), £840,272 was spent on prescriptions for silk garments per annum in the UK (for all indications). By 2014, this amount had risen to £2,082,810 per annum [36-39].

Strengths and limitations

The CLOTHES Trial was an adequately powered RCT, with high follow-up rates and good adherence. The pragmatic study design meant that use of silk garments was evaluated as they might be used in normal practice, with mixed patterns of adherence. The trial placed special emphasis on objective outcome measures in order to minimise response bias.

It is possible that our emphasis on objective eczema severity 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 (especially itch and sleep loss, as measured by POEM), may be important drivers in determining whether or not patients feel that the garments are helpful. Nevertheless, we found no evidence of improved quality of life amongst trial participants using a range of validated scales.

Eczema severity scores improved for both groups during the trial, probably due to a combination of regression to the mean, and regular monitoring of the eczema resulting in enhanced adherence to standard care. It is possible that treatment effects were masked by these general trial effects.

Generalisability

The study has strong external validity as it was pragmatic in design to reflect normal clinical practice, and participants were recruited from five UK centres covering a range of urban and rural settings. We recruited children with a range of eczema severities but the majority had moderate to severe disease, and 32% had at least one mutation on the gene encoding for *FLG;* a proportion typical of eczema patents with moderate or severe disease [35]. Overall, 49% had self-reported food allergy and 15% reported a history of anaphylaxis, which is high for children with moderate to severe disease. However, these data were collected by self-report and so may include food intolerance as well as food allergy.

We are unable to comment on effectiveness of the silk garments if used continuously day and night, although sensitivity analysis found no evidence of improved outcomes in those who adhered more fully in wearing the garments. It is also possible that the beneficial effects of silk garments are best realised during a period of eczema flare, and daily use of the garments in the CLOTHES trial could have led to more rapid deterioration of the clothing than might have been seen if the garments were worn occasionally when the eczema was at its worst.

Conclusion

This is the first large, independent trial to have evaluated silk garments for the management of eczema. The nested economic evaluation suggests that use of these garments is unlikely to be cost-effective for health providers, even if the small observed benefits were genuine. These trial results provide health commissioners with a better evidence-base on which to make informed decisions about silk garments for eczema. Whether or not parents feel that the small benefits identified in some of the secondary outcomes are sufficient to justify purchasing these garments is something for individuals to consider on a case-by-case basis.

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Members of the CLOTHES Trial Team (contributors)

Nottingham Clinical Trials Unit: Lelia Duley, Director of NCTU and advisor on trial design; Andrew Jadowski, Trial Administrator; Jennifer White, Trial Coordinator; Sarah Walker, Data Coordinator; Tessa Clarke, Senior Trial Manager; Trish Hepburn, Senior Medical Statistician; Justin Fenty, Senior Statistician; Lucinda Murphy, Data Manager; Daniel Simpkins, IT and Data Manager; Chris Rumsey, IT Programmer

Other support staff at recruiting centres: Hannah Buckley, Principal Investigator; Sharon McCready, Research Nurse Lead; Rachel Watson, Clinical Trials Assistant; Gill Glasbey, Research Study Coordinator

Contributors to the qualitative study: Eileen Wake, Paediatric Nurse Lecturer; Rachel Harding, Paediatric Nurse; Jo Aspland, Research Associate.

Professor Irwin McLean, Ms Linda Campbell & Ms Stephanie MacCallum were responsible for DNA extraction and genotyping of saliva samples.

Antony Colles, Norwich CTU Senior Data Programmer, Norwich Medical School, University of East Anglia, assisted with formatting data for analysis.

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REFERENCES

1. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, Group IPTS. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. Journal of Allergy and Clinical Immunology. 2009;124(6):1251-8. e23.

2. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. International journal of clinical practice. 2006;60(8):984-92.

3. Batchelor JM, Ridd MJ, Clarke T, Ahmed A, Cox M, Crowe S, et al. The Eczema Priority Setting Partnership: a collaboration between patients, carers, clinicians and researchers to identify and prioritize important research questions for the treatment of eczema. Br J Dermatol. 2013;168(3):577-82. Epub 2012/09/12. doi: 10.1111/bjd.12040. PubMed PMID: 22963149.

4. National Eczema Society23/03/2016. Available from: http://www.eczema.org/itching-scratching.

5. Totté J, van der Feltz W, Hennekam M, van Belkum A, van Zuuren E, Pasmans S. Prevalence and odds of Staphylococcus aureus carriage in atopic dermatitis: a systematic review and meta-analysis. British Journal of Dermatology. 2016.

6. Koller DY, Halmerbauer G, Bock A, Engstler G. Action of a silk fabric treated with AEGIS in children with atopic dermatitis: a 3-month trial. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2007;18(4):335-8. Epub 2007/03/10. doi: 10.1111/j.1399-3038.2006.00511.x. PubMed PMID: 17346297.

7. Stinco G, Piccirillo F, Valent F. A randomized double-blind study to investigate the clinical efficacy of adding a non-migrating antimicrobial to a special silk fabric in the treatment of atopic dermatitis. Dermatology. 2008;217(3):191-5. Epub 2008/06/28. doi: 10.1159/000141648. PubMed PMID: 18583910.

8. Fontanini C, Berti I, Monasta L, Longo G. DermaSilk in long-term control of infantile atopic dermatitis: a double blind randomized controlled trial. Giornale italiano di dermatologia e venereologia : organo ufficiale, Societa italiana di dermatologia e sifilografia. 2013;148(3):293-7. Epub 2013/05/15. PubMed PMID: 23670066.

9. Nankervis H, Thomas K, Delamere F, Barbarot S, Rogers N, Williams H. Scoping systematic review of treatments for eczema. Programme Grants for Applied Research. 2016;4(7). doi: 10.3310/pgfar04070

10. Harrison EF, Haines RH, Cowdell F, Sach TH, Dean T, Pollock I, et al. A multi-centre, parallel group superiority trial of silk therapeutic clothing compared to standard care for the management of eczema in children (CLOTHES Trial): study protocol for a randomised controlled trial. Trials. 2015;16(1):390.

11. Williams H, Burney P, Hay R, Archer C, Shipley M, Hunter J, et al. The UK working party's diagnostic criteria for atopic dermatitis. I. Derivation of a

minimum set of discriminators for atopic dermatitis. Br J Dermatol. 1994;131(3):383-96.

12. Emerson RM, Charman, C.R., Williams, H.C. The Nottingham Eczema Severity Score: preliminary refinement of the Rajka and Langeland grading. British Journal of Dermatology. 2000;142:288-97.

13. NICE. NICE clinical guideline 57: Management of atopic eczema in children from birth up to the age of 12 years. Department of Health; December 2007.

14. Schmitt J, Spuls P, Boers M, Thomas K, Chalmers J, Roekevisch E, et al. Towards global consensus on outcome measures for atopic eczema research: results of the HOME II meeting. Allergy. 2012;67(9):1111-7.

15. Chalmers JR, Simpson E, Apfelbacher CJ, Thomas KS, von Kobyletzki L, Schmitt J, et al. Report from the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). British Journal of Dermatology. 2016;175(1):69-79. doi: 10.1111/bjd.14773.

16. Barbier N, Paul C, Luger T, Allen R, De Prost Y, Papp K, et al. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. British journal of dermatology. 2004;150(1):96-102.

17. Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. Journal of Allergy and Clinical Immunology. 2014;134(4):800-7.

18. Futamura M, Leshem YA, Thomas KS, Nankervis H, Williams HC, Simpson EL. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards. Journal of the American Academy of Dermatology. 2016;74(2):288-94.

19. Charman C, Venn A, Williams H. The Patient-Oriented Eczema Measure: Development and Initial Validation of a New Tool for Measuring Atopic Eczema Severity From the Patients' Perspective. Arch Dermatol. 2004;140(12):1513-9.

20. Wolkerstorfer A, De Waard van der Spek F, Glazenburg E, Mulder P, Oranje A. Scoring the severity of atopic dermatitis: three item severity score as a rough system for daily practice and as a pre-screening tool for studies. ACTA DERMATOVENEREOLOGICA-STOCKHOLM-. 1999;79:356-9.

21. Lawson V, Lewis-Jones S, Finlay A, Reid P, Owens R. The family impact of childhood atopic dermatitis: the dermatitis family impact questionnaire. Br J Dermatol. 1998;138:107-13.

22. Brooks R, Group E. EuroQol: the current state of play. Health policy. 1996;37(1):53-72.

23. Stevens KJ, Brazier JE, McKenna SP, Doward LC, Cork MJ. The development of a preference-based measure of health in children with atopic dermatitis. Br J Dermatol. 2005;153(2):372-7. Epub 2005/08/10. doi: 10.1111/j.1365-2133.2005.06736.x. PubMed PMID: 16086752.

24. Stevens K. Valuation of the Child Health Utility 9D Index. PharmacoEconomics. 2012;30(8):729-47. Epub 2012/07/14. doi: 10.2165/11599120-000000000-00000. PubMed PMID: 22788262.

25. Schram M, Spuls PI, Leeflang M, Lindeboom R, Bos J, Schmitt J. EASI,(objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012;67(1):99-106.

26. Bland JM, Altman DG. Statistics notes: Transformations, means, and confidence intervals. BMJ: British Medical Journal. 1996;312(7038):1079. doi: 10.1136/bmj.312.7038.1079

27. Bland JM, Altman DG. Statistics notes: the use of transformation when comparing two means. Bmj. 1996;312(7039):1153. doi: 10.1136/bmj.312.7039.1153

28. Curtis L, Burns A. Unit Costs of Health and Social Care 2015. PSSRU [21st April 2016]. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/.

29. Department of Health. National Schedule of Reference Costs 2014-15 2015 [22nd April 2016]. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.

30. HSCIC. Prescription Cost Analysis, England - 2015 [8th April 2016]. Available from: http://www.hscic.gov.uk/article/2021/Website-Search?productid=20437&q=prescription+cost+analysis&sort=Relevance&size=10&page=1&area=both#top.

31. Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. Health economics. 2004;13(5):461-75.

32. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: A non-parametric approach to confidence interval estimation. Health economics. 1997;6(4):327-40.

33. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health economics. 2001;10(8):779-87.

34. NHS Business Services Authority, Drug Tariff: http://www.nhsbsa.nhs.uk/PrescriptionServices/Documents/PPD%20Drug%20Tariff/March_2015.pdf. 2015, last accessed 21st December 2016

35. Thomas KS, Dean T, O'Leary C, Sach TH, Koller K, Frost A, et al. A randomised controlled trial of ion-exchange water softeners for the treatment of eczema in children. PLoS medicine. 2011;8(2):e1000395.

36. Health and Social Care Information Centre. Prescription Cost Analysis, England [9th June 2016]. Available from: https://data.gov.uk/dataset/prescription-cost-analysis-england.

37. ISD Scotland. Prescription Cost Analysis for 2008 2009 [13th June 2016]. Available from: http://www.isdscotlandarchive.scot.nhs.uk/isd/2241.html.

38. Primary Care Services, NHS Wales Shared Services Partnership. Prescription Cost Analysis 2015 2016 [9th June 2016]. Available from: http://gov.wales/statistics-and-research/prescriptions-dispensed-community/?lang=en.

39. HSC Business Services Organisation. Prescription Cost Analysis 2015 2016 [9th June 2016]. Available from: http://www.hscbusiness.hscni.net/services/1806.htm.

Supplementary files

S1 Table: Unit costs in 2014/15 UK pounds sterling

S2 Table: Adherence according to age and baseline severity of eczema, plus sensitivity analysis for adherence

S3 Table: Sensitivity analyses adjusting for variables with baseline imbalance and imputation for missing primary outcome scores

S4 Table: Sub-group analysis of primary outcome (*FLG* status)

S5 Table: Post hoc subgroup analysis for primary EASI outcome of eczema severity according to baseline eczema severity

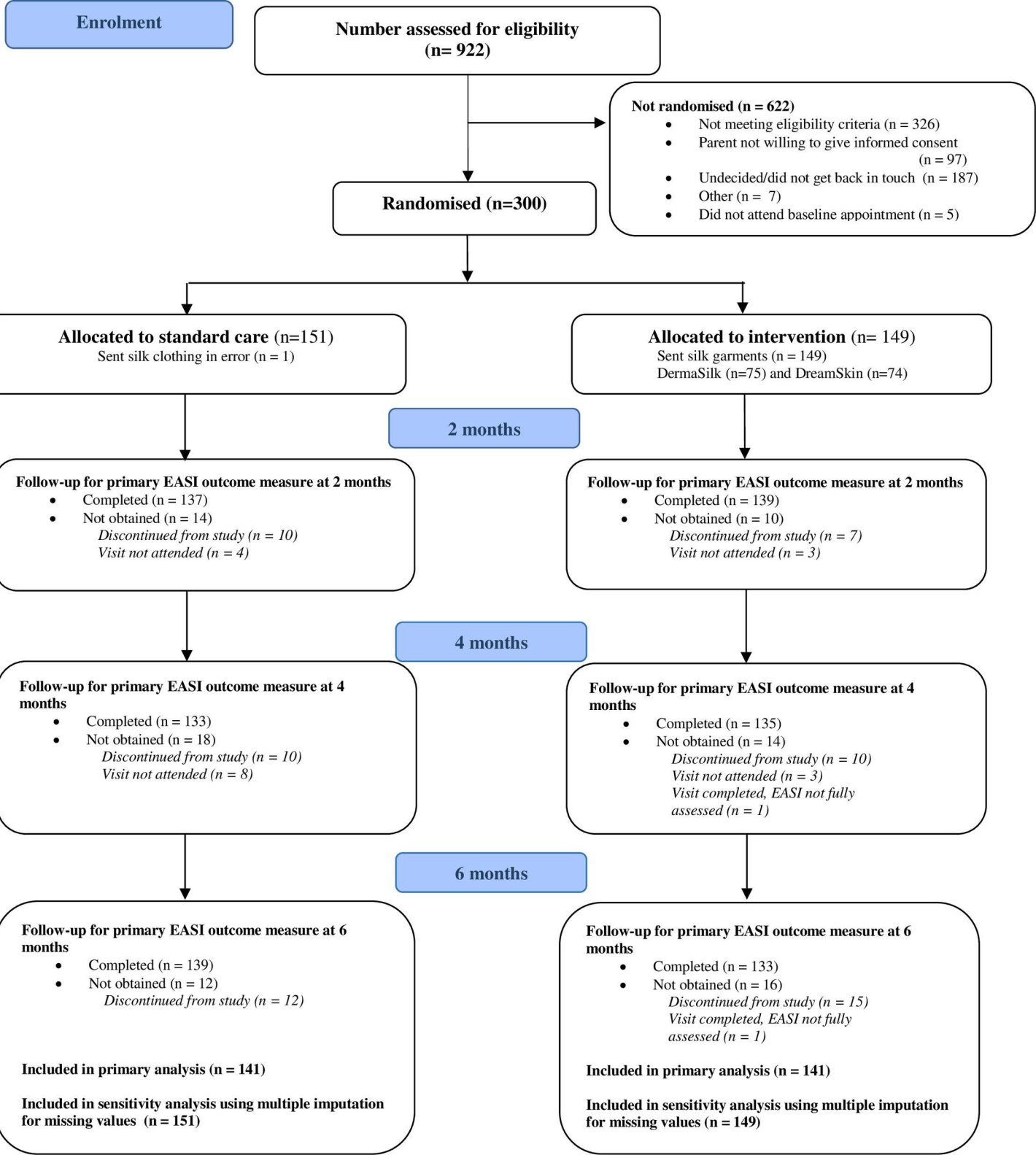
S6 Table: Mean (Standard Deviation) Resource Use and Mean Difference in Resource Use per Participant (95% Confidence Interval)

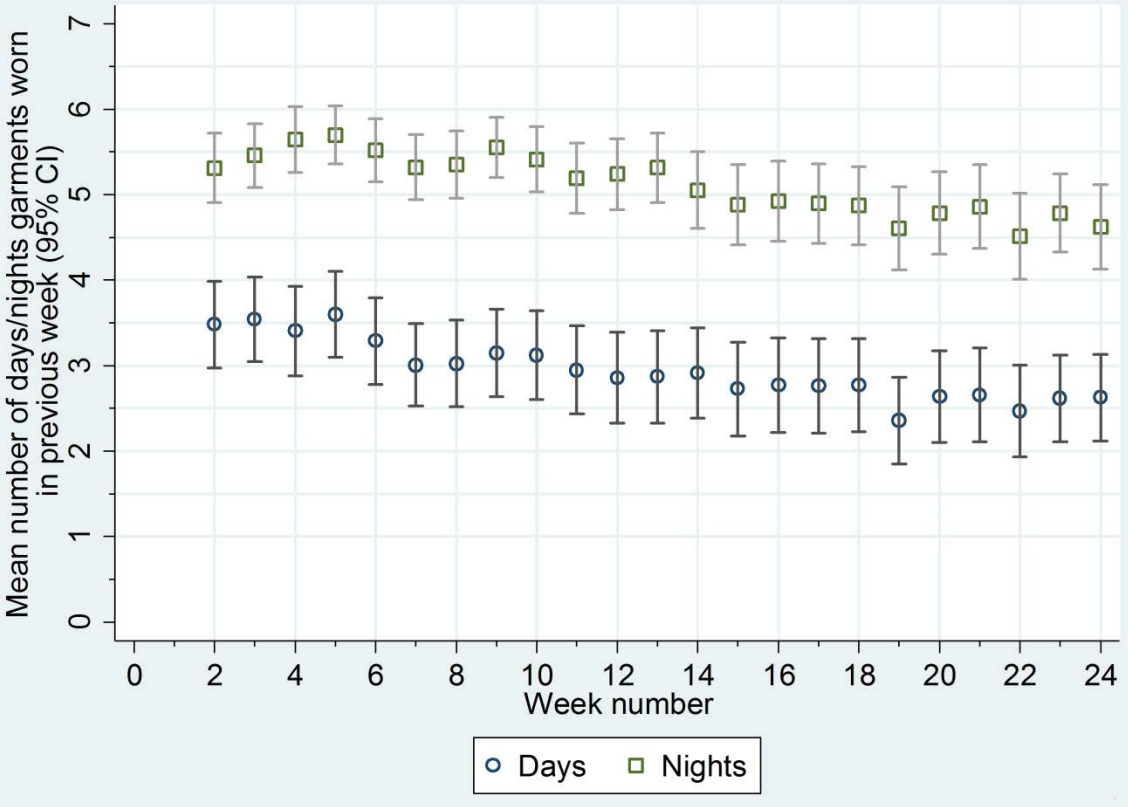
S7 Table: Mean (Standard Deviation) Cost and Cost Difference (95% Confidence Interval) per Participant over the 6 months (in 2014/15 UK pounds sterling)

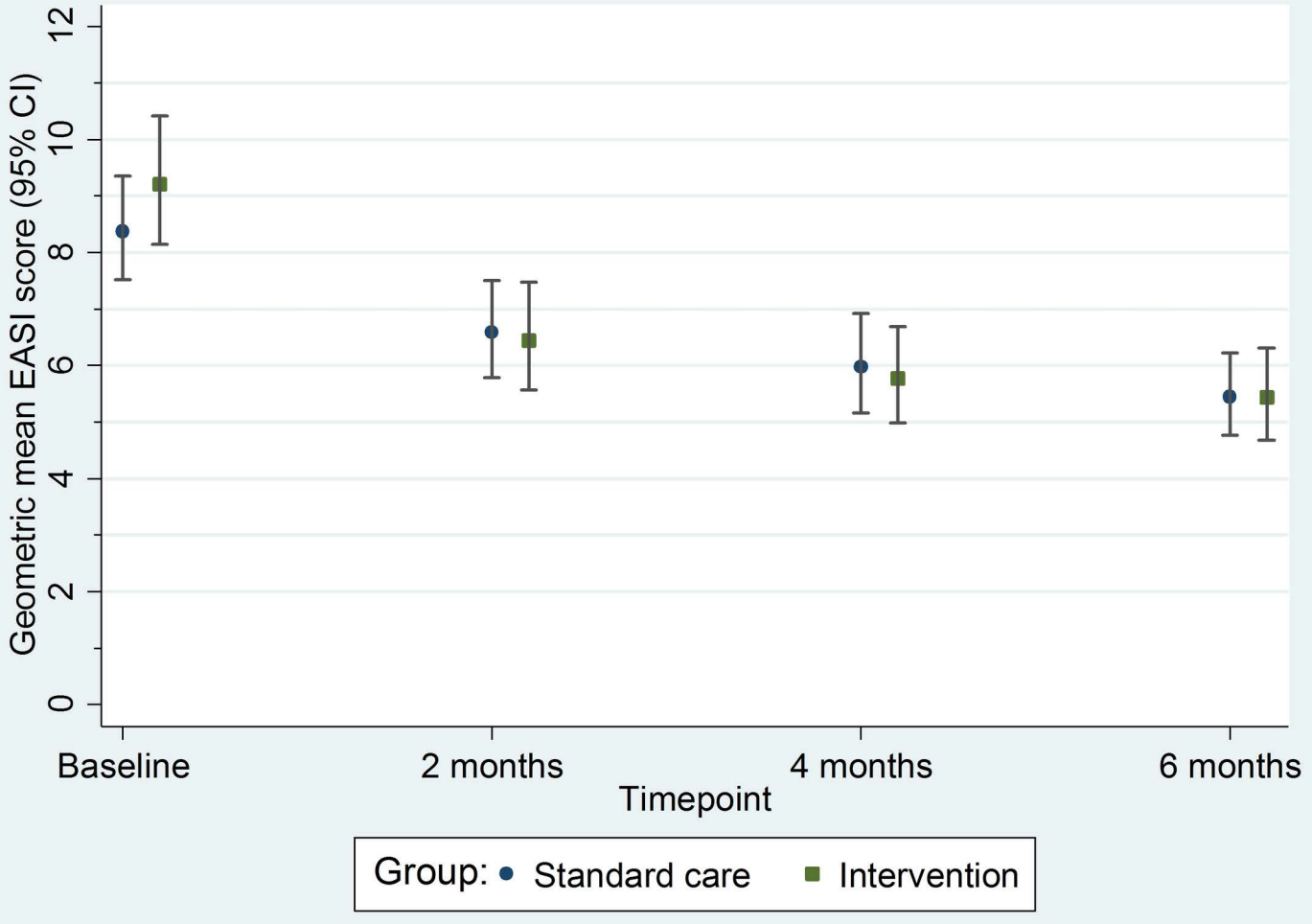
S8 Table: Incremental Cost-Effectiveness Analyses Results for base case and sensitivity analysis testing an alternative approach to costing silk garments

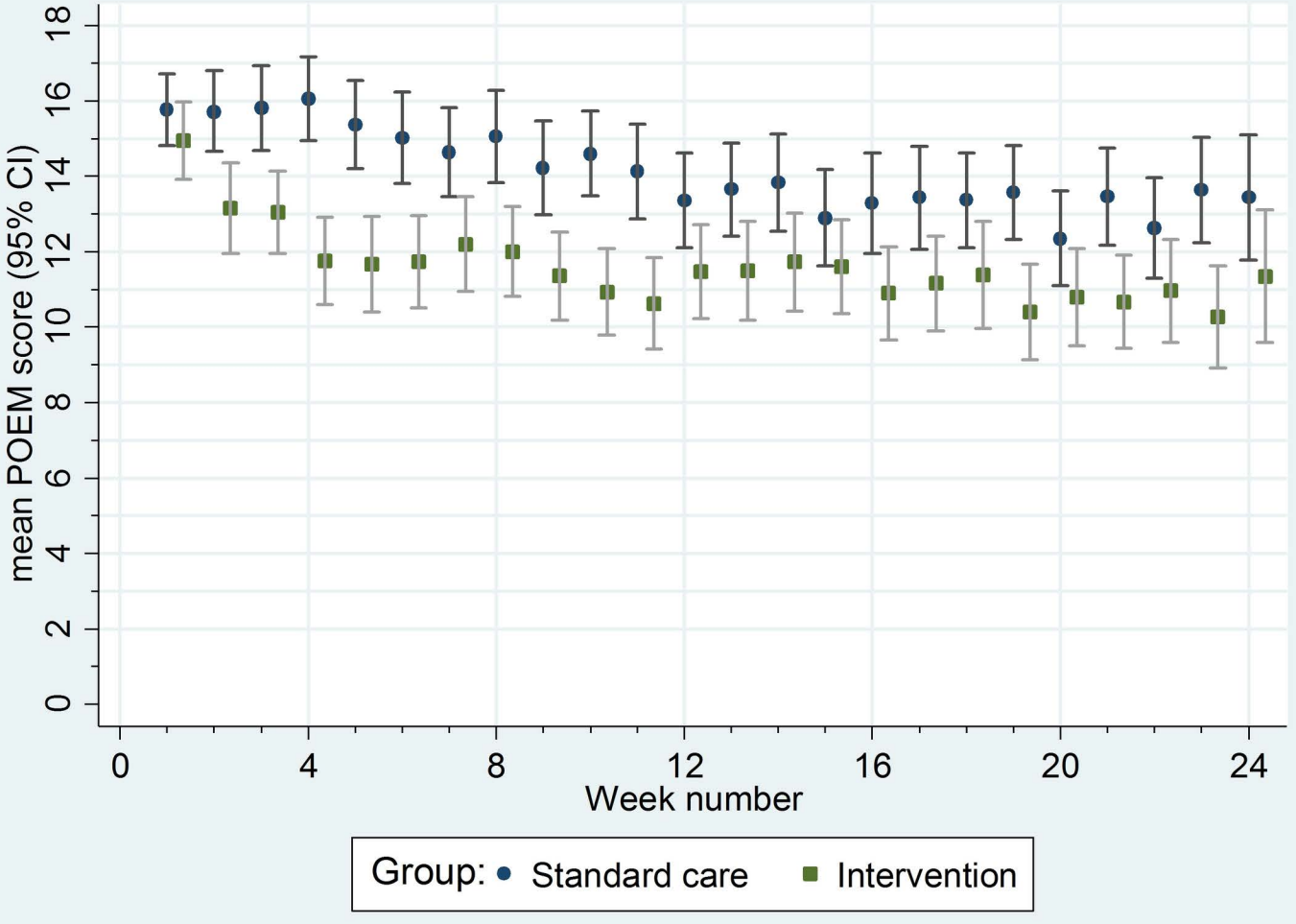
S1 Protocol: CLOTHES Protocol Final v3.0_11 Feb 2014

S1 Checklist: CONSORT Checklist


Enrolment
Number assessed for eligibility (n= 922)
Not randomised (n = 622)
Not meeting eligibility criteria (n = 326)
Parent not willing to give informed consent (n = 97)
Undecided/did not get back in touch (n = 187)
Other (n = 7)
Did not attend baseline appointment (n = 5)
Randomised (n=300)
Allocated to standard care (n=151)
Sent silk clothing in error (n = 1)
Allocated to intervention (n= 149)
Sent silk garments (n = 149)
DermaSilk (n=75) and DreamSkin (n=74)
2 months
Follow-up for primary EASI outcome measure at 2 months
Completed (n = 137)
Not obtained (n = 14)
Discontinued from study (n = 10)
Visit not attended (n = 4)
Follow-up for primary EASI outcome measure at 2 months
Completed (n = 139)
Not obtained (n = 10)
Discontinued from study (n = 7)
Visit not attended (n = 3)
4 months
Follow-up for primary EASI outcome measure at 4 months
Completed (n = 133)
Not obtained (n = 18)
Discontinued from study (n = 10)
Visit not attended (n = 8)
Follow-up for primary EASI outcome measure at 4 months
Completed (n = 135)
Not obtained (n = 14)
Discontinued from study (n = 10)
Visit not attended (n = 3)
Visit completed, EASI not fully assessed (n = 1)
6 months
Follow-up for primary EASI outcome measure at 6 months
Completed (n = 139)
Not obtained (n = 12)
Discontinued from study (n = 12)
Included in primary analysis (n = 141)
Included in sensitivity analysis using multiple imputation for missing values (n = 151)
Follow-up for primary EASI outcome measure at 6 months
Completed (n = 133)
Not obtained (n = 16)
Discontinued from study (n = 15)
Visit completed, EASI not fully assessed (n = 1)
Included in primary analysis (n = 141)
Included in sensitivity analysis using multiple imputation for missing values (n = 149)


Mean number of days/nights garments worn in previous week (95% CI)
0
1
2
3
4
5
6
7
0
2
4
6
8
10
12
14
16
18
20
22
24
Week number
Days
Nights


Geometric mean EASI score (95% CI)
0
2
4
6
8
10
12
Baseline
2 months
4 months
6 months
Timepoint
Group:
Standard care
Intervention


mean POEM score (95% CI)
0
2
4
6
8
10
12
14
16
18
0
4
8
12
16
20
24
Week number
Group:
Standard care
Intervention