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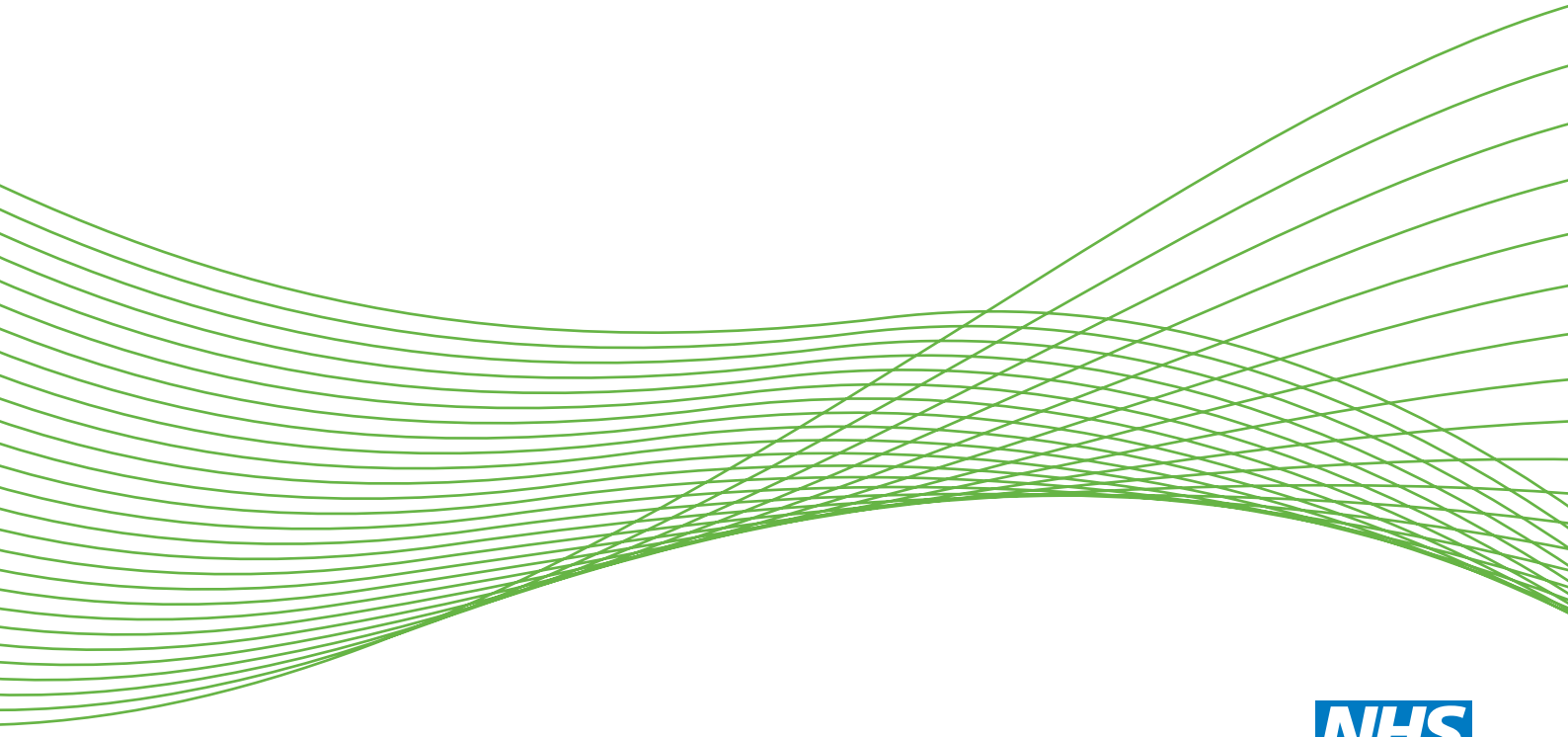

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Randomised controlled trial of silk therapeutic garments for the management of atopic eczema in children: the CLOTHES trial

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[1]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK
[2]Nottingham Clinical Trials Unit, University of Nottingham, Queen's Medical Centre, Nottingham, UK
[3]Health Economics Group, Norwich Medical School, University of East Anglia, Norwich, UK
[4]Faculty of Health Education and Life Sciences, Birmingham City University, Birmingham, UK
[5]Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK
[6]Patient and public involvement representative, Nottingham, UK
[7]Faculty of Science, University of Portsmouth, Portsmouth, UK
[8]Research and Enterprise, University of Brighton, Brighton, UK
[9]Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK
[10]Royal Free London NHS Foundation Trust, Barnet Hospital, Barnet, UK
[11]Portsmouth Hospitals NHS Trust, Queen Alexandra Hospital, Cosham, UK
[12]Isle of Wight NHS Trust, St Mary's Hospital, Newport, UK
[13]Skin Research Group, University of Dundee, Dundee, UK
[14]Department of Dermatology, Ninewells Hospital and Medical School, Dundee, UK

*Corresponding author

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Abstract

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

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[1]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK
[2]Nottingham Clinical Trials Unit, University of Nottingham, Queen's Medical Centre, Nottingham, UK
[3]Health Economics Group, Norwich Medical School, University of East Anglia, Norwich, UK
[4]Faculty of Health Education and Life Sciences, Birmingham City University, Birmingham, UK
[5]Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK
[6]Patient and public involvement representative, Nottingham, UK
[7]Faculty of Science, University of Portsmouth, Portsmouth, UK
[8]Research and Enterprise, University of Brighton, Brighton, UK
[9]Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK
[10]Royal Free London NHS Foundation Trust, Barnet Hospital, Barnet, UK
[11]Portsmouth Hospitals NHS Trust, Queen Alexandra Hospital, Cosham, UK
[12]Isle of Wight NHS Trust, St Mary's Hospital, Newport, UK
[13]Skin Research Group, University of Dundee, Dundee, UK
[14]Department of Dermatology, Ninewells Hospital and Medical School, Dundee, UK

*Corresponding author kim.thomas@nottingham.ac.uk

Background: Atopic eczema (AE) is a chronic, itchy, inflammatory skin condition that affects the quality of life of children and their families. The role of specialist clothing in the management of AE is poorly understood.

Objectives: To assess the effectiveness and cost-effectiveness of silk garments for the management of AE in children with moderate to severe disease.

Design: Parallel-group, observer-blind, randomised controlled trial of 6 months' duration, followed by a 2-month observational period. A nested qualitative study evaluated the beliefs of trial participants, health-care professionals and health-care commissioners about the use of silk garments for AE.

Setting: Secondary care and the community in five UK centres.

Participants: Children aged 1–15 years with moderate or severe AE.

Interventions: Participants were randomised (1 : 1 using online randomisation) to standard care or standard care plus 100% silk garments made from antimicrobially protected knitted sericin-free silk [DermaSilk™ (AlPreTec Srl, San Donà di Piave, Italy) or DreamSkin™ (DreamSkin Health Ltd, Hatfield, UK)]. Three sets of garments were supplied per participant, to be worn for up to 6 months (day and night). At 6 months the standard care group received the garments to use for the remaining 2-month observational period.

Main outcome measures: Primary outcome – AE severity using the Eczema Area and Severity Index (EASI) assessed at 2, 4 and 6 months, by nurses blinded to treatment allocation. EASI scores were log-transformed for analysis. Secondary outcomes – patient-reported eczema symptoms (Patient Oriented Eczema Measure); global assessment of severity (Investigator Global Assessment); quality of life of the child (Atopic Dermatitis Quality of Life, Child Health Utility – 9 Dimensions), family (Dermatitis Family Impact Questionnaire) and main carer (EuroQoL-5 Dimensions-3 Levels); use of standard eczema treatments (e.g. emollients, topical corticosteroids); and cost-effectiveness. The acceptability and durability of the clothing, and adherence to wearing the garments, were assessed by parental/carer self-report. Safety outcomes – number of skin infections and hospitalisations for AE.

Results: A total of 300 children were randomised (26 November 2013 to 5 May 2015): 42% female, 79% white, mean age 5 years. The primary analysis included 282 out of 300 (94%) children ($n = 141$ in each group). Garments were worn for at least 50% of the time by 82% of participants. Geometric mean EASI scores at baseline, 2, 4 and 6 months were 8.4, 6.6, 6.0, 5.4 for standard care and 9.2, 6.4, 5.8, 5.4 for silk clothing, respectively. There was no evidence of difference between the groups in EASI score averaged over all follow-up visits adjusted for baseline EASI score, age and centre (ratio of geometric means 0.95, 95% confidence interval 0.85 to 1.07; $p = 0.43$). This confidence interval is equivalent to a difference of –1.5 to 0.5 in the original EASI scale units. Skin infections occurred in 39 out of 141 (28%) and 36 out of 142 (25%) participants for standard care and silk clothing groups, respectively. The incremental cost per QALY of silk garments for children with moderate to severe eczema was £56,811 from a NHS perspective in the base case. Sensitivity analyses supported the finding that silk garments do not appear to be cost-effective within currently accepted thresholds.

Limitations: Knowledge of treatment allocation may have affected behaviour and outcome reporting for some of the patient-reported outcomes.

Conclusions: The addition of silk garments to standard AE care is unlikely to improve AE severity, or to be cost-effective compared with standard care alone, for children with moderate or severe AE. This trial adds to the evidence base to guide clinical decision-making.

Future work: Non-pharmacological interventions for the management of AE remain a research priority among patients.

Trial registration: Current Controlled Trials ISRCTN77261365.

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List of abbreviations

ADQoL	Atopic Dermatitis Quality of Life
AE	atopic eczema
CACE	complier average causal effect
CC	Complications and Comorbidities
CE	Conformité Européenne
CHU-9D	Child Health Utility-9 Dimensions
CI	confidence interval
CLOTHES	CLOTHing for the relief of Eczema Symptoms
CTU	Clinical Trials Unit
DFI	Dermatitis Family Impact
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EQ-5D-3L	EuroQoL-5 Dimensions-3 Levels
FLG	filaggrin
GP	general practitioner
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IGA	Investigator Global Assessment
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PGA	Patient Global Assessment
POEM	Patient Oriented Eczema Measure
PPI	public and patient involvement
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SD	standard deviation
SWET	Softened Water Eczema Trial
TIS	Three-Item Severity

Plain English summary

Eczema is a common childhood skin condition that impacts on quality of life as a result of symptoms such as itchiness, sore skin and impaired sleep. Patients are often keen to find non-drug treatments for eczema.

Some small studies had suggested that specialist silk clothing might help to improve the symptoms of eczema, but larger, well-designed studies are needed to be sure of these results.

The CLOTHing for the relief of Eczema Symptoms (CLOTHES) Trial tested whether or not silk clothing could reduce the severity of eczema in children aged > 6 months. A total of 300 children, aged 1–15 years, with moderate to severe eczema, took part. A computer was used to decide whether the children received silk clothing plus usual eczema care (moisturisers and topical corticosteroids) or usual care alone. Children in the clothing group were asked to wear silk tops and leggings as often as possible, day and night, for 6 months. Weekly questionnaires and visits to the nurse at 2, 4 and 6 months were used to assess the impact of the clothing.

Three hundred children took part in the study. Most of the children taking part were aged < 6 years, and three-quarters had previously seen a hospital doctor about their eczema. The silk garments were worn for at least half of the time by 82% of the trial participants. We found no difference between the two groups for nurse-assessed eczema severity, use of topical corticosteroid creams, number of skin infections or quality of life. Wearing the clothing did not reduce the number of visits to the doctor for their eczema, or the use of eczema medications.

Overall, the trial suggested that specialist silk clothing is not a useful treatment for eczema in children and does not represent good value for money.

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 ≥ 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.

Funding

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

Chapter 1 Introduction

Background

Atopic eczema (AE) (also known as atopic dermatitis or eczema) is a chronic, itchy, inflammatory skin condition that is common throughout the world.[1] Childhood AE has a substantial impact on the quality of life of both children and their families.[2–4] Standard treatment options for AE focus on topical medications: emollients, with the addition of topical corticosteroids and topical calcineurin inhibitors, tailored according to the severity of the AE.[5] Although most cases of AE can be successfully treated with topical medications, many parents express inconvenience and/or concern in using these preparations and are keen to identify new ways of managing the symptoms of AE using non-pharmacological approaches.[6]

Clothing may play a role in either soothing or exacerbating AE 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.[7] Specialist clothing is now available on prescription in the UK in a variety of forms, including sericin-free silk, viscose and silver-impregnated fabrics.[8] The therapeutic silk garments included in this study are available on prescription in the UK, at a cost ranging from £66 to £155 per set of top and leggings (2014/15 prices).[8] These garments are claimed to be beneficial for the management of AE, as they can help to regulate the humidity and temperature of the surface of the skin, are smooth in texture and may reduce skin damage from scratching. Some products have antimicrobial properties that may help to reduce the bacterial load on the skin, which may be important in AE.[9] However, the evidence from randomised controlled trials (RCTs) supporting the use of silk garments is limited.[10,11]

To identify RCTs published prior to the CLOTHES trial, we searched the Global Resource of Eczema Trials database.[12] At the time of starting the CLOTHES trial, 14 small RCTs assessing the effects of therapeutic clothing had been published: three RCTs investigated silk clothing [DermaSilk™ (AlPreTec Srl, San Donà di Piave, Italy)];[13–15] two investigated silver-coated textiles;[16,17] three investigated cellulose seaweed fibres with silver;[18–20] one investigated cellulose;[21] one investigated an anion textile;[22] two investigated types of ethylene vinyl alcohol fibre;[23,24] one investigated borage oil-coated garments;[25] and one investigated cotton and synthetic fibres.[26] Since the start of the trial, an additional study on chitosan-coated textiles has been published.[27]

The three previously published silk clothing RCTs are summarised in *Table 1* (for further details of all trials of therapeutic clothing for AE, see *Appendix 1*).

In view of the limited evidence for silk garments in AE, the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme issued a funding call in 2011 and, subsequently, 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 AE care reduces AE severity in children with moderate to severe disease over a period of 6 months.

TABLE 1 Summary of RCTs investigating silk garments for AE

Reference	Duration (months)	Participants	Interventions	Main results	Comments on study design and interpretation
Koller *et al.* (2007)[13]	3	22 children with mild to moderate AE (unclear how many included in analysis) Within-person trial	Intervention A: DermaSilk arm tubes (with antimicrobial coating). Worn all day on one arm for 3 months Intervention B: silk (without antimicrobial coating) arm tubes worn all day for 2 weeks, followed by cotton arm tubes for the remaining time in the trial Concurrent medication: emollients and antihistamines were permitted, but not topical corticosteroids	No difference in local SCORAD of DermaSilk group compared with cotton group at week 2 [median (quartile 1–quartile 3)] [7.5 (6–9) vs. 8 (6.25–9.75); $p = 0.274$] Significant reduction of local SCORAD index in the DermaSilk-covered arm observed after 4, 8 and 12 weeks in comparison with cotton-covered arm [4 weeks: 6.5 (5–8) vs. 8 (7–9; $p < 0.002$; 8 weeks: 6 (5.25–7.75) vs. 8 (7–9); $p < 0.0001$; and 12 weeks: 6 (5–6) vs. 8 (7.25–10); $p < 0.0001$]	• Method of randomisation and allocation concealment unclear • Primary outcome not specified • Multiple significance testing at different time points • Small between-group differences of unclear clinical relevance
Stinco *et al.* (2008)[14]	1	30 children and adults with AE (26 analysed) Within-person trial	Intervention A: DermaSilk (knitted fabric sleeves with bonded antimicrobial AEGIS AEM 5772/5) Intervention B: knitted silk fabric sleeves without antimicrobial finish Both interventions were worn all night and all day. One change per day, for 28 days	No difference between groups in mean local SCORAD at 7 and 14 days. At 21 days and 28 days, mean local SCORAD of the DermaSilk group was better than the unmodified silk group ($p = 0.02$ and $p \leq 0.0001$, respectively; confidence interval for difference in means not given). Difference of mean local SCORAD between groups over whole study was significant [mean 10.05 (SD ±9.22); $p < 0.0001$] No difference in mean pruritus values at day 7. At 14, 21 and 28 days, mean value of pruritus in DermaSilk group was better than unmodified silk group ($p = 0.03$, $p = 0.01$ and $p \leq 0.0001$, respectively)	• Allocation concealment unclear • Primary outcome not specified • Multiple significance testing of different time points • Participants instructed to always put the same colour sleeve on the same arm throughout the study (green seam or red seam) • Described as a double-blind trial, but the within-person design means that blinding of participants is unlikely to be maintained

Reference	Duration (months)	Participants	Interventions	Main results	Comments on study design and interpretation
Fontanini *et al.* (2013)[15]	24	22 infants aged 4–18 months (20 analysed) Parallel-group trial	Group A ($n = 9$): DermaSilk long-sleeved top and trousers Group B ($n = 11$): cotton clothing Both interventions were to be worn every day for 24 months, except during the summer and on very hot days in other seasons Both groups also received antimite mattresses, pillows and mometasone furoate for management of flares	Topical corticosteroid use was significantly lower in the DermaSilk group [median 0.07 (interquartile range 0.05–0.09) tubes/month] than in the cotton group [0.17 (0.09–0.33) tubes/month] ($p = 0.006$) All parents in the DermaSilk group were satisfied with outcome (regarding itching reduction), compared with five (45%) in the cotton group	• Method of randomisation and allocation concealment unclear • Blinding of participant unlikely to be maintained (silk and cotton garments easily differentiated) • Primary outcome not specified • SCORAD collected at baseline but not reported as an outcome • Topical steroid use recorded through participant diaries over the 24 months • Clinical relevance of the small difference between the groups in topical corticosteroid use is unclear

SCORAD, SCORing Atopic Dermatitis; SD, standard deviation.

Secondary objectives

- To estimate the within-trial cost-effectiveness of silk therapeutic garments from a NHS and wider (family and employer) 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.

Role of the funder

The study was funded by the NIHR HTA programme. Espère Healthcare Ltd (UK and Ireland distributor for DermaSilk) and DreamSkin™ Health Ltd (Hatfield, UK) donated the garments. The NIHR had input into trial design through peer review of the funding proposal and the garment companies provided advice in defining how the intervention should be used. Neither of the clothing companies had a role in data collection, analysis or interpretation or writing of the report. However, both had sight of the report prior to publication and had the opportunity to comment. The corresponding author had full access to all the data and had final responsibility for the decision to submit.

Chapter 2 Methods

Extracts of text, figures and tables throughout this report have been published in Thomas KS, Bradshaw LE, Sach TH, Batchelor JM, Lawton S, Harrison EF, *et al.* Silk garments plus standard care for treating eczema in children: a randomised controlled observer-blind pragmatic trial (CLOTHES TRIAL). *PLOS Med* 2017; in press. https://doi.org/10.1371/journal.pmed.1002280.[28]

Trial design

The CLOTHES trial was a multicentre, parallel-group, observer-blind, pragmatic RCT of 6 months' duration, followed by a 2-month observational period (*Figure 1*). Children aged 1–15 years with moderate to severe

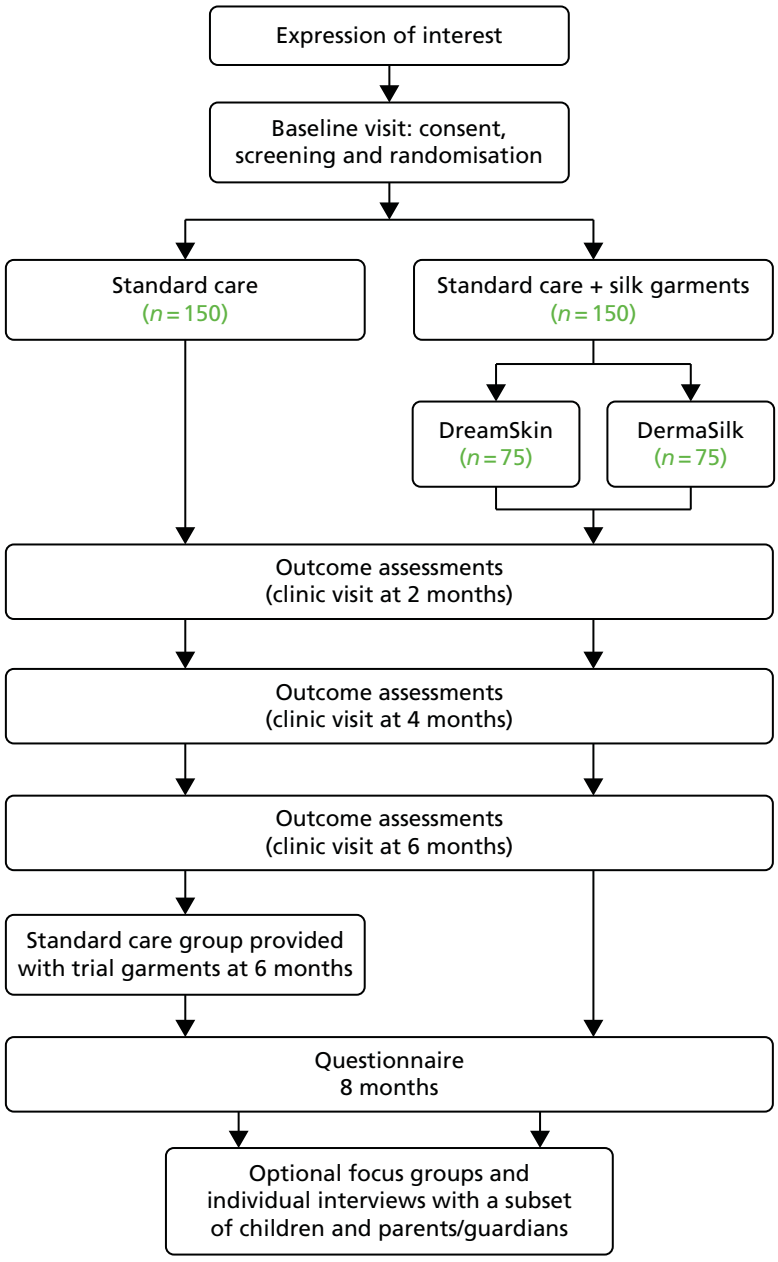

FIGURE 1 CLOTHES trial flow chart.

AE were randomised (1 : 1) to receive either silk garments plus standard AE care or standard AE care alone. The primary outcome was assessed by research nurses blinded to the treatment allocation at baseline, 2, 4 and 6 months.

Participants randomised to silk garments were further randomised to receive one of the two brands of garments used in the trial (DermaSilk or DreamSkin). Two products were used in the trial in order to improve the generalisability of the trial findings and to avoid commercial advantage to one particular company.

Participants allocated to the standard care group were given the silk garments after the primary outcome had been recorded at 6 months and used the garments for the remaining 2-month observational period. This was done in order to minimise loss to follow-up and potential contamination in the standard care group.

The trial included a nested qualitative evaluation, health economic analysis and subgroup analysis based on presence or absence of loss-of-function mutations in the gene encoding filaggrin (*FLG*). This was performed because loss-of-function mutations in *FLG* are known to increase the risk of eczema and it is possible that they affect response to silk clothing.

During the first 6 months of trial recruitment, an internal pilot was conducted to assess ability to recruit, adherence to the intervention and retention in the trial.

The study was approved by Health Research Authority East Midlands – Nottingham 1 Research Ethics Committee (reference number 13/EM/0255) and the local research and development department for each participating centre prior to recruitment commencing at that site. The trial was registered on Current Controlled Trials prior to start of recruitment (ISRCTN77261365 11 October 2013).

Recruiting centres

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 and primary care, or by self-referral in response to adverts placed in local media, in the community and online. Potential participants were identified when they attended a secondary care clinic or by responding to invitation letters and patient information sheets that were sent to parents of children identified from secondary care clinic lists. A parent information sheet and three separate age-appropriate child information sheets (for children aged 0–5, 6–10 and 11–15 years) were used in the study (see *Appendices 2–5*).

A number of press releases were issued at the start of the trial. Posters and flyers were displayed in recruiting centres and research nurses also took an active role in advertising the trial in the community by placing posters and flyers in local schools, shops and community centres. The trial was promoted online by the National Eczema Society and the Nottingham Support Group for Carers of Children with Eczema and adverts were also posted in relevant web forums using ethics-approved text. If parents were interested, either they contacted the recruiting centres directly or they enquired at the trial co-ordinating centre and their details were passed on to the relevant recruiting centre.

General practice surgeries and other hospitals local to the recruiting centres were used as patient identification centres by displaying trial posters and flyers.

Participants

Children were considered for entry into the trial if the following inclusion criteria were met:

- they were aged 1–15 years at baseline
- they had a diagnosis of AE according to the UK Working Party's diagnostic criteria[29] and a score of ≥ 9 on the Nottingham Eczema Severity Score,[30] denoting moderate or severe AE over the preceding 12 months
- they had at least one area of active AE on a part of the body that would be covered by the silk garments
- they were resident within travelling distance of a recruiting centre.

In addition, children were not entered into the trial if any of the following exclusions applied:

- they had taken systemic medication (e.g. ciclosporin, oral corticosteroids) or received light therapy for AE in the preceding 3 months
- they had used wet/dry wraps at least five times in the last month
- they had started a new medication or treatment regimen that may affect AE in the last month
- they were currently using silk garments for their AE and were unwilling to stop during the trial
- they were currently taking part in another clinical trial
- they had expressed a wish not to take part in the trial.

Only one child was enrolled per family; if more than one child in a family was eligible, the decision as to which child would be involved was made by the parents and children concerned.

Informed consent

Written informed consent was obtained from the parent/guardian of each participant at the baseline visit, prior to any trial procedures being carried out. In addition, assent was provided by the children if they wanted to. Consent to take part in the genetic study (*FLG* genotyping), and for samples to be stored and used for potential future research, was included as optional.

Interventions

Silk garments

The silk garments used in the study are licensed as a medical device with a Conformité Européenne (CE) mark for use in AE, denoting that they comply with European Union legislation and safety requirements. They are 100% silk garments made from antimicrobially protected, knitted, sericin-free silk. Sericin is removed from the silk fibres during manufacturing because it is a protein that coats the outside of the fibres and has the potential to cause allergic reactions.

Two products were chosen for inclusion in the trial (DermaSilk and DreamSkin), as these were the two brands available on prescription in the UK at the time of trial design. Distribution of the intervention to participants was handled from the co-ordinating centre, where a stock of garments across a range of sizes in both brands was maintained. Participants received three sets of garments (long-sleeved vest and leggings or long-sleeved 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, either as underwear or as pyjamas (*Figure 2*). Three sets were provided to allow for the washing and rotation of garments. The child's height at randomisation was used to determine the correct size of garments, which were posted out to participants as soon as possible after randomisation. On receipt of the garments, participants were instructed to try on one set to check that they fitted correctly and then confirm this with the co-ordinating centre. Standardised care instructions were provided on a paper insert included in the garment package (*Box 1*) and instructions were also replicated in the participant diary.

Garments were replaced as required during the 6-month RCT (if they were worn out, were lost or no longer fitted the child). If replacement garments were required, the participants returned the worn garments to

FIGURE 2 Garments being worn.

BOX 1 Care instructions for garments

Washing instructions for trial clothing

How do I use the garments?

Please wear the garments as often as possible, both during the day and at night (either as underwear or as pyjamas).

Moisturising creams should be applied thinly to the skin (just enough for the skin to glisten) and should be applied a few minutes before putting on the clothing to allow the creams to be absorbed into the skin.

How do I care for the garments?

You will be given three sets of garments during the trial. This will allow one set to be in use, one in the wash and one spare. We recommend that you use all three sets within 1 week, rotating frequently.

To machine wash: wash at up to 40 °C using your usual mild non-biological detergent. The fibres of the garment are quite delicate and washing the garment inside a pillowcase on a delicate cycle will protect it during the wash. If possible, lay the garment flat to dry.

To hand wash: place in hand-hot water containing your usual mild non-biological detergent and agitate by hand for a few minutes. Rinse well with plenty of warm, clean water and squeeze dry. Do not wring. If possible, lay the garment flat to dry.

Other important points

Please do not use bleach. Make sure there are no bleaching agents in your detergent [such as Vanish (Reckitt Benckiser, Slough, UK)].

Please do not use fabric softeners.

Please do not tumble dry.

Any reduction in garment length is likely to be a result of a tightening of the knit. A cool steam iron can be used to restore the shape of a garment that appears to have shrunk.

the co-ordinating centre with a completed garment request form and new garments were sent out. After the 6-month RCT period was over, garments were not replaced.

Standard care

All participants continued with their standard AE care in line with National Institute for Health and Care Excellence (NICE) guidance,[5] including regular emollient use, avoidance of irritants and topical corticosteroids (or calcineurin inhibitors) for controlling inflammation. Participants were asked not to change their standard AE treatment for the duration of the trial unless medically warranted.

Participants who frequently used wet- or dry-wrap dressings for their AE were excluded, but occasional use of wet or dry wraps was monitored but not prohibited.

If a research nurse suspected that the AE had become infected, participants were advised to contact their normal medical team for confirmation of diagnosis and subsequent treatment.

Outcomes

Details of derivations for outcomes can be found in the statistical analysis plan (see *Appendix 6*).

Primary outcome

The primary outcome of AE severity measured using the objective Eczema Area and Severity Index (EASI)[31] was assessed at baseline and at 2, 4 and 6 months. Baseline EASI score was used as a covariate in the analysis model. EASI score was assessed by trained research nurses who were blinded to treatment allocation. EASI score was chosen as the primary outcome as it is a validated scale recommended as the core outcome instrument for AE signs.[32] EASI involves an evaluation of four AE 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). EASI score ranges from 0 to 72, with higher scores representing more severe disease.

All research nurses received training in the use of EASI (using standardised training photographs and assessment of patients with AE by two independent assessors until concordance was reached). Resources were provided to assist in assessing the signs and body surface area (see *Appendix 7*).

Participants were assessed by the same research nurse at all time points in order to minimise interobserver variability.

Secondary outcomes

- Global assessment of AE by research nurses [Investigator Global Assessment (IGA)] and by participants [Patient Global Assessment (PGA)] at baseline and at 2, 4 and 6 months, using a six-point scale (clear, almost clear, mild, moderate, severe and very severe).
- Self-reported AE symptoms using the recommended core outcome instrument,[33] the Patient Oriented Eczema Measure (POEM), which captures frequency of itch, sleep loss, bleeding, weeping/oozing, cracking, flaking and dryness.[34] It has a range from 0 to 28, with higher scores representing more severe disease. POEM scores were collected weekly using an online questionnaire for the first 6 months and once again at 8 months. Obtaining self-reported eczema severity every week for 6 months was used to capture long-term control of flares as well as self-reported eczema symptoms.
- Three-Item Severity (TIS) scale[35] at baseline and at 2, 4 and 6 months, assessed by research nurses at a single representative body site (defined as the most bothersome patch of AE that was covered by the garments). The selected representative body site did not have to be the same at each visit. The TIS measures three clinical signs (erythema, oedema/papulation and excoriation) and the total score ranges from 0 to 9, with higher scores representing more severe disease. Given the importance of an objective measure to capture eczema severity in this observer-blind trial, it was felt that a second validated eczema severity scale was warranted.

- Use of AE treatments: number of days of use of topical steroids, topical calcineurin inhibitors, emollients and wet/dry wrapping, assessed weekly throughout the trial. At each visit, research nurses assessed change in AE treatment regimen and categorised as no change, neutral change, reduction or escalation.
- Health-related quality of life at baseline and at 6 months from the perspectives of the family [Dermatitis Family Impact (DFI)],[36] the main carer [EuroQoL-5 Dimensions-3 Levels (EQ-5D-3L)][37] and the child [Atopic Dermatitis Quality of Life (ADQoL) preference-based index[38] and Child Health Utility-9 Dimensions (CHU-9D)[39] in those aged ≥ 5 years].
- Durability of the garments, adherence and acceptability of use (as assessed by children and parents/carers). Adherence was collected weekly, and information on durability and acceptability was captured at 6 and 8 months in the participant questionnaires. Sticker charts were provided for children to record how many days/nights the garments had been worn for the intervention group and how many days/nights they had been in the study for the standard care group (see *Appendix 8*). These were intended to help keep children engaged in the study and to assist in completing the adherence data in the weekly questionnaires.
- Health resource use for treatment of AE throughout the trial: health-care visits, inpatient stays, medications, tests, personal items for AE and time off work or school.

Safety outcomes

Skin infections requiring antibiotic or antiviral treatment self-reported by parents and serious adverse events related to AE (hospitalisation as a result of AE) were recorded.

Tertiary outcomes

Although it was assumed that the different brands of garments were similar, the effects of receiving different brands of garments were also explored. Another additional exploratory analysis was conducted based on AE severity scores in areas covered by the garments (body and limbs) compared with areas uncovered by the garments (head and neck). All tertiary analyses were considered exploratory.

Data collection

Trial data generated by all centres were entered by research nurses directly into a web-based MACRO database (MACRO 4 version 3800, Elsevier, London, UK), maintained by the Nottingham Clinical Trials Unit (CTU). Access to the trial database was controlled by user logins and research nurses could enter/edit data for their site only. Paper worksheets were provided for research nurses to record data during the clinic visit (see *Appendix 9*) and were transcribed after the visit. Participant questionnaires completed at clinic visits were transcribed by the research nurses into the trial database. Data entry was checked against the paper record for 100% of the primary outcome and for a 10% sample of all data.

Participants were provided with a diary booklet in which they were encouraged to record all health-care visits for eczema, eczema prescriptions, purchases for AE and time off work/school because of AE (see *Appendix 10*). The diary was reviewed by the research nurse at each clinic appointment and used as an aide memoir to complete the relevant sections of the trial database.

Missing and/or ambiguous data were queried with research nurses and resolved whenever possible.

Weekly questionnaires were completed by the participant online or in paper format (see *Appendix 11*) and sent to the Nottingham CTU for data entry on the bespoke in-house system. The preference for paper or online questionnaires was recorded at baseline. Participants completing online questionnaires were emailed a unique web link to the questionnaire each week on the day completion was due. A further reminder e-mail was sent at the beginning of day 3 if the questionnaire had not been completed. Links remained active until the end of day 3, after which time the week's entry was classed as missing. Participants who failed to complete the weekly questionnaire for ≥ 3 weeks in a row were contacted by the Nottingham CTU and encouraged to complete the questionnaires.

For the week 24 (6-month) (see *Appendix 12*) and week 32 (8-month) (see *Appendix 13*) questionnaires, online submission remained open for 14 and 7 days, respectively, in order to ensure maximum data completion at the

primary end point and end of trial. For these time points, non-responders were contacted by telephone and a paper copy of the questionnaire was sent by post if required.

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. Although this between-group difference is approximately half the published minimum clinically important difference for EASI that was suggested from one study in adults,[40] we wanted to be sure that a clinically important difference to patients was not missed as a result of our focus on an objective outcome for the primary outcome. Sample size was based on repeated measures analysis of covariance, assuming a standard deviation (SD) of 13, a correlation between EASI scores at different time points of 0.6 and loss to follow-up of 10%.

Stopping rules and discontinuation

An internal pilot RCT was conducted over the first 6 months of trial recruitment to ensure delivery of the trial to time and target. Pre-defined stop/go criteria were assessed by the Trial Steering Group at 6 months as outlined in *Table 2*. Target recruitment for the RCT phase was ≥ 75 participants.

Adherence to wearing the clothing was defined as a trigger for concern if participants reported using the clothing < 50% of the time.

Randomisation and blinding

Randomisation was stratified by recruiting hospital and by participant's age: < 2, 2–5 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 CTU, in accordance with their standard operating procedure, and held on a secure University of Nottingham server. Research staff at sites were not aware of the block sizes. Participants were further randomised to one of the two silk garment brands (DermaSilk or DreamSkin) using a computer-generated pseudo-random code with random permuted blocks of randomly varying size, stratified by allocated group.

Research nurses accessed the randomisation website by means of a remote, internet-based randomisation system developed and maintained by the Nottingham CTU. Access was controlled by unique user logins. The sequence of treatment allocations was concealed until interventions had all been assigned and recruitment and data collection were complete. Study statisticians were blinded to treatment allocations until the database was locked.

TABLE 2 Stop/go criteria for the pilot RCT phase

Criteria to be assessed at 6 months of recruitment	Proposed action
≥ 90% of target recruitment and retention	Continue with main trial as planned
70–89% of target recruitment and retention	Continue with main trial, implement strategies for improvement
50–69% of target recruitment and retention	Urgent measures required, discuss plans with Trial Steering Committee and NIHR HTA
< 50% of target recruitment and retention	Stop trial unless good reason for delay and rectifiable solution can be readily implemented

After each allocation, the randomisation system notified staff at the Nottingham CTU, who then sent a letter confirming the treatment allocation to the participant (along with the silk garments as necessary). Staff at the Nottingham CTU removed branding labels from the garments and repackaged them in plain trial packaging before sending so that participants were not aware of which brand of garments they had received.

Although 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 AE was limited and that it was not yet known if such garments offered any benefit over standard care. Participant-facing study documents also avoided the use of value-laden terms such as 'specialist' or 'therapeutic' garments.

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 garments when they attended the clinic nor to mention the garments when talking to the research nurses. Additionally, children were sent cards, both to thank them for their participation and remind them not to disclose to the research nurse whether or not they had been given the garments. All questions relating to the acceptability and use of the garments were completed by either postal or online questionnaires, and telephone and e-mail contact with participants was made by staff from the Nottingham CTU whenever possible. If the research nurses became unblinded, this was recorded. Full details of blinding arrangements are summarised in *Table 3*.

FLG genotype analysis

If participants gave written informed consent to collect a saliva sample, these samples were collected using SalivaGene™ Collection Module II (Stratec Biomedical Systems, Birkenfeld, Germany), or SalivaGene™ Buccal Swab (Stratec Biomedical Systems, Birkenfeld, Germany) if children were unable to spit into the container. After collection, samples were packaged by research nurses and posted to the University of Dundee, UK, where deoxyribonucleic acid (DNA) extraction was performed.

Samples were tested for the six most prevalent *FLG* loss-of-function mutations in the white European population as previously reported: R501X, 2282del4, R2447X, S3247X, 3702delG and 3673delC.[41] Only participants of white European ethnicity were included in the *FLG* genotype subgroup analysis because *FLG* mutations are known to be ethnically specific. Individuals in whom the four most prevalent mutations (R501X, 2282del4, R2447X and S3247X) were successfully genotyped were categorised as *FLG* wild type (none of the prevalent mutations was identified; these individuals constituted the control cohort), *FLG* heterozygotes (carrying one *FLG* null mutation) or *FLG* homozygotes or compound heterozygotes (individuals carrying two *FLG* null mutations).

TABLE 3 Summary of blinding arrangements

Role in trial	Blinding status	Comments
Participants	Not blinded	Not possible to blind participants, efforts made to minimise expectation bias
Research nurses and principal investigators	Blinded	Participants were reminded in their clinic appointment letters not to wear the clothing when attending the clinic or to mention the clothing in any way when talking to the research nurses
Trial staff at the Nottingham CTU	Not blinded	Acted as the main point of contact for participants wishing to contact the research team, packaged and posted the clothing to the participants according to the randomisation schedule, and provided general advice
Statistician	Blinded	Statistician finalised the statistical analysis plan prior to revealing the treatment codes

Statistical methods

Analyses are detailed in the statistical analysis plan (see *Appendix 6*), which was finalised prior to database lock and release of treatment allocation codes for analysis. All analyses were carried out using Stata 13.1 (StataCorp LP, College Station, TX, USA). 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. Estimates of the intervention effect are presented with 95% confidence intervals (CIs) and *p*-values.

All outcomes collected at the 2-monthly clinic visits were summarised by time point and treatment group. All outcomes collected from the weekly questionnaires were summarised by week and treatment group. Correlation matrices between outcomes at the 2-monthly clinic visits are given in *Appendix 14* (see *Table 53*) and between POEM scores at 8, 16 and 24 weeks are given in *Appendix 15* (see *Table 55*). 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 for the intervention group compared with the standard care group are presented for continuous outcomes, and adjusted risk differences and relative risks for binary outcomes.

Preliminary analyses

Descriptive statistics of demographic and clinical measures were used to examine balance between the randomised arms at baseline.

Primary outcome

The primary analysis used a multilevel model with observations at 2, 4 and 6 months, nested within participants, and included participants in whom EASI was assessed at least once at follow-up. The model assumed that missing EASI scores were missing at random given the observed data. The model used a random intercept and slope at the participant level, with an unstructured covariance matrix for these random effects. Diagnostic plots to check the normality of the residuals from the fixed part of the model, homogeneity of the variance of the residuals and the normality of the random effects when the model was initially fitted indicated that the assumptions for the multilevel model were not met. The score was therefore log-transformed for analysis and the effect of the trial garments is presented as a ratio of geometric means.[42,43] This ratio was back-transformed to the original EASI scale to facilitate interpretation of findings.

The effect of trial garments on AE severity changing over the study period was explored by including an interaction term between group and time point in the model. There was no evidence of a differential effect over time, so a single treatment effect has been reported that averages the treatment effect over all time points.

Sensitivity analyses for the primary outcome were performed:

- To adjust for variables that had an observed imbalance between the groups at baseline.
- Using multiple imputation (by chained equations) for missing outcome data.
- To explore the impact of adherence in wearing the garments on the primary outcome by estimating the complier average causal effect (CACE) at 6 months using instrumental variable regression methods. This analysis aims to provide an unbiased estimate of the treatment effect among compliers, defined as participants who would comply with their allocation regardless of the treatment arm to which they were randomised. Estimates are presented for two measures of compliance:

  i. binary compliance, defined as participants who wore the trial garments for at least 50% of the days or 50% of the nights
  ii. continuous compliance, defined as each additional 10% of time that the garments were worn. This was calculated by summing the number of days and nights that the trial garments were reported to be worn, then dividing by the total number of days and nights in questionnaires completed about garment wear.

A planned subgroup analysis based on the presence or absence of loss-of-function mutations in *FLG* was conducted by adding an interaction term between allocated treatment and *FLG* genotype (none, one or two *FLG* null mutations) to the primary analysis model.

Secondary outcomes

The global assessment scores (IGA and PGA) were dichotomised into 'clear, almost clear or mild AE' versus 'moderate, severe or very severe AE', and analysed using generalised estimating equations to allow estimation of risk difference and risk ratio. The TIS score was analysed using the multilevel model framework as outlined above for the primary outcome (not transformed). For the global assessment scores and the TIS score, the effect of the trial garments changing over the study period (2-, 4- and 6-month visits) was explored by including an interaction term between group and time point in the models. There was no evidence of a differential effect over time for any outcomes, so a single treatment effect per outcome has been reported that averages the treatment effect over all time points.

For each participant from the weekly questionnaire data, the mean of their weekly POEM scores between week 1 and week 24 and the percentage of days that topical treatments were used were calculated. The participant mean POEM scores and percentage of days that topical steroids were used were analysed using a linear model weighted according to the number of weekly questionnaires completed.

Quality-of-life outcomes at 6 months were analysed using linear models. Changes to treatment regimen were based on whether or not a participant had reported any treatment escalation over the 6-month RCT period and analysed using a generalised linear model. Skin infections were analysed using negative binomial regression.

Adherence to wearing the trial garments was summarised using the percentage of days and nights that the study garments were worn. Participants were classified as adherent if they wore the trial garments for at least 50% of the days or 50% of the nights. This was done for participants who completed at least half (12/24) of the weekly questionnaires. Sensitivity analyses explored adherence for all participants by making different assumptions about garment wear during periods in which the questionnaire was not completed. Adherence to wearing the trial garments was explored descriptively according to age group and baseline eczema severity.

Serious adverse events, durability and acceptability of use of the garments and information from the follow-up questionnaire at 8 months were summarised descriptively.

Tertiary outcomes

The primary analysis assumed that the effect of the different brands of garments was similar, but the impact of garment brand on AE severity was explored in a tertiary analysis. AE severity according to brand was explored by adding a term for garment brand to the primary analysis model for the EASI described above. AE symptoms according to brand were explored by comparing POEM scores after 2 months of garment wear (baseline and 2 months for the intervention group and 6 and 8 months for the standard care group).

During the study there was a supply problem with one of the garment suppliers (DreamSkin), which meant that the randomised schedule was not followed during this time and participants received the alternative brand (DermaSilk). Any participants randomised to the intervention group during a time period that DreamSkin garments of the required size were out of stock were not included in the tertiary analysis by brand of garments. Similarly, any participants in the standard care group who completed their 6-month visit during a period when DreamSkin garments of the required size were out of stock were not included.

Adherence and acceptability of the garments at 6 and 8 months were summarised descriptively by allocated group and allocated garment brand.

Additional analyses

On completion of the pre-planned analyses, and 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. This was conducted by adding an interaction term between allocated group and baseline EASI score (log-transformed and continuous) to the primary analysis model.

Summary of changes to the protocol

The full protocol and statistical analysis plan are available on the CLOTHES website (www.nottingham.ac.uk/CLOTHES). Changes to the protocol initiated after the start of recruitment included an increase in the number of *FLG* genotype mutations to be included in the genetic analysis (two additional mutations were added: 3702delG and 3673delC) and addition of details of the nested qualitative evaluation.

Chapter 3 Results: clinical findings

Recruitment and follow-up

Recruitment to the study took place between 26 November 2013 and 5 May 2015 (*Figure 3*). During this time, 922 children were assessed for eligibility and 300 were subsequently randomised (*Figure 4*). Eighty-nine children were randomised within the first 6 months of recruitment, meeting the target of 75 participants as specified for the internal pilot phase.

Attendance at follow-up visits was ≥ 90% for all clinic visits. In both groups, 129 (85%) attended all three follow-up visits. The same nurse performed the outcome assessments for all study visits for all but four participants.

The primary analysis included 141 participants in each group (participants were included if the primary outcome was assessed at least once after baseline) (see *Figure 4*).

In the case of the weekly online questionnaires (24 questionnaires over 6 months), 127 out of 151 (84%) participants in the standard care group and 126 out of 149 (85%) participants in the intervention group completed 12 or more. The median number completed was 22 (25th to 75th centile, 17 to 24) in both groups. The number of participants completing the questionnaire each week was very similar in the standard care and intervention groups (*Figure 5*).

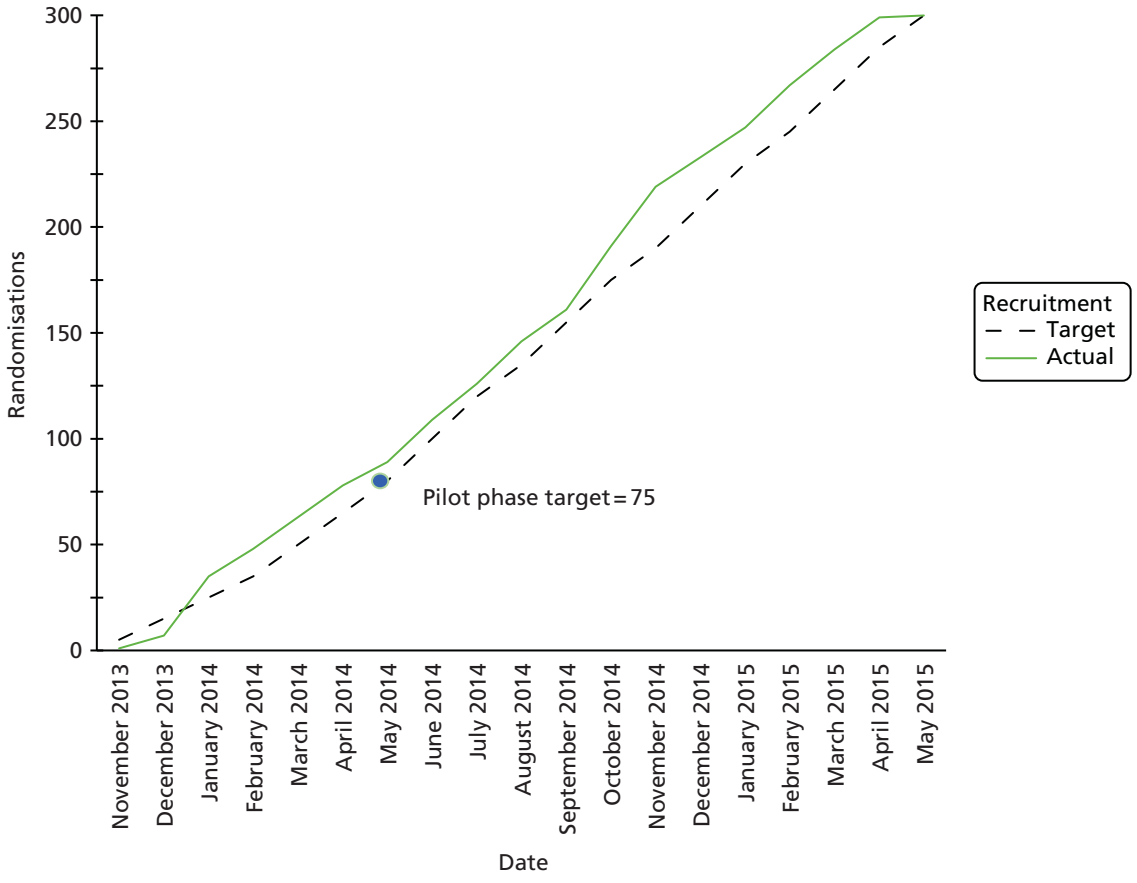

FIGURE 3 Cumulative recruitment.

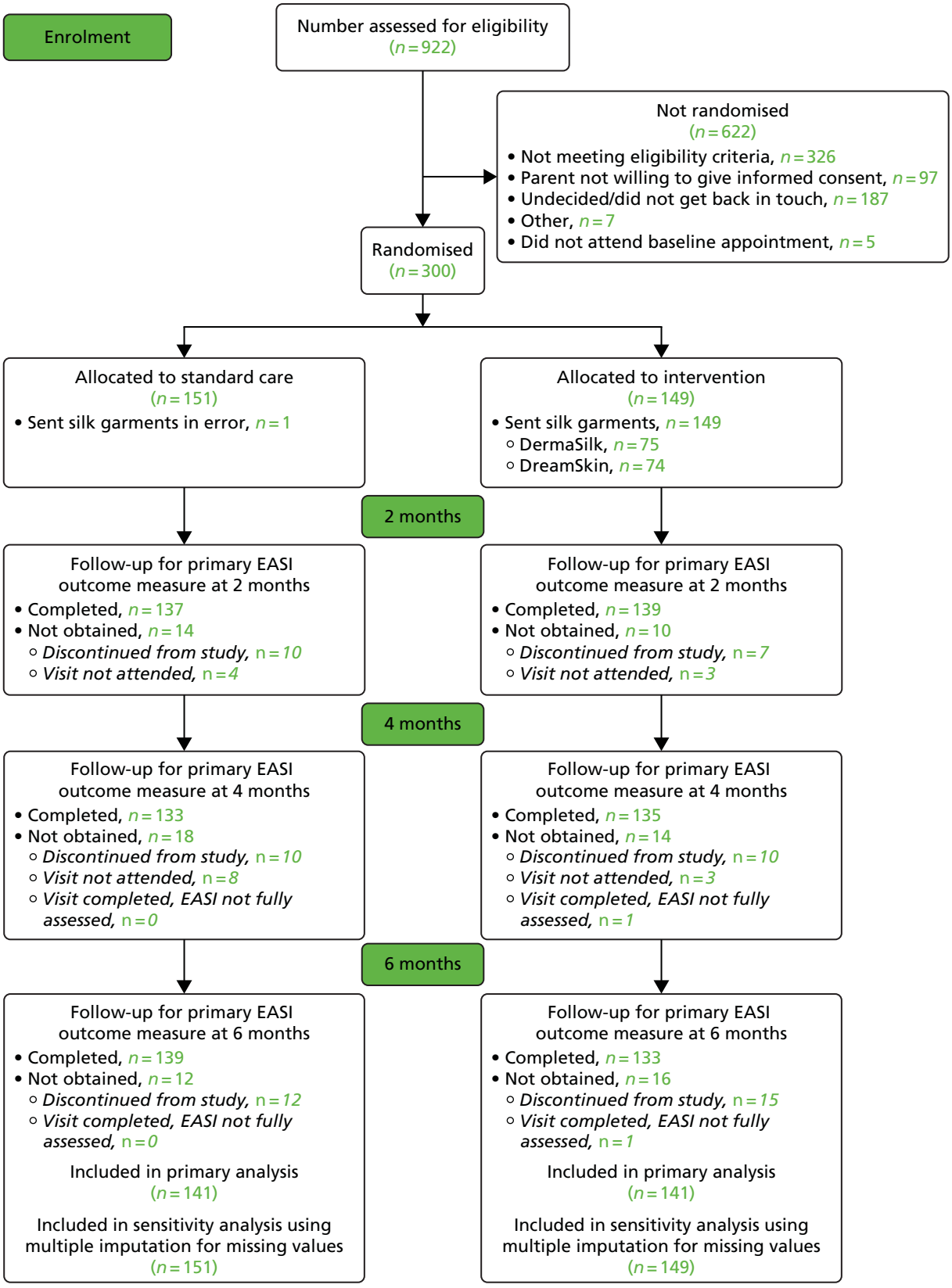

FIGURE 4 Participant flow through the study.

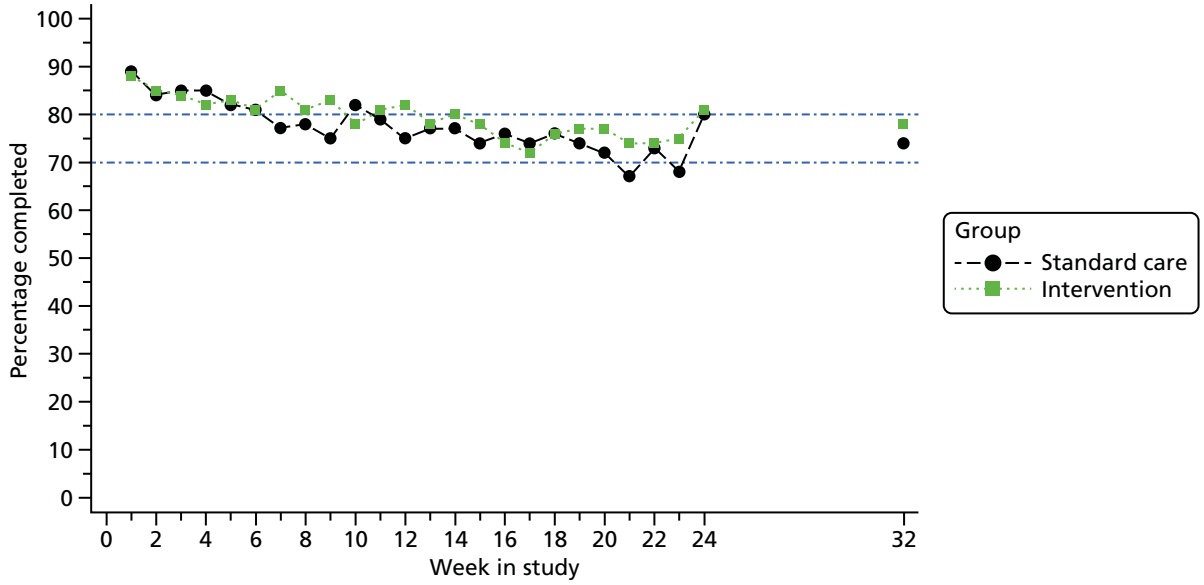

FIGURE 5 Percentage questionnaire completion by week and group.

Baseline data

Participants

The mean age of participants was 5 years (SD 3.6); 58% were male and 79% were of white ethnicity (*Table 4*). The majority (72%) had previously been treated in secondary care for their AE, 72% had moderate or severe AE (based on IGA scores at baseline) (*Table 5*) and 37% were reported to use a potent or very potent steroid as their main steroid (*Table 6*).

The demographic and AE characteristics were well balanced at baseline, although there were slightly more boys in the intervention group than in the standard care group, and parent-reported history of asthma and food allergy was higher in the standard care group than in the intervention group (see *Table 4*). The mean EASI score was slightly higher in the intervention group than in the standard care group, as more children had a baseline EASI score of > 30 (intervention, 14 participants; standard care, 4 participants; *Figure 6*); however, the median and interquartile ranges were similar between the groups (see *Table 5*). Other AE severity measures were similar between the two groups apart from the PGA scores [a greater proportion of participants in the standard care group rated their AE as moderate, severe or very severe than the intervention group (75% vs. 66%) (see *Table 5*)]. Health-related quality of life in the two groups was similar at baseline (*Table 7*).

FLG genotype

Table 8 shows the *FLG* genotyping results for participants of white ethnicity. Samples from 219 participants were tested for the six most prevalent *FLG* loss-of-function mutations in the white European population: R501X, 2282del4, R2447X, S3247X, 3702delG and 3673delC. Genotyping methods for the four most prevalent genotypes (R501X, 2282del4, R2447X and S3247X) were largely successful ($n = 217$ were included in the analysis), but the genotyping methods used for 3703delG and 3673delC were unsuccessful for 24 participants (11% of samples tested) owing to the suboptimal quality and quantity of DNA obtained from paediatric saliva samples.

In total, 217 participants of white European ethnicity were categorised as *FLG* wild type (individuals in whom none of the prevalent mutations was identified), *FLG* heterozygotes (carrying one *FLG* null mutation) and *FLG* homozygotes or compound heterozygotes (individuals carrying two *FLG* null mutations) for the four most prevalent mutations (R501X, 2282del4, R2447X and S3247X). Of these, 74 participants had at least one mutation.

TABLE 4 Baseline characteristics

Characteristic	Standard care (*N* = 151)	Intervention (*N* = 149)	Total (*N* = 300)
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)
Minimum, maximum	1, 14	1, 15	1, 15
1–4, *n* (%)	86 (57)	77 (52)	163 (54)
5–11, *n* (%)	57 (38)	62 (42)	119 (40)
12–15, *n* (%)	8 (5)	10 (7)	18 (6)
Sex, *n* (%)			
Male	82 (54)	92 (62)	174 (58)
Female	69 (46)	57 (38)	126 (42)
Ethnicity, *n* (%)			
White	123 (81)	114 (77)	237 (79)
Indian	5 (3)	2 (1)	7 (2)
Pakistani	3 (2)	3 (2)	6 (2)
Bangladeshi	0	2 (1)	2 (1)
Black Caribbean	1 (1)	2 (1)	3 (1)
Black African	3 (2)	4 (3)	7 (2)
Black (other)	2 (1)	0	2 (1)
Chinese	1 (1)	3 (2)	4 (1)
Other Asian (non-Chinese)	0	4 (3)	4 (1)
Mixed race	12 (8)	13 (9)	25 (8)
Other	1 (1)	2 (1)	3 (1)
History of atopy, *n* (%)			
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 AE, *n* (%)			
Discoid	19 (13)	17 (11)	36 (12)
Flexural	144 (95)	147 (99)	291 (97)
Location of AE, *n* (%)			
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, *n* (%)			
No previous treatment	–	–	–
GP only	41 (27)	40 (27)	81 (27)
GP and in secondary care	110 (73)	109 (73)	219 (73)

GP, general practitioner.
Categories for history of AE, type of AE and location of AE are not mutually exclusive.

TABLE 5 Atopic eczema severity assessments at baseline

Severity assessment	Standard care (*N* = 151)	Intervention (*N* = 149)	Total (*N* = 300)
EASI[a]			
Mean (SD)	9.6 (7.8)	11.4 (10.6)	10.5 (9.3)
Median (25th, 75th centile)	7.3 (4.2, 12)	7 (4.1, 15.4)	7.2 (4.1, 13.7)
Min., max.	1.1, 41.1	1, 47	1, 47
TIS[b]			
Mean (SD)	4.9 (1.8)	4.9 (1.8)	4.9 (1.8)
Median (25th, 75th centile)	5 (4, 6)	5 (3, 6)	5 (4, 6)
Min., max.	1, 9	1, 9	1, 9
Nottingham Eczema Severity Score[c]			
Mean (SD)	13.1 (1.6)	13.2 (1.7)	13.1 (1.6)
Median (25th, 75th centile)	13 (12, 14)	13 (12, 15)	13 (12, 14)
Min., max.	9, 15	9, 15	9, 15
Moderate AE (9–11), *n* (%)	28 (19)	30 (20)	58 (19)
Severe AE (12–15), *n* (%)	123 (81)	119 (80)	242 (81)
IGA, *n* (%)			
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)
PGA, *n* (%)			
Almost clear	5 (3)	6 (4)	11 (4)
Mild	33 (22)	45 (30)	78 (26)
Moderate	83 (55)	67 (45)	150 (50)
Severe	27 (18)	25 (17)	52 (17)
Very severe	3 (2)	6 (4)	9 (3)
PGA completed by, *n* (%)			
Parent/guardian	129 (85)	125 (84)	254 (85)
Child	22 (15)	24 (16)	46 (15)
POEM[d]			
Mean (SD)	16.6 (4.8)	17.3 (5.8)	17 (5.4)
Median (25th, 75th centile)	16 (13, 20)	17 (13, 21)	17 (13, 20)
Min., max.	4, 28	4, 28	4, 28
POEM completed by, *n* (%)			
Parent/guardian	128 (85)	122 (82)	250 (83)
Child	23 (15)	27 (18)	50 (17)

Max., maximum; min., minimum.
a Scores range between 0 and 72, with higher scores indicating more severe AE (assesses AE on the day).
b Scores range between 0 and 9, with higher scores indicating more severe AE (assesses AE on the day).
c Scores range between 0 and 15, with higher scores indicating more severe AE (assesses AE over the previous 12 months).
d Scores range between 0 and 28, with higher scores indicating more severe AE (assesses AE in the last week).

TABLE 6 Medication used for AE in the month prior to randomisation

Medication usage	Standard care (*N* = 151), *n* (%)	Intervention (*N* = 149), *n* (%)	Total (*N* = 300), *n* (%)
Used emollient within the last month	150 (99)	146 (98)	296 (99)
Consistency of main emollient			
Light	13 (9)	6 (4)	19 (6)
Creamy	53 (35)	57 (38)	110 (37)
Greasy	20 (13)	21 (14)	41 (14)
Very greasy	64 (42)	62 (42)	126 (42)
Topical steroid used within the last month	136 (90)	130 (87)	266 (89)
Potency of main steroid			
Mild	40 (26)	34 (23)	74 (25)
Moderate	43 (28)	40 (27)	83 (28)
Potent	51 (34)	53 (36)	104 (35)
Very potent	2 (1)	3 (2)	5 (2)
Calcineurin inhibitors used within the last month	14 (9)	15 (10)	29 (10)
Strength of main calcineurin inhibitor			
Mild	9 (6)	8 (5)	17 (6)
Moderate	4 (3)	4 (3)	8 (3)
Strong	1 (1)	3 (2)	4 (1)
Use of wet/dry wraps in the past month			
No	138 (91)	135 (91)	273 (91)
Yes	13 (9)	14 (9)	27 (9)

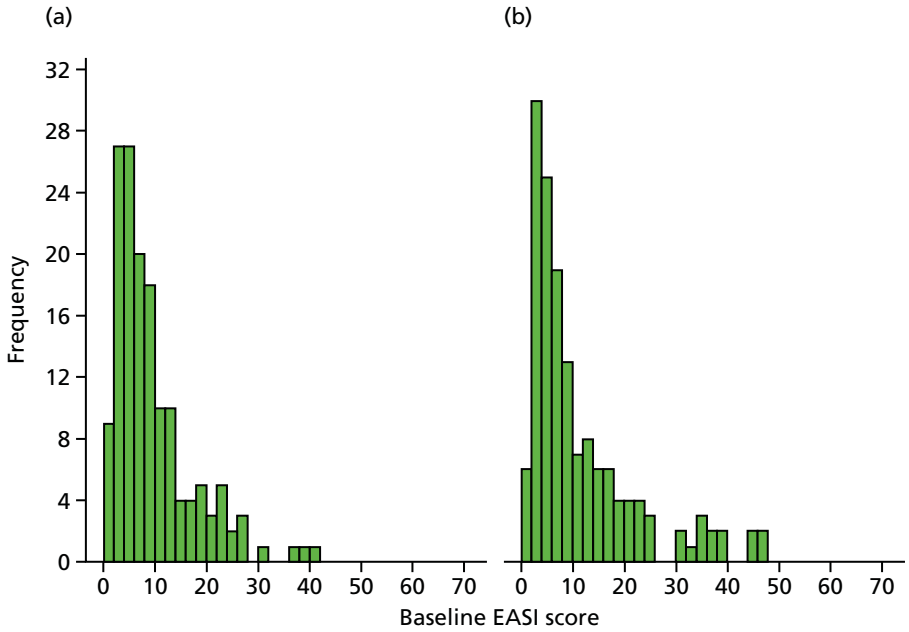

FIGURE 6 Histogram of baseline EASI scores by group. (a) Standard care; and (b) intervention group.

TABLE 7 Quality-of-life measures at baseline

Quality-of-life measure	Standard care (*N* = 151)	Intervention (*N* = 149)	Total (*N* = 300)
DFI[a]			
Mean (SD)	12.0 (6.3)	12.4 (6.6)	12.2 (6.4)
Median (25th, 75th centile)	11 (7, 15)	12 (7, 16)	11 (7, 16)
Min., max.	0, 29	0, 30	0, 30
Health state from EQ-5D-3L for parent[b,c]			
Mean (SD)	79.5 (17.5)	77.3 (18.2)	78.4 (17.9)
Median (25th, 75th centile)	80 (72, 90)	80 (70, 90)	80 (70, 90)
Min., max.	8, 100	8, 100	8, 100
Utility from EQ-5D-3L for parent[b,d]			
Mean (SD)	0.8983 (0.1612)	0.9018 (0.1710)	0.9 (0.1658)
Median (25th, 75th centile)	1 (0.812, 1)	1 (0.812, 1)	1 (0.812, 1)
Min., max.	–0.016, 1	0.101, 1	–0.016, 1
n	151	147	298
CHU-9D[b,e]			
Mean (SD)	0.8292 (0.1263)	0.8386 (0.1115)	0.8341 (0.1184)
Median (25th, 75th centile)	0.849 (0.7853, 0.9058)	0.8561 (0.7524, 0.92)	0.8503 (0.7637, 0.9189)
Min., max.	0.4661, 1	0.5584, 1	0.4661, 1
n	64	70	134
Completed by (*n*)			
Parent/guardian	17	23	40
Child	47	47	94
ADQoL[f]			
Mean (SD)	0.6952 (0.13)	0.6883 (0.1409)	0.6918 (0.1354)
Median (25th, 75th centile)	0.744 (0.648, 0.768)	0.744 (0.634, 0.768)	0.744 (0.648, 0.768)
Min., max.	0.356, 0.841	0.356, 0.841	0.356, 0.841
n	151	149	300
Completed by [*n* (%)]			
Parent/guardian	104 (69)	102 (68)	206 (69)
Child	47 (31)	47 (32)	94 (31)

Max., maximum; min., minimum.

a Assesses the impact of the child's skin condition on family life over the previous week and ranges between 0 and 30, with higher scores indicating greater impact of the child's skin condition on family life.

b Questions are asked about feelings/abilities on the day of the baseline clinic visit.

c Score ranges between 0 and 100, with higher scores indicating better health on the day.

d Score ranges between –0.56 and 1, with higher scores indicating better quality of life.

e Only completed for children aged ≥ 5 years (65 children in standard care and 72 in the intervention group were aged ≥ 5 years at baseline). Utility scores range between 0.32 and 1, with higher scores indicating better quality of life.

f Scores range between 0.36 and 0.84, with higher scores indicating better health states.

TABLE 8 Genetic study participation for participants of white ethnicity

Genotype status	Standard care (*N* = 123), *n* (%)	Intervention (*N* = 114), *n* (%)	Total (*N* = 237), *n* (%)
Informed consent provided for genetic study			
No	6 (5)	5 (4)	11 (5)
Yes	117 (95)	109 (96)	226 (95)
If yes, saliva sample collected			
No[a]	1 (1)	5 (4)	6 (3)
Yes	116 (94)	104 (91)	220 (93)
Result obtainable on *FLG* mutation from sample[b]			
No	1 (1)	1 (1)	2 (1)
Yes	115 (93)	102 (89)	217 (92)
Sample not received by Dundee	0 (0)	1 (1)	1 (0.4)
Result not obtainable for each mutation tested			
R501X	0	0	0
2282del4	1	0	1
R2447X	1	1	2
S3247X	1	0	1
3702delG	9	15	24
3673delC	9	15	24
FLG genotype (using mutations R501X, 2282del4, R2447X and S3247X)			
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)

a Reasons saliva sample not collected despite informed consent having been given: child too distressed, child declined, parents changed their minds, participant did not attend any follow-up visits, and consent withdrawn from RCT for two participants.
b Based on the mutations R501X, 2282del4, R2447X and S3247X. The rare mutations 3702delG and 3673delC were not used for the purposes of the subgroup analysis.

Adherence to intervention

All participants in the intervention group were sent the silk garments, on average, 1 day after randomisation. One participant allocated to the standard care group was sent the silk garments in error, but was included in the analysis according to randomised allocation (see *Figure 4*).

Adherence in wearing the garments was high: 102 out of 124 (82%) participants wore the clothes for ≥ 50% of the time (see *Table 9*). The garments were worn more often at night than during the day (median 81% of nights and 34% days) (*Table 9* and *Figure 7*). The mean number of times that the garments were worn remained fairly constant throughout the study period (see *Figure 7*). Adherence to wearing the garments was not associated with age or eczema severity at baseline (correlation coefficients 0.003 to 0.20; *Table 10*). Sensitivity analyses for adherence according to questionnaire completion are shown in *Table 9*.

Contamination

Only six participants in the standard care group reported wearing silk clothing during the 6-month study period.

TABLE 9 Adherence with trial garments in the intervention group[a]

Adherence	Main analysis (participants with ≥ 12 questionnaires completed) (*N* = 124)	Sensitivity analysis 1[b,c] (*N* = 149)	Sensitivity analysis 2[b,d] (*N* = 149)
Proportion of nights that garments were worn for at least some of the night, median (25th, 75th centile)	80.7 (56.8, 95.9)	74.4 (52.1, 94.8)	61.5 (32.9, 87)
Percentage of days that clothing was worn for at least some of the day, median (25th, 75th centile)	34.1 (9.8, 75.9)	28.6 (3.7, 74.3)	19.3 (2.5, 63.4)
Adherence to wearing trial garments, *n* (%)			
Adherent[e]	**102 (82)**	**117 (79)**	**87 (58)**
Worn for at least 50% of days and 50% of nights	50 (40)	54 (36)	45 (30)
Worn for at least 50% of days only	–	1 (1)	–
Worn for at least 50% of nights only	52 (42)	62 (42)	42 (28)
Not adherent (wore clothing for < 50% of the time)	**22 (18)**	**32 (21)**	**62 (42)**

a Adherence to wearing trial garments summarised from week 2 onwards.
b Both sensitivity analyses include all participants in the interventon group regardless of the number of questionnaires completed and assumes that participants never wore the garments if they did not complete any questionnaires about how often they wore the garments (five participants).
c Sensitivity analysis 1: assuming garments worn for the same proportion of time when the questionnaire was not completed as when the questionnaires were returned.
d Sensitivity analysis 2: assuming garments not worn when the questionnaire was not completed.
e Participants were defined as adherent with trial garments if they were worn for at least 50% of the days or at least 50% of the nights.

Notes
Bold signifies the total numbers for adherent and non-adherent rows (with further breakdown of adherence).
Note that two participants completed 12 or more questionnaires, but completed information about the clothing wear on fewer than 12 questionnaires.

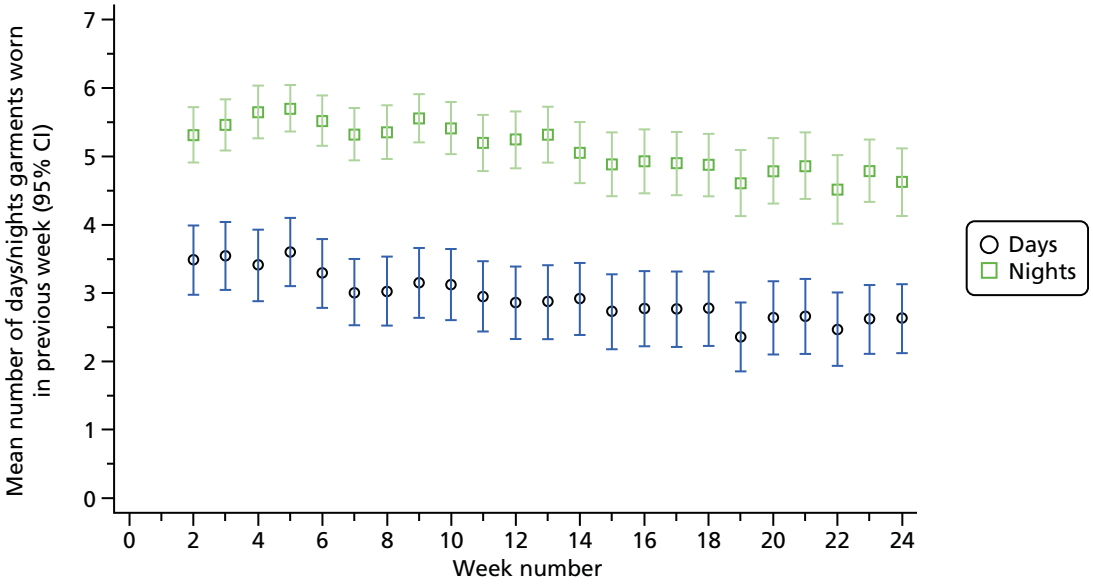

FIGURE 7 Mean number of days/nights trial garments worn each week.

TABLE 10 Spearman correlation coefficients between percentage of days/nights that clothing worn with age and baseline eczema severity

Variable	Percentage of days that clothing was worn for at least some of the day ($n = 124$)	Percentage of nights that clothing was worn for at least some of the night ($n = 124$)
Age	0.003	0.20
Baseline EASI score	–0.03	0.03
Baseline POEM score	0.08	0.13

Spearman correlation coefficients range between –1 (perfect negative correlation) and 1 (perfect postive correlation). Correlation coefficient of 0 indicates no correlation.

Durability of the garments

Information about the number of garments and replacement garments sent out by the co-ordinating centre during the trial is presented in *Chapter 4*. This section presents information reported by parents on the 6-month questionnaire about the condition of the trial garments. Just over half of parents reported that at least one garment (top or leggings) could no longer be worn (*Table 11*). Children aged 4 years or under were more likely than older children to require replacement garments, as they outgrew the garments over the 6-month study period. Just over one-third of responders at 6 months reported that garments could no longer be worn as they had worn out or torn.

Acceptability of use of silk clothing

At 6 months, 85 out of 121 (70%) participants reported being satisfied or very satisfied with the garments (95% CI 61% to 78%) and 89 out of 121 (74%) participants were either happy or very happy to wear the garments (95% CI 64% to 81%).

Blinding

Blinding appeared to be successful. Research nurses remained blinded to treatment allocation for 289 out of 300 (96%) participants. Unblinding occurred for three participants in the standard care group and eight participants in the intervention group. This unblinding was first reported at 2 months for one participant in the standard care group and seven participants in the intervention group and at the 4-month visit for all other participants.

Unblinding mainly occurred as a result of the child or parents saying that they had or had not received the garments. Unblinding occurred for two participants because they wore the garments to the assessment visit.

TABLE 11 Parent-reported condition of trial garments at 6 months

Condition of garments at 6 months	Age (years)			
	1–4 ($N = 63$)	5–11 ($N = 51$)	12–15 ($N = 7$)	Intervention ($N = 121$)
At least one garment no longer able to be worn at 6 months, *n*/*N* (%)	41/61 (67)	18/46 (39)	1/5 (20)	60/112 (54)
Reasons that garments can no longer be worn, *n*				
Too small	22	6	0	28
Worn out/torn	26	14	1	41
Lost	3	2	0	5
Other	6	2	0	8

Primary outcome: Eczema Area and Severity Index

Primary analysis

Mean AE severity based on EASI scores improved in both groups during the 6-month follow-up period; however, there was no clinically important difference between the groups in the nurse-assessed EASI scores (*Table 12* and *Figure 8*). Averaged over the 2-, 4- and 6-month follow-up visits, the ratio of geometric mean EASI scores was 0.95 (95% CI 0.85 to 1.07; $p = 0.43$). This CI is equivalent to a difference of approximately 1.5-point improvement to 0.5 points worse for the intervention group, compared with the standard care group in the original EASI scale units.

TABLE 12 Primary outcome: EASI scores

Allocated group	Baseline	2 months	4 months	6 months	Adjusted ratio of geometric means (95% CI); *p*-value
Standard care					
n	151	137	133	139	
Median	7.3	5.3	4.3	4.2	
25th, 75th centile	4.2, 12	2.5, 10.5	2.1, 10	2, 9.2	
Geometric mean	8.4	6.6	6.0	5.4	
Intervention					
n	149	139	135	133	0.95 (0.85 to 1.07); 0.43[a]
Median	7	4.9	4.1	4	
25th, 75th centile	4.1, 15.4	2.2, 9.9	2.2, 9.4	1.9, 7.9	
Geometric mean	9.2	6.4	5.8	5.4	

a This CI is approximately equivalent to a difference of –1.5 to 0.5 in the original EASI scale units.
EASI score was log-transformed and analysed using a multilevel model adjusting for baseline EASI score and the stratification variables age and site as covariates. A total of 282 participants were included in the analysis model ($n = 141$ each group).
EASI scores range between 0 and 72, with higher scores indicating more severe AE.

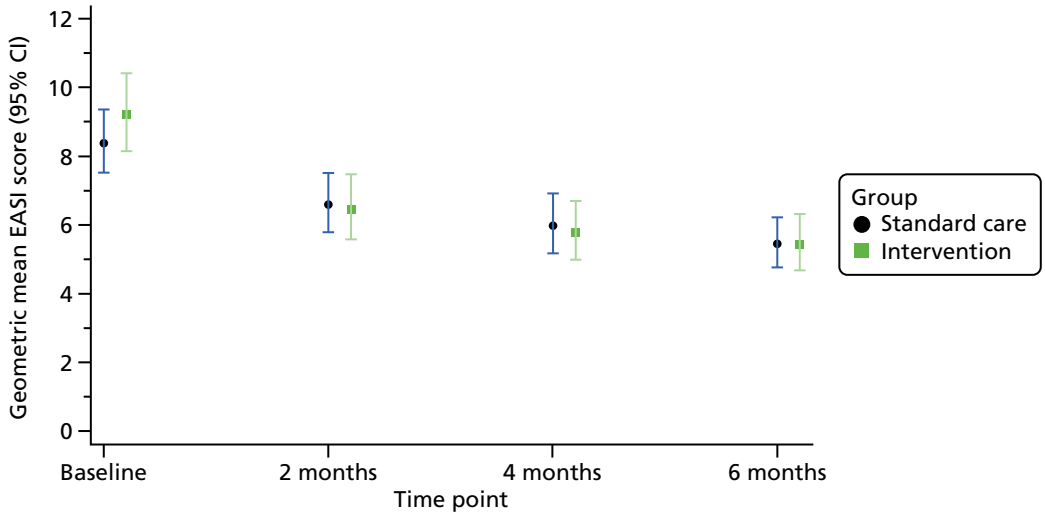

FIGURE 8 Primary outcome: geometric mean EASI scores with 95% CIs.

Arithmetic means of the EASI scores and log-transformed EASI scores for each group and time point are given in *Appendix 14* (see *Table 52*).

Sensitivity analyses for the primary outcome

Sex, history of food allergy and history of asthma were added as covariates into the analysis model because of baseline imbalance. This estimate of the ratio of the geometric mean was the same as for the primary analysis (0.95, 95% CI 0.85 to 1.07).

Multiple imputation of missing EASI data, assuming that scores were missing at random, gave a very similar result to the primary analysis (*Table 13*). When it was assumed that missing scores were systematically worse in the standard care group, the 95% CI for the geometric mean was equivalent to scores of 2 points lower to 0.1 points higher for the intervention group than for the standard care group.

Further exploratory analysis of the EASI scores for areas covered by the garments (body and limbs) and areas uncovered by the garments (head and neck) can be found in *Appendix 16*.

Causal effect of adherence with wearing trial garments on primary outcome

The CACE was estimated using the EASI scores at 6 months for participants who completed 12 or more questionnaires (standard care, $n = 127$; intervention, $n = 124$). *Table 14* presents the CACE estimate based on a binary definition of adherence of wearing the trial garments for at least 50% of the days or 50% of the nights and the CACE estimate for each additional 10% of the time the garments were worn. The intention-to-treat estimate for participants included in the CACE analysis is also presented using the EASI scores at 6 months for comparison (analysis according to randomised group).

The intention-to-treat and CACE estimate based on wearing the garments for at least 50% of the days or 50% of the nights are similar (see *Table 14*) as a result of 82% of intervention participants satisfying this definition (see *Table 9*). The ratio of geometric means for all comparisons is greater than 1, favouring the standard care group. The CACE estimate for each additional 10% of time that garments were worn suggests that eczema severity (EASI scores) did not improve with greater amounts of garment wear. A further summary table using all data at 6 months is shown in *Appendix 17*.

TABLE 13 Sensitivity analysis for the primary outcome using multiple imputation for missing data

Sensitivity assumptions	Adjusted ratio of geometric means (95% CI)
Assuming that missing EASI scores are MAR	0.93 (0.83 to 1.05)
Assuming missing EASI scores are missing not at random	
Favouring intervention group	
Assuming that missing EASI scores are 3 points higher (worse) than under MAR in the standard care group and assuming MAR in intervention group	0.89 (0.80 to 1.01)
Favouring standard care group	
Assuming that missing EASI scores are 3 points higher than under MAR in the intervention group and assuming MAR in standard care group	0.97 (0.86 to 1.09)

MAR, missing at random.
Multiple imputation using chained equations. The imptuation model included age, site, sex, POEM scores at the clinic visits, whether or not there had been a treatment escalation during the study and mean POEM score from the weekly questionnaires (as well as number of questionnaires included). A total of 20 data sets were imputed and estimates from the multilevel model of the log-transformed EASI score adjusting for baseline EASI score and the stratification variables age and site as covariates were combined using Rubin's rules. A total of 300 participants were included.

TABLE 14 Causal effect of adherence in wearing trial garments on eczema severity (EASI)

Estimate	*n*	Adjusted ratio of geometric means (95% CI)
ITT at 6 months[a]	243	1.026 (0.87 to 1.21)
CACE: binary – garments worn for at least 50% of days or 50% of the nights[b]	243	1.031 (0.85 to 1.25)
CACE: each additional 10% of time garments worn[b,c]	243	1.004 (0.977 to 1.032)

ITT, intention to treat.
a Analysed using linear regression with log-transformed EASI score at 6 months as the outcome variable, and adjusted for randomisation stratification variables and baseline EASI score.
b Analysed using instrumental variable regression.
c Percentage of time worn calculated as (total number of days and nights clothing worn × 100)/(total number of questionnaires completed × 14).
Analysis includes participants with EASI assessed at 6-month follow-up and completing 12 or more questionnaires.

Subgroup analysis for primary outcome according to FLG status

Eczema Area and Severity Index scores according to group and *FLG* status (none, one or two *FLG* null mutations) for participants of white ethnicity are shown in *Table 15* and *Figure 9*. Participants with *FLG* gene mutations were no more likely to benefit from the silk clothing than participants without a mutation (*p*-value for interaction effect 0.47).

Post hoc subgroup analysis for primary outcome according to baseline eczema severity

Eczema Area and Severity Index scores according to group and baseline eczema severity (almost clear or mild EASI scores and moderate or severe EASI scores)[44] are shown in *Table 16*. There was no evidence that the clothing was more or less effective depending on the severity of eczema at baseline.

TABLE 15 Subgroup analysis for primary EASI outcome of eczema severity according to *FLG* genotype (none, one or two *FLG* null mutations) for participants of white European ethnicity

Subgroup and allocated group	Baseline	2 months	4 months	6 months	Adjusted subgroup-specific ratio of geometric means (95% CI)[a]	Adjusted interaction effect[b] (95% CI)[a]
FLG *wild type: no mutations (+/+)*						
Standard care						
n	72	67	65	69		
Median (25th, 75th centile)	6.2 (3.9, 10.7)	4.5 (2.4, 9.0)	3.2 (2.1, 9.9)	3.3 (1.8, 6.8)		
Geometric mean	7.7	6.1	5.5	4.8		
Intervention						
n	71	67	67	67		
Median (25th, 75th centile)	5.4 (3.3, 13.8)	4.3 (2.1, 10.3)	3.8 (2.2, 8.4)	4.0 (2.3, 9.9)		
Geometric mean	8.1	6.4	5.7	6.1		
Analysis					1.04 (0.89 to 1.21)	

continued

TABLE 15 Subgroup analysis for primary EASI outcome of eczema severity according to *FLG* genotype (none, one or two *FLG* null mutations) for participants of white European ethnicity (*continued*)

Subgroup and allocated group	Baseline	2 months	4 months	6 months	Adjusted subgroup-specific ratio of geometric means (95% CI)[a]	Adjusted interaction effect[b] (95% CI)[a]
One* FLG *null mutation (+/–)						
Standard care						
n	31	28	27	29		
Median (25th, 75th centile)	8.0 (3.8, 12.0)	5.3 (2.9, 11.4)	4.6 (2.7, 8.6)	4.4 (1.6, 10.7)		
Geometric mean	8.5	7.1	6.5	5.4		
Intervention						
n	20	19	19	19		
Median (25th, 75th centile)	8.7 (5.0, 15.7)	6.1 (3.0, 8.4)	4.4 (2.2, 9.5)	4.0 (1.9, 8.0)		
Geometric mean	10.1	6.9	5.5	5.2		
Analysis					0.87 (0.67 to 1.14)	0.84 (0.61 to 1.15)
Two* FLG *null mutations (–/–)						
Standard care						
n	12	11	12	12		
Median (25th, 75th centile)	17.9 (7.7, 23.4)	10.7 (3.8, 23.6)	10.8 (3.6, 16.1)	9.9 (4.1, 14.3)		
Geometric mean	13.7	10.3	9.3	9.9		
Intervention						
n	11	11	9	9		
Median (25th, 75th centile)	12.4 (8.6, 16.6)	6.6 (5.4, 16.8)	9.3 (5.3, 23.4)	7.4 (2.6, 16.5)		
Geometric mean	13.0	8.9	10.2	7.8		
Analysis					0.89 (0.60 to 1.30)	0.85 (0.56 to 1.29)

a Ratio of geometric means and the interaction effect adjusted for baseline EASI score and the stratification variables age and site as covariates.

b Ratio of geometric means for intervention vs. standard care in individuals with one of two *FLG* null mutations compared with ratio of geometric means for intervention vs. standard care for *FLG* wild-type genotype. A total of 209 participants were included in the analysis model (110 participants in standard care and 99 participants in the intervention); *p*-value for interaction effect = 0.47.

We also compared the *FLG* wildtype genotype with the combined group having one or two *FLG* null mutations in a further exploratory analysis: the interaction effect for any mutation compared with no mutation was 0.85 (95% CI 0.65 to 1.11; $p = 0.24$).

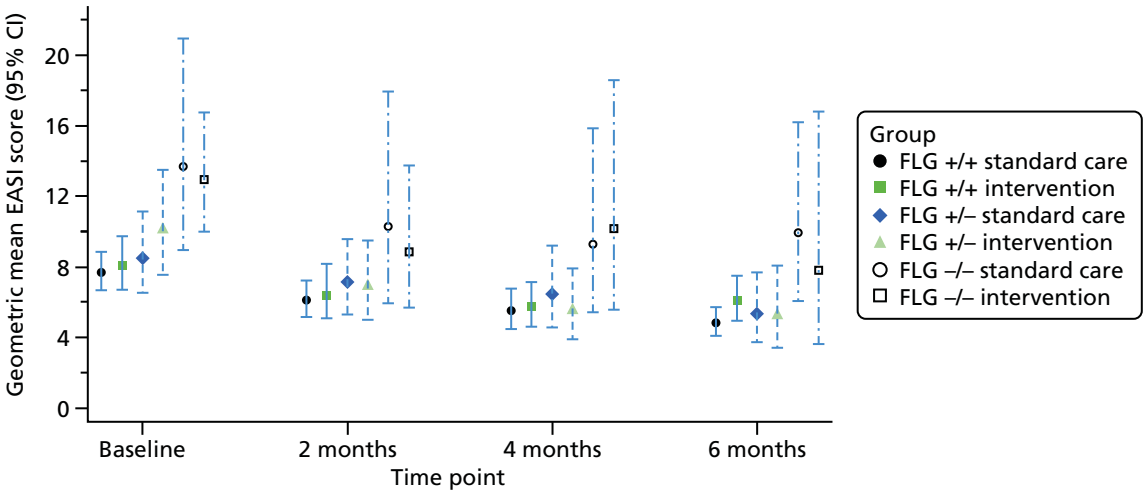

FIGURE 9 Geometric mean EASI scores by group and *FLG* status. *FLG* +/+ denotes no mutations; *FLG* +/– denotes one *FLG* null mutation; and *FLG* –/– denotes two *FLG* null mutations.

TABLE 16 Subgroup analysis for primary EASI outcome of eczema severity scores according to EASI eczema severity at baseline

Subgroup and allocated group	Baseline	2 months	4 months	6 months	Adjusted subgroup-specific ratio of geometric means (95% CI)
Almost clear/mild baseline EASI scores (1 to 7)					
Standard care					
n	73	66	65	68	
Median (25th, 75th centile)	4 (2.6, 5.5)	2.9 (1.8, 4.8)	2.7 (1.5, 4)	2.3 (1.4, 4.3)	
Geometric mean	4.8	4.2	3.7	3.5	
Intervention					
n	75	72	72	70	0.95 (0.81 to 1.12)
Median (25th, 75th centile)	4.1 (2.8, 5.5)	2.8 (1.6, 4.3)	2.7 (1.6, 4.3)	2.5 (1.2, 4.2)	
Geometric mean	4.9	3.8	3.7	3.7	
Moderate/severe baseline EASI scores (7.1–50)					
Standard care					
n	78	71	68	71	
Median (25th, 75th centile)	12 (8.8, 18.8)	9.2 (5.2, 15.8)	9.4 (4.7, 16.4)	7.7 (4.1, 12.3)	
Geometric mean	14.2	10.0	9.5	8.2	
Intervention					
n	74	67	63	63	0.95 (0.81 to 1.12)
Median (25th, 75th centile)	15.4 (10, 23.1)	9.6 (5.6, 19.6)	8 (4, 17.3)	6.9 (3.9, 13.8)	
Geometric mean	17.3	11.3	9.5	8.3	

Note
Ratio of geometric means and the interaction effect adjusted for baseline EASI score and the stratification variables age and site as covariates.
A total of 282 participants were included in the analysis model ($n = 141$ each group).
Coefficient from multilevel model from interaction term between baseline EASI (log-transformed and continuous) and treatment group: 0.0827 (95% CI –0.0801 to 0.2454); back-transformed 1.086 (95% CI 0.923 to 1.278; $p = 0.32$).

Secondary outcomes

Global assessment of atopic eczema

The proportion of participants with a nurse-assessed IGA of AE of moderate severity or worse decreased in both groups during the follow-up period, but there was no difference between the two groups: relative risk 0.98 (95% CI 0.82 to 1.12; $p = 0.63$; *Table 17*).

In contrast, for the participant-rated IGA, fewer participants rated their AE as moderately severe or worse in the intervention group than standard care: relative risk 0.83 (95% CI 0.70 to 0.98; $p = 0.03$; see *Table 17*).

Self-reported atopic eczema symptoms using the Patient Oriented Eczema Measure

Mean weekly POEM scores by group are shown in *Figure 10*. The mean of the participants' mean weekly POEM scores over the 6-month study was 2.8 points lower in the intervention group than in the standard care group (95% CI –3.9 to –1.8; $p < 0.001$; *Table 18*). There was a more obvious separation of the groups in the first 3 months of the trial than in the final 3 months.

Three-Item Severity scale

The mean TIS scores improved in both groups during the follow-up period. No between-group differences were observed: difference in means 0.09 (95% CI –0.22 to 0.40; $p = 0.57$; *Table 19*).

Use of atopic eczema treatments

The percentage of days during the study that emollients, topical corticosteroids, calcineurin inhibitors and wet/dry wraps were used is shown in *Table 20*.

The mean percentage of topical corticosteroid use was slightly less in the intervention group than the standard care group, equivalent to using topical corticosteroids on 6 days fewer over the 24 weeks (95% CI equivalent to using steroids for between 16 days fewer and 4 days more). The mean frequency of usage was similar in the two groups for the other topical treatments. Details of the amount of topical corticosteroid prescribed over the 6-month trial are summarised in *Chapter 4*, *Table 30*.

The potency of participants' main topical corticosteroid was similar in the two groups at 6 months (*Figure 11*).

TABLE 17 Global assessment of moderate, severe or very severe AE

Outcome and allocated group	Baseline, *n/N* (%)	2 months, *n/N* (%)	4 months, *n/N* (%)	6 months, *n/N* (%)	Adjusted risk difference (95% CI); *p*-value	Adjusted relative risk (95% CI); *p*-value
IGA						
Standard care	108/151 (72)	72/137 (53)	63/133 (47)	56/139 (40)	–0.1% (–9.3% to 6.3%); 0.70	0.98 (0.82 to 1.12); 0.63
Intervention	108/149 (72)	71/139 (51)	60/136 (44)	58/134 (43)		
PGA						
Standard care	113/151 (75)	82/137 (60)	72/133 (54)	60/139 (43)	–10.1% (–18.3% to –2.0%); 0.01	0.83 (0.70 to 0.98); 0.03
Intervention	98/149 (66)	62/139 (45)	56/135 (41)	51/134 (38)		

Note
A total of 283 participants were included in the analysis models for both IGA and PGA (standard care, $n = 141$; intervention, $n = 142$).
Risk difference and relative risk for IGA adjusted for age and baseline IGA of moderate, severe or very severe eczema (binary). The model for IGA did not converge when recruiting site was included.
Risk difference and relative risk for PGA adjusted for stratification variables site and age and baseline PGA of moderate, severe or very severe eczema.

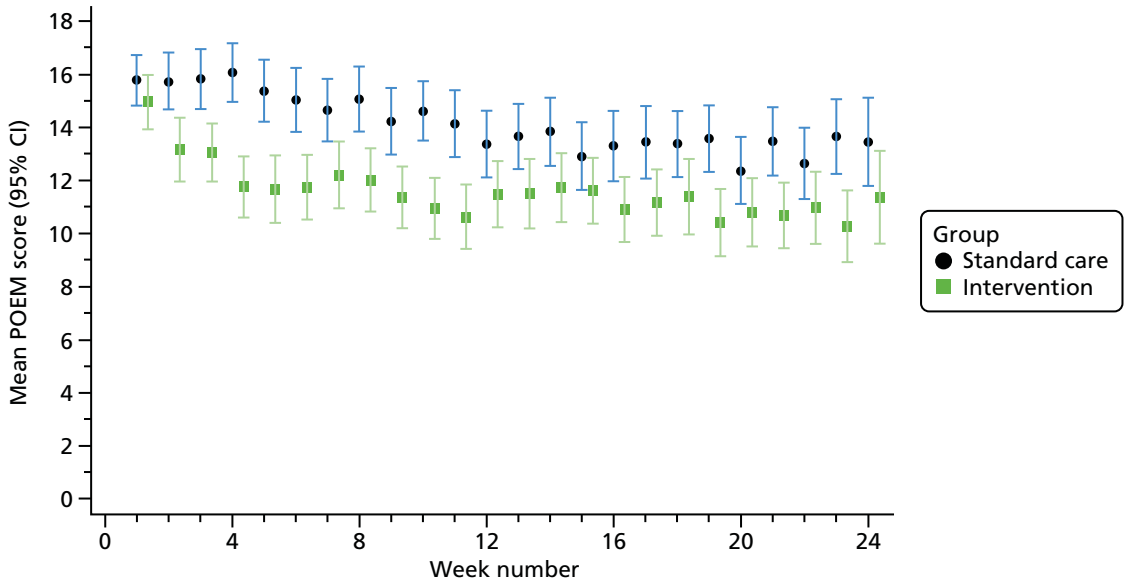

FIGURE 10 Mean weekly patient reported symptoms (POEM scores) with 95% CI. Baseline POEM scores (16.6 standard care; 17.3 intervention): data not shown on graph as scores were collected in clinic rather than by online questionnaire.

TABLE 18 Participant mean of weekly POEM scores

POEM scores	Standard care ($n = 147$), mean (SD)	Intervention ($n = 145$), mean (SD)	Adjusted difference in means (95% CI); *p*-value
POEM score at baseline clinic visit	16.6 (4.8)	17.3 (5.8)	
Participant mean of weekly POEM score during the 6-month RCT	14.2 (5.5)	11.6 (5.6)	–2.8 (–3.9 to –1.8); < 0.001

Note
Shows data for participants who completed at least one questionnaire.
Summary statistics and analysis reported are weighted according to the number of questionnaires completed. POEM scores range between 0 and 28, with higher scores indicating more severe AE. Difference in means adjusted for baseline POEM score (collected in clinic) and stratification variables, age and site.
Summary statistics for the POEM for each group and week are given in *Appendix 15* (see *Table 54*).

TABLE 19 Three-Item Severity scale scores

Allocated group	Baseline	2 months	4 months	6 months	Adjusted difference in means (95% CI); *p*-value
Standard care					
n	151	137	133	139	
Mean (SD)	4.9 (1.8)	4 (1.9)	4.1 (2.2)	3.7 (1.9)	
Intervention					
n	149	139	136	134	0.09 (–0.22 to 0.40); 0.57
Mean (SD)	4.9 (1.8)	4.1 (2)	4.1 (2.1)	3.7 (2)	

Note
A total of 283 participants were included in the analysis model (standard care, $n = 141$; intervention, $n = 142$). Difference in means adjusted for baseline TIS score and the stratification variables age and site as covariates. TIS scores range between 0 and 9, with higher scores indicating more severe AE.

TABLE 20 Frequency of AE treatments

Frequency of medication use	Standard care ($n = 147$), mean (SD)	Intervention ($n = 145$), mean (SD)	Adjusted difference in means (95% CI); p-value
Percentage of days topical steroids used	44.1 (28.2)	39.3 (27.8)	–3.7 (–9.6 to 2.3); 0.23
Percentage of days emollients used	88.4 (20.1)	86.0 (22.1)	
Percentage of days calcineurin inhibitors used	5.8 (15.9)	5.7 (16.3)	
Percentage of days wet/dry wraps used	5.2 (17.1)	3.1 (12.5)	

Note
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 for percentage of days topical steroids used adjusted for topical steroid use at baseline (yes/no) and stratification variables age and site.
Between-group analysis not performed for percentage of day's emollient used as assumptions for model not met as most participants were using these most of the time. Similarly, assumptions were not met for the analysis for the percentage of day's calcineurin inhibitors used and wet/dry wraps used because of the large number of participants that were not using these treatments.

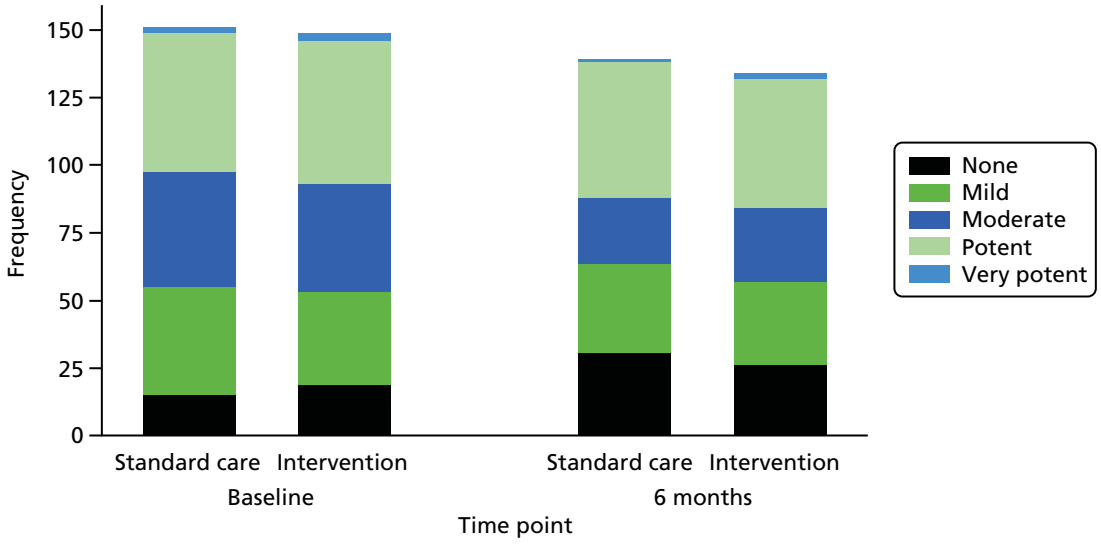

FIGURE 11 Potency of main steroid at baseline and follow-up.

Changes in AE treatments during the trial are shown in *Table 21*. There were no differences between the groups in the percentage of participants who escalated their AE treatment between baseline and 6 months, although participants in the standard care group were more likely to have escalated treatment within the first 2 months of the study.

Health-related quality of life

Health-related quality-of-life outcomes for the DFI, EQ-5D-3L, ADQoL and CHU-9D are shown in *Table 22*. There were no differences between any of these quality-of-life outcomes between the two groups. The difference in means were all close to 0 and favoured the intervention group for DFI, EQ-5D-3L and ADQoL, and favoured the standard care group for CHU-9D.

TABLE 21 Atopic eczema treatment changes between clinic visits

Change in medication use	Standard care ($N = 151$), *n* (%)	Intervention ($N = 149$), *n* (%)	Adjusted risk difference (95% CI); *p*-value	Adjusted relative risk (95% CI); *p*-value
Between baseline and 2 months				
Treatment escalation	34 (25)	15 (11)		
Neutral change	18 (13)	13 (9)		
No change	81 (59)	105 (76)		
Treatment reduction	4 (3)	6 (4)		
n	137	139		
Between 2 and 4 months				
Treatment escalation	16 (12)	16 (12)		
Neutral change	17 (13)	8 (6)		
No change	96 (72)	107 (79)		
Treatment reduction	4 (3)	5 (4)		
n	133	136		
Between 4 and 6 months				
Treatment escalation	16 (12)	16 (12)		
Neutral change	10 (7)	15 (11)		
No change	105 (76)	93 (69)		
Treatment reduction	8 (6)	10 (7)		
n	139	134		
Any treatment escalation between baseline and 6 months[a]	50 (36)	42 (30)	–5.3% (–16.3% to 5.7%); 0.34	0.87 (0.62 to 1.22); 0.43

a Based on 140 participants in the standard care group and 138 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. Risk difference and relative risk adjusted for stratification variables age and site.

Safety outcomes

The number of participants reporting a skin infection was similar in the two groups (*Table 23*).

Four participants in the intervention group and two in the standard care group had a hospital inpatient stay because of AE. The two hospital inpatient stays required by one participant in the intervention group were classified as potentially related to trial treatment by the medical monitor.

Open follow-up period

The questionnaire at 8 months was completed by 111 participants (74%) in the standard care group and 116 participants (78%) in the intervention group.

The frequency with which the clothing was worn during the open follow-up period (when all participants received the garments) is shown in *Table 24*. Just under half of the responders reported that the garments were worn for all or most of the time for the days and/or nights between 6 and 8 months.

TABLE 22 Quality-of-life outcomes

Quality-of-life outcome and allocated group	Baseline	6 months	Adjusted difference in means (95% CI); *p*-value
DFI			
Standard care			–0.8 (–2.1 to 0.4); 0.18
n	151	138	
Mean (SD)	12.0 (6.3)	8.6 (6.8)	
Intervention			
n	149	133	
Mean (SD)	12.4 (6.6)	7.6 (6.1)	
ADQoL			
Standard care			0.0260 (–0.0018 to 0.0539); 0.07
n	151	139	
Mean (SD)	0.6952 (0.1300)	0.7292 (0.1308)	
Intervention			
n	149	134	
Mean (SD)	0.6883 (0.1409)	0.7515 (0.1273)	
CHU-9D (aged ≥ 5 years only)			
Standard care			–0.0243 (–0.0584 to 0.0098); 0.16
n	64	67	
Mean (SD)	0.8292 (0.1263)	0.8828 (0.1059)	
Intervention			
n	70	65	
Mean (SD)	0.8386 (0.1115)	0.8677 (0.1114)	
EQ-5D-3L index for parents health-related quality of life			
Standard care			0.0115 (–0.0185 to 0.0415); 0.45
n	151	138	
Mean (SD)	0.8983 (0.1612)	0.9107 (0.1529)	
Intervention			
n	147	134	
Mean (SD)	0.9018 (0.1710)	0.9184 (0.1564)	

Note
Ranges for quality-of-life-life scores: DFI (0–30, with higher scores indicating greater impact of the child's skin condition on family life); ADQoL (0.356–0.841, with higher scores indicating better quality of life); CHU-9D (0.33–1, with higher scores indicating better quality of life); EQ-5D-3L (–0.594 to 1, with higher scores indicating better quality of life).
Difference in means adjusted for stratification variables age and site, and baseline score.

Overall, 135 out of 227 participants (59%, 95% CI 53% to 66%) were satisfied or very satisfied with the clothing at 8 months, and 139 out of 227 participants (61%, 95% CI 54% to 68%) were happy or very happy to wear the clothing.

Opinions of trial clothing at 8 months are shown in *Table 24*. Just over one-third of respondents thought that their/their child's AE had improved as a result of wearing the trial garments, with a similar proportion responding that they were not sure. Just under half of respondents would ask their general practitioner (GP) to prescribe the garments. Only 14 responders had asked their GP to prescribe the clothing and six responders reported purchasing silk clothing during the trial.

TABLE 23 Safety outcomes: skin infections and inpatient stays because of AE

Safety outcomes	Standard care ($n = 141$)	Intervention ($n = 142$)	Adjusted relative risk (95% CI); p-value
Any skin infection during 6-month RCT, n (%)[a,b]	39 (28)	36 (25)	0.89 (0.54 to 1.47); 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 because of AE, n (%)[a,c]			
0	139 (99)	138 (97)	
1	1 (1)	2 (1)	
2	1 (1)	2 (1)	
≥ 3	0	0	
Total number of nights in hospital because of AE			
Mean (SD)	2.5 (2.1)	2.8 (1.7)	
Median (25th, 75th centile)	2.5 (1, 4)	2.5 (1.5, 4)	
Min., max.	1, 4	1, 5	
n	2	4	

Max., maximum; min., minimum.
a Percentages for any skin infection and inpatient stay use the number of participants attending at least one follow-up visit as the denominator.
b Skin infections are reported by the parent/main carer and are defined as any skin infections that required treatment with antivirals or antibiotics. Relative risk adjusted for stratification variables age and site.
c Inpatient hospital stays for AE (for any reason) are reported by the parent/main carer.

Change in POEM scores and topical treatment usage between 6 and 8 months is shown in *Table 25* for the standard care group and in *Table 26* for the intervention group. POEM scores decreased slightly in the standard care group (who had been sent the silk garments at 6 months) between 6 and 8 months. POEM scores were similar at 8 months to the scores at 6 months for the intervention group. Topical treatment usage at 8 months was similar to that at 6 months in both groups.

Tertiary outcomes

Brand of garments

Figure 12 shows the numbers of participants randomised to the two brands of clothing. Garments were required during a DreamSkin out-of-stock period for 19 participants randomised to the intervention group (eight randomised to DermaSilk and 11 to DreamSkin) and 26 participants at 6 months who were allocated to the standard care group (nine randomised to DermaSilk and 17 to DreamSkin). These participants are not included in the analysis according to brand of clothing.

The EASI scores during the 6-month RCT were similar according to garment brand (*Figure 13*). There was no differential effect of the garments according to brand (ratio of geometric means for DermaSilk vs. DreamSkin was 0.98, 95% CI 0.83 to 1.16). Adherence, satisfaction and the child being happy to wear the clothing were all similar at 6 months regardless of brand (*Table 27*). Further comparisons of the brands using data from the 8-month questionnaires can be found in *Appendix 18*.

TABLE 24 Frequency of wear and opinion of trial clothing at 8 months

Qualitative feedback	Standard care (*N* = 111), *n* (%)	Intervention (*N* = 116), *n* (%)	Total (*N* = 227), *n* (%)
Frequency clothing worn during the follow-up period (6–8 months)			
Never	8 (7)	17 (15)	25 (11)
Rarely	20 (18)	18 (16)	38 (17)
Some of the time	26 (23)	27 (23)	53 (23)
All/most of the time (days only)	3 (3)	2 (2)	5 (2)
All/most of the time (nights only)	42 (38)	25 (22)	67 (30)
All/most of the time (days and nights)	7 (6)	24 (21)	31 (14)
Not answered	5 (5)	3 (3)	8 (4)
Feel that AE improved because of trial clothing			
Yes[a]	25 (23)	57 (49)	82 (36)
No	28 (25)	27 (23)	55 (24)
Not sure	49 (44)	28 (24)	77 (34)
Not answered	9 (8)	4 (3)	13 (6)
Would ask GP to prescribe clothing			
Yes[b]	48 (43)	61 (53)	109 (48)
No	32 (29)	31 (27)	63 (28)
Not sure	22 (20)	20 (17)	42 (19)
Not answered	9 (8)	4 (3)	13 (6)
Have asked GP to prescribe clothing			
Yes	5 (5)	9 (8)	14 (6)
No	94 (85)	103 (89)	197 (87)
Not answered	12 (11)	4 (3)	16 (7)
GP prescribed clothing			
Yes	3	5	8
No	2	4	6
Reason GP did not prescribe clothing[c]			
Too expensive	1	4	5
No evidence of efficacy	1	4	5
Not available in postcode	1	–	1
Bought silk clothing for AE during the study			
Yes	3	3	6

GP, general practitioner.
a 95% CI 29% to 43%.
b 95% CI 41% to 55%.
c Reasons not mutually exclusive.

TABLE 25 Patient Oriented Eczema Measure and topical treatment usage at 6 and 8 months in the standard care group

Outcomes	6 months		8 months	Change from 6 months	95% CI
	All participants (*N* = 121)	Completed questionnaire at 8 months (*N* = 105)	(*N* = 111)	(*N* = 105)	
POEM					
Mean (SD)	13.2 (6.7)	13.2 (6.5)	11.8 (7.4)	–1.6 (6.5)	–2.8 to –0.4
n	120	104	111	104	
Number of days emollients used in previous week					
Mean (SD)	6 (1.9)	5.9 (1.9)	6 (2)	0 (1.7)	–0.4 to 0.3
n	119	104	111	104	
Number of days topical corticosteroids used in previous week					
Mean (SD)	2.9 (2.6)	2.9 (2.6)	3 (2.6)	0 (2.1)	–0.4 to 0.4
n	118	103	110	103	
Topical calcineurin inhibitors used in previous week, *n*/*N* (%)	10/117 (9)	8/103 (8)	7/109 (6)		
Topical wet/dry wraps used in previous week, *n*/*N* (%)	10/117 (9)	9/102 (9)	8/108 (7)		

TABLE 26 Patient Oriented Eczema Measure and topical treatment usage at 6 and 8 months in the intervention group

Outcomes	6 months		8 months	Change from 6 months	95% CI
	All participants (*N* = 121)	Completed questionnaire at 8 months (*N* = 112)	(*N* = 116)	(*N* = 112)	
POEM					
Mean (SD)	11.3 (7.2)	11.5 (7.2)	11.1 (6.8)	–0.4 (4.6)	–1.2 to 0.5
n	121	112	114	110	
Number of days emollients used in previous week					
Mean (SD)	6.2 (1.9)	6.3 (1.6)	6.2 (1.8)	0 (1.7)	–0.4 to 0.3
n	120	111	111	106	
Number of days topical corticosteroids used in previous week					
Mean (SD)	3 (2.5)	3 (2.6)	2.8 (2.4)	–0.2 (2.4)	–0.7 to 0.2
n	120	111	112	107	
Topical calcineurin inhibitors used in previous week, *n*/*N* (%)	14/119 (12)	13/110 (12)	12/108 (11)		
Topical wet/dry wraps used in previous week, *n*/*N* (%)	7/119 (6)	7/110 (6)	8/108 (7)		

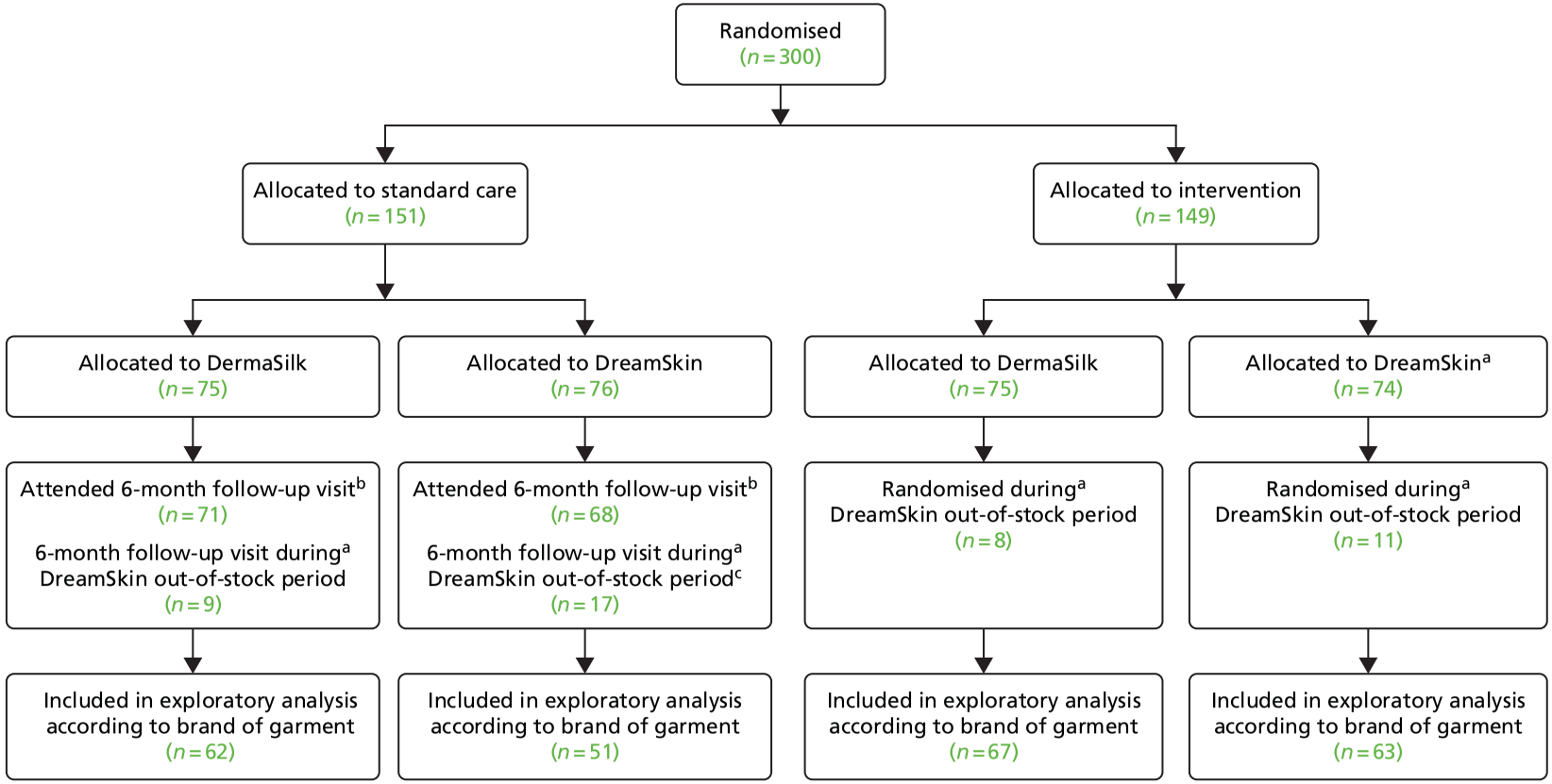

FIGURE 12 Randomisation to brands of garments. a, Four participants in the intervention group randomised to DreamSkin initially received DreamSkin garments but were issued DermaSilk replacements as the required size of DreamSkin clothing was out of stock when the replacements were required; b, 12 participants in the standard care group were not sent any clothing at 6 months because they did not attend the 6-month visit; however, two of these participants completed the questionnaire at 8 months; c, clothing supply at 6 months was delayed for five of these participants so that they could receive DreamSkin garments.

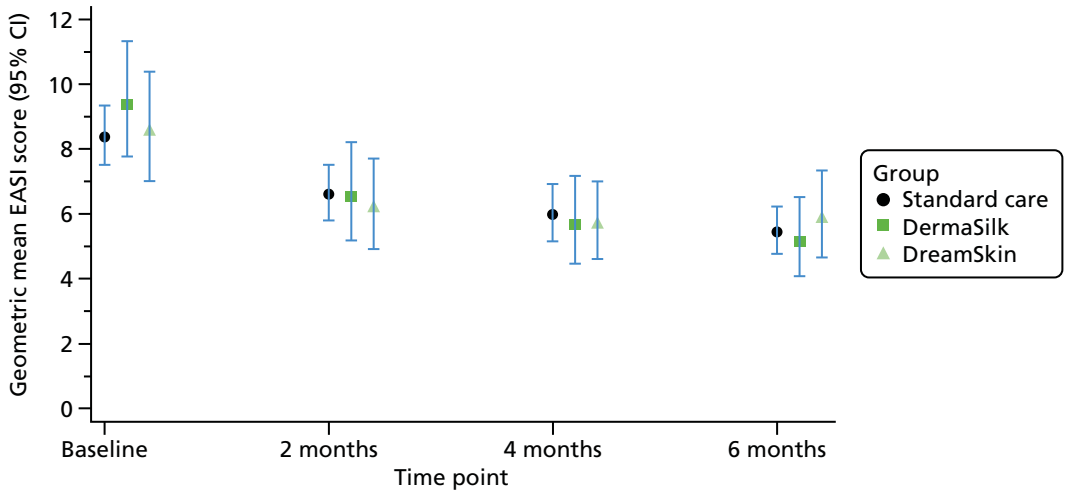

FIGURE 13 Geometric mean EASI scores by brand of garment.

TABLE 27 Adherence and acceptability by brand of clothing

Feedback on clothing	DermaSilk	DreamSkin
Adherence[a]		
≥ 12 weekly questionnaires completed on clothing wear (*n*)	56	54
Percentage of nights that clothing was worn for at least some of the night, median (25th, 75th centile)	80.7 (60.8, 93.9)	73.4 (50.7, 95.7)
Percentage of days that clothing was worn for at least some of the day, median (25th, 75th centile)	29.8 (8.7, 74.8)	31.6 (6.8, 70.2)
Adherence to wearing trial clothing, *n* (%)		
Not adherent	9 (16)	12 (22)
Adherent[b]	47 (84)	42 (78)
Worn for at least 50% of days and nights	21 (38)	18 (33)
Worn for at least 50% of days only	–	–
Worn for at least 50% of nights only	26 (46)	24 (44)
Acceptability[c]		
6-month questionnaire completed (*n*)	54	52
Satisfied/very satisfied with the clothing overall, *n* (%)	41 (76)	32 (62)
Child happy/very happy to wear clothing, *n* (%)	43 (80)	35 (67)

a Adherence to wearing trial clothing summarised from week 2 onwards, and summarised provided that at least 12 of the weekly questionnaires were completed from week 2 (i.e. half).
b Participants were defined as adherent with trial garments if they were worn for at least 50% of the days or at least 50% of the nights.
c Percentage use of the number of participants with the 6-month questionnaire completed as the denominator.

Chapter 4 Health economic evaluation

Introduction

Childhood eczema has been shown to have an impact on health-related quality of life similar to that of other common childhood conditions, such as asthma and diabetes.[3] Eczema also has a substantial cost impact on society and the individual families affected; for example, the total annual UK cost of eczema in children aged ≤ 5 years is estimated to be £70.6M (or £120.19 per child) (inflated from 1996 to 2015 price year),[45] of which 64% was accounted for by NHS health-care costs.[46] A further UK study looking at patients of all ages estimated the total annual cost of eczema for the UK to be in the order of £726.7M, of which £195.3M was incurred by the NHS, £464.1M by the patients and £67.2M by society in terms of lost working days (inflated from 1995 to 2015 price year;[45] original price year not reported but most likely to be 1995).[47]

Core eczema treatment involves the regular use of emollients and topical corticosteroid creams. Children with more severe eczema may also need to occasionally use topical antibiotics, oral antibiotics, wet wraps, oral antihistamines, systemic immunosuppressive agents (such as ciclosporin or methotrexate) and special dietary products.[5]

Silk therapeutic garments have been available as a prescription on the NHS since 2008. In that year the net cost of silk garments in the UK was £168.779 for 5507 items.[48–51] Since this time, the cost of prescribing silk garments has risen to ≥ £2M for 81,797 prescription items (for all indications) (*Figure 14*). Silk garments are also available for private purchase by any individual who has the means and willingness to pay for them.

At the time this research was commissioned, there were only two companies supplying silk garments to the UK NHS (DermaSilk and DreamSkin). In 2012, a third company (Skinnies™, Dermacea Ltd, Stourbridge, UK) had products prescribed via the NHS. In 2015, the net ingredient cost (per quantity) of a set of silk garments to the NHS varied from £66.02 for a DreamSkin bodysuit and leggings for a child aged 12–18 months to £155.47 for a DermaSilk top and bottom set (size: adult, small). As the qualitative work (see *Chapter 5*) undertaken alongside the trial reveals, commissioners thought that the garments were expensive and were uncertain about how many garments would need to be prescribed owing to a lack of knowledge about the quality and lifespan of the garments. For such items to be cost-effective for the NHS, they need to have

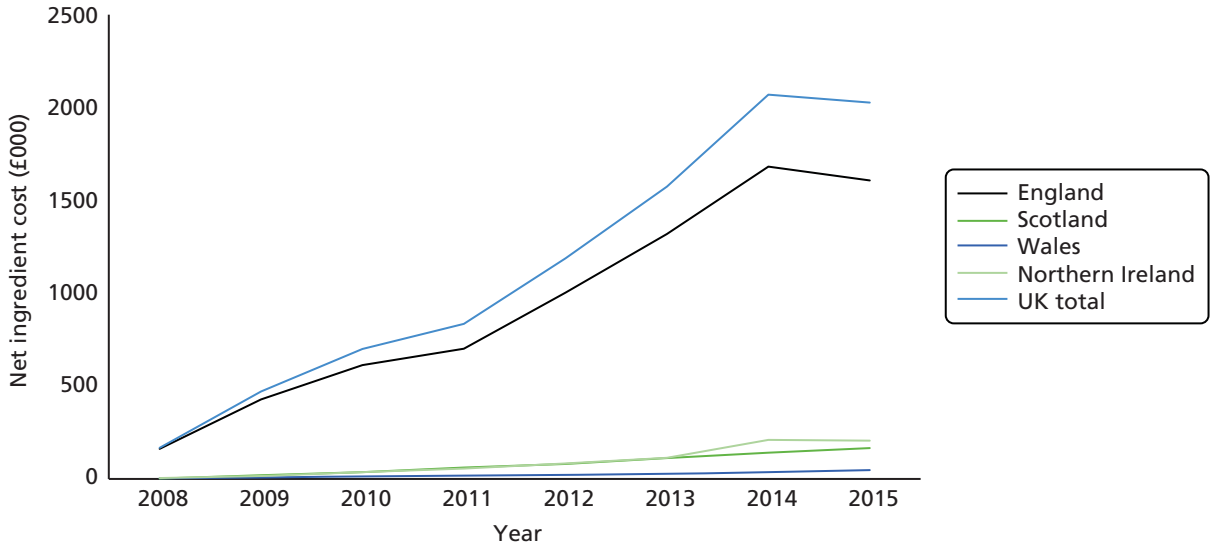

FIGURE 14 Net cost of silk garments prescribed in the UK (2008–15).

clinical benefit that is either sufficiently large to justify the cost of the garments [i.e. have an incremental cost-effectiveness ratio (ICER) that is below the cost-effectiveness threshold] and/or lead to cost savings to the NHS via potential reduced consultations with health professionals or reduced prescriptions of other medications for eczema.

Prior to this trial, there was no scientific evidence about the cost-effectiveness of silk garments for the treatment of moderate to severe eczema. As a result, the national health-care system in the UK has been prescribing something for which there is not a strong evidence base demonstrating either clinical effectiveness or cost-effectiveness. One of the aims of the economic component of this trial was to assess if silk garments for eczema represent value for money for the NHS and, thus, whether or not the NHS should be funding this intervention.

This chapter presents the economic evaluation, which was conducted alongside the trial as planned in the original research in order to estimate the mean incremental cost and mean quality-adjusted life-year (QALY) change (per patient) with silk garments and standard care, compared with standard care without silk garments.

Methods

Aims and perspective

The aim of the economic evaluation was to estimate the within-trial cost-effectiveness of silk therapeutic clothing plus standard care compared with standard care alone from a NHS perspective in the base case, and from a NHS and wider (family and employer) perspective in secondary analyses. Personal Social Services costs were not explicitly asked about, as the clinical team felt that these were unlikely to be relevant to those with childhood eczema.

Two forms of economic evaluation were used, cost–utility analysis and cost-effectiveness analysis, in order to enable comparisons with non-eczema interventions and other eczema interventions, respectively.

The economic evaluation adhered to published and well-accepted guidelines for the economic evaluation of health-care interventions, as appropriate.[52–54]

Resource use: identification, measurement and valuation

The range of resource use and costs captured was in keeping with the chosen perspective. Three categories of resource use were identified as important to capture. These were intervention resource use, other health resource use and wider family/employer costs. All resources were costed at 2014/15 price year levels in UK pounds sterling.

Intervention resource use (silk garments)

Intervention resource use was measured during the trial using an inventory that recorded number, type and size of garments issued to and returned by participants. At baseline each participant was issued with the equivalent of three sets of pyjamas (tops and leggings) or leggings and a bodysuit for younger children.

Garments were removed from their original packaging and repackaged in trial packaging. The inventory in some cases recorded tops and bottoms as individual items when in reality we expect that they had actually come from a single pyjama set, which would be cheaper than the two items separately. In valuing the resources, the base case thereby assumed that all those issued between the ages of 3 and 12 years (the age range within which a pyjama set is available) were from a pyjama set as this is what is most likely to be prescribed in routine care.

Some garments were returned to be exchanged for a different size. Where one of these sets had been tried on for size, these could not re-enter stock and had to be disposed of (as would be the case if the NHS

prescribed them and they did not fit); these items were included in the cost. However, if items were returned unused such that they could be sent to another participant, this was recorded and these items were not included in the cost, to avoid double counting. Some participants needed replacement garments during the 6-month trial period because of a child's growth or wear and tear. The issuing of such garments was recorded in the inventory and included in the intervention cost. In valuing the silk garments, the cost was not annuitised to take account of a lifespan longer than 6 months as data collected within the trial suggest that a lifespan of 6 months for the garments is a reasonable assumption to make.

In the base case, the silk garments were valued using the net ingredient cost per quantity from the *Prescription Cost Analysis 2015* published by the Health and Social Care information Centre.[55] However, this is not the only method available for costing prescriptions. In the sensitivity analysis, an alternative approach based on the NHS Business Services Authority actual cost formula (obtained from the NHS Business Services Authority website) was used.[56] The actual cost is based on the net ingredient cost minus the national average discount percentage (where the average discount was 7.43% based on March 2015 data) plus payment for consumables, containers and a professional fee (although in the case of silk garments, payments for consumables and containers are not incurred).[57]

In the trial the silk garments were posted to participants, but this does not reflect how the garments are distributed in the NHS, where patients would collect their prescription from a pharmacy. As a result we did not include the cost of posting silk garments in the trial.

Other health resource use

Health resource use beyond the intervention cost was recorded by the participant or a parent on the weekly diary card and recorded by the research nurse at each of the study visits (baseline, 2, 4 and 6 months). To aid memory, an online questionnaire prompted participants to complete their diary if a health-care professional was visited, or a prescription issued, for eczema in the last week. Participants were asked to record only those resources consumed as a result of the child's eczema; all items reported by parents were included. This included health-care visits to primary care professionals (number of appointments to GP and practice nurse), secondary care visits (number of outpatient visits, nights in inpatient care, and accident and emergency) and prescriptions [including topical corticosteroids, topical calcineurin inhibitors, emollients (including bath emollients), wet/dry wraps, antibiotics/antivirals for skin infections and other eczema-related prescriptions].

These resource items were valued using published national sources of unit costs in UK pounds sterling for the 2014/15 price year.[55,58,59] The individual items of resource use and their unit cost can be seen in *Table 28*.

Primary care resource use items were valued using the published Personal Social Services Research Unit health and social care unit costs.[58] The unit cost for GPs assumed that the per patient contact lasted 12 minutes for a face-to-face appointment and 7 minutes for a telephone consultation, including direct care staff cost and qualification cost. The practice nurse visit assumed a face-to-face contact lasted 16 minutes. NHS homeopathic appointments were assumed to have taken place in primary care. Consultations with a pharmacist were assumed to have lasted 20 minutes and the unit cost of a community pharmacist was assumed to have been the same as that of a hospital pharmacist. The cost of a nutritionist or dietitian appointment was taken from the NHS reference costs[59] for community health services dietitian.

Unit costs for secondary care resource use items were largely sourced from the NHS reference costs for 2015.[59] Short inpatient stays (one night) were assumed to be for skin disorders without interventions, with a Complications and Comorbidities (CC) score of 0–1; medium stays (three nights) were assumed to be for skin disorders without interventions, with a CC score of 2–5; and longer stays (four nights) were assumed to be for skin disorders without interventions, with a CC score of 6–9. Patch tests were assumed to be standard patch tests for children aged $\leq$ 12 years. Accident and emergency visits were assumed to be non-admitted, with category 2 investigation and category 3 treatment. The unit cost per consultation with a consultant eczema nurse was assumed to be the same as for 'other specialist nursing, child, face to face' (currency code N29CF) under community health services.[59]

TABLE 28 Unit costs in 2014/15 UK pounds sterling

Resource item	Unit cost (£)	Source
Intervention: silk therapeutic garments		
Base case: prescription cost analysis approach (per set)	66.02–155.49	HSCIC[55]
Sensitivity analysis: tariff approach (per set)	62.83–145.02	NHSBSA[57]
Primary health care		
GP (per surgery consultation)	37.00	PSSRU[58]
GP (per telephone consultation)	22.00	PSSRU[58]
GP (per consultation out of hours)	68.91	PSSRU[58]
Practice nurse (per consultation)	12.14	PSSRU[58]
Community eczema nurse (per consultation)	38.00	PSSRU[58]
Community nurse (per consultation)	38.00	PSSRU[58]
Pharmacist (per contact)	14.67	PSSRU[58]
Health visitor (per contact)	54.00	PSSRU[58]
Nutritionist (per telephone contact)	82.66	DH[59]
Homeopathic visit	57.00	[a]
Blood test (per test)	9.07	DH[59]
Influenza vaccination (per vaccine and nurse time)	30.14	HSCIC[55]/PSSRU[58]
Secondary health care		
A&E (per visit)	93.00	PSSRU[58]
Outpatient first visit (dermatology, per consultation)	128.40	DH[59]
Consultant eczema nurse (per consultation)	161.03	DH[59]
Eczema nurse (per telephone contact)	42.57	DH[59]
Paediatric assessment	299.51	DH[59]
Inpatient stay for skin disorder without intervention (one night)	1185.48	DH[59]
Inpatient stay for skin disorder without intervention (three nights)	1756.10	DH[59]
Inpatient stay for skin disorder without intervention (four nights)	2267.63	DH[59]
Patch test (per test)	91.81	DH[59]
Medications		
Various	Various	HSCIC[55]
Wider family/employer costs		
Gross mean hourly wage for all employee jobs in UK	15.27	*Annual Survey of Hours and Earnings*[60]
Out-of-pocket costs	Various	As reported by parents

A&E, accident and emergency; DH, Department of Health; HSCIC, Health and Social Care Information Centre; PSSRU, Personal Social Services Research Unit.
a Estimate based on the range of values provided on: www.nhs.uk/Conditions/Homeopathy/Pages/Introduction.aspx.

Wider family/employer costs

The resource items recorded in this category reflect a more societal perspective. They include the additional out-of-pocket costs incurred by the family and productivity costs to employers of time taken off work as a result of parents' caring for their child with eczema.

Out-of-pocket costs incurred by the family

In our previous NIHR HTA-funded eczema trial,[61] only 33% of families taking part in the trial reported any out-of-pocket costs incurred as a result of their child's eczema. The rate of reporting seemed low and, therefore, to try and improve reporting of such costs, in this trial we undertook to further develop the question eliciting this information. We informed this development by using the out-of-pocket data we did manage to collect in the Softened Water Eczema Trial (SWET). We categorised the types of out-of-pocket costs reported and developed a table of examples to help families understand the types of things that may be relevant. The range of items included over-the-counter purchases, special clothing, laundry and bedding, special foods, equipment and travel costs for appointments.

The information provided and the wording of the question eliciting this information can be seen in *Appendix 10*. Respondents were asked to place a monetary value on the additional cost incurred as a result of eczema. For instance, if they bought a more expensive washing detergent because it was 'skin kind', they were asked to state the amount over and above that which they would have paid for a normal washing detergent.

Productivity costs

In addition, families were asked to record time off work and school as a result of eczema. Parents' time off work was valued using the mean gross hourly wage rate for all employee jobs in the UK, as reported in the Annual Survey of Hours and Earnings in 2015, because we did not ask respondents to report their personal earnings.[60] This approach is known as the 'human capital approach' and assumes that a person's productivity is equal to their wage rate to place a maximum cost on their time off work. This is not the only available approach to costing lost productivity and research has shown that different approaches can lead to different estimates that may impact on the conclusion reached about cost-effectiveness;[62] we therefore also report the actual time lost. Time taken off school as a result of eczema is reported in hours and minutes and is not valued in monetary terms because of the lack of evidence about the cost of lost schooling.

Measurement of outcomes and quality-adjusted life-years

The main economic analysis is the cost–utility analysis, whereby effectiveness is measured in terms of QALYs for the child. This will be presented as the base case because it enables decision-makers to compare the value for money afforded by this intervention with that for other conditions. It also enables us to clearly differentiate the results of the cost–utility analysis based on the ADQoL from the other cost–utility analyses based on the CHU-9D and the parental EQ-5D-3L.

In the base-case analysis, utility was measured in all children using the disease-specific ADQoL.[38] The ADQoL consists of four binary choice questions,[38] in answer to which respondents were asked to indicate whether they agreed more with the statement on the left or on the right:

1. you cannot join in some activities with other children/you are not limited in joining in activities with other children
2. you are very moody/you are not very moody
3. you cannot be comforted/you are quite settled
4. you sleep badly most nights/generally, you sleep very well.

The ADQoL was completed by parental proxy for children aged < 7 years and by self-report in those aged ≥ 7 years. The developer of the ADQoL used standard gamble methods to estimate utility values for the 16 health states described by the instrument. This involved asking adult participants to imagine that they were 10 years old and would be in the health state described for the rest of their life. The utility values generated ranged from 0.356 to 0.841.[38]

The primary measure of effectiveness for the cost-effectiveness analysis was the difference in the proportions achieving treatment success at 6 months – defined as those with at least a 50% improvement compared with baseline on the primary outcome measure, EASI.[31] Secondary analysis was conducted using continuous data from the DFI, where scores range from 0 (no impact on family life, best score) to 30 (maximum impact on family score, worst score).[36]

In addition, the main carer was asked to record their own utility using the EQ-5D-3L in order to see if the intervention impacted on parental quality of life (e.g. through sleep loss). The EQ-5D-3L is a generic preference-based health-related quality-of-life instrument with five dimensions, each of which has three levels.[37] The UK tariff was valued using time trade-off methods with a sample of the general adult population. Utility values on the EQ-5D-3L range from –0.594 to 1.[63] As there is no guidance to the best method for analysing adult utility data in combination with data on the child's utility,[64] we present a cost per QALY for the child as the base case and a cost per QALY per carer in secondary analyses, such that we do not combine the two sets of utility in a single analysis. It should be noted that the cost per QALY analysis for the main carer excludes any QALYs gained by the child with eczema and also probably underestimates the impact on the wider family in cases where a child with eczema lives with more than one adult, and in cases where they have siblings.

All utility instruments were measured at baseline and 6 months, and used to estimate QALYs for the trial period by using linear interpolation and area under the curve with and without baseline adjustment,[65] and adjustment by centre and age. The total area under the curve (without baseline adjustment) was measured as:

$$(\text{utility\_baseline} + \text{utility\_follow-up})/2 \times 0.5 \quad (1)$$

to reflect the 6-month time frame. The primary cost–utility analysis reports the incremental cost per QALY based on the ADQoL because children of all ages, or their main carer, were asked to complete this instrument. Secondary analyses will report the cost per QALY based on the main carer's EQ-5D-3L values separately. Previous work has not explored the ability of the EQ-5D-3L to detect impacts on carers' quality of life for this condition.

Statistical analysis and analysis of uncertainty

Neither costs nor benefits were discounted,[53] reflecting the 6-month time horizon of the analysis. A complete-case analysis approach was undertaken, with participants included only if they had complete cost and effect data at each time point.

In line with the statistical analyses, the primary analysis was conducted using the principles of intention to treat: all participants with data at baseline and follow-up were included, regardless of adherence to the allocated intervention. If > 10% of participants had missing data, then imputation of missing values was to be conducted as a sensitivity analysis.

The economic evaluation is a 'within-trial analysis'. This means that costs and benefits were only evaluated for the trial follow-up period (6 months). Costs and outcomes in both arms of the study were estimated using the methods described in *Measurement of outcomes and quality-adjusted life-years*. This information on costs and benefits was used to conduct a complete-case incremental economic analysis comparing the silk garments in addition to standard care with standard care alone. This was completed for both the cost-effectiveness and cost–utility analyses. Conclusions are based on the estimated results. ICERs were calculated using accepted methodology.[52,53]

The statistical analysis estimated both the unadjusted and adjusted estimates, where the latter controlled for any differences in baseline characteristics (i.e. the cost regression adjusted for baseline costs, age and recruiting centre, whereas the QALY regression adjusted for baseline utility, age and recruiting centre). All adjusted analyses used a regression-based approach (seemingly unrelated regression equations)[66] to

estimate incremental costs and QALYs with the exception of the cost-effectiveness analysis for EASI. As EASI was analysed as a binary variable (coded 1 for treatment success and 0 otherwise), generalised linear models, assuming costs and effects were independent, were employed. The cost regression used the Poisson family and identify link function, whereas the effects regression used the binomial family and identify link function.

As cost data were skewed, we used non-parametric bootstrapping to estimate adjusted mean (95% CI) incremental cost and mean (95% CI) incremental QALY estimates. Bootstrapping was also used to estimate cost-effectiveness acceptability curves;[67,68] these show the probability that each of the intervention groups is the most cost-effective option at different monetary valuations of the outcome variable. A range of ceiling ratio (or willingness to pay per QALY) values were tested, including the £20,000 and £30,000 per QALY thresholds used by NICE in cost–utility calculations.[69]

Sensitivity analysis tests the robustness of results in the face of any uncertainties.[53] It also improves the generalisability of results by indicating what could happen with different values of a parameter. Two areas of uncertainty were considered worth exploring. The first was the cost of the silk therapeutic garments, because 46% of total costs from a NHS perspective were accounted for by the cost of the silk garments in the study. Instead of using the Health and Social Care Information Centre Prescription Cost Analysis net ingredient cost per item, we reran the analysis using unit costs for silk garments based on the NHS Business Services Authority actual cost formula to estimate the actual cost to the NHS:[56]

$$\begin{aligned}\text{actual cost} = {} & (\text{net ingredient cost less the discount}) + \text{payment for consumables} \\ & + \text{out-of-pocket expenses.}\end{aligned} \tag{2}$$

In particular, this approach takes account of the average discount enjoyed by the NHS when purchasing prescription items. As payment for consumables and out-of-pocket expenses is not relevant for silk garments, we did not include these but did include the 90p fee pharmacists receive for dispensing. We did not do this for all prescription items as medication costs were not significantly different between the two treatment arms.

Second, as there is uncertainty about how best to capture utility in children, we included a second generic preference-based instrument, the CHU-9D,[39] at baseline and 6 months in order to compare the results with those gained using the disease-specific ADQoL.[38] The generic health-related quality-of-life instrument, CHU-9D,[39] was used only in children aged ≥ 5 years at baseline. The CHU-9D consists of nine dimensions (worry, sadness, pain, tired, annoyed, school work/homework, sleep, daily routine, ability to join in activities) using a recall period of today or last night, dependent on the question; each dimension has five levels.[39] The wording of the dimensions and levels resulted from qualitative work with children and young people. It can be self-completed by children and young people aged 7–17 years with a proxy version for parents to complete for children aged < 7 years. At the time the CLOTHES trial was designed, the CHU-9D had not been used with the under-fives and so we did not use it with those aged < 5 years. Additional guidance now exists to help parental proxies complete the CHU-9D for this age range (personal communication with K Stevens, University of Sheffield, 2014). The CHU-9D was valued by the UK general adult population using standard gamble methods and utility using this instrument can range between 0.33 and 1.[39] In this study, the CHU-9D was self-completed by children and young people aged ≥ 7 years and parental proxy completed for 5- and 6-year-olds. QALYs for the trial period based on the CHU-9D were estimated using the same methods described for estimating QALYs based on the ADQoL and main carer EQ-5D-3L (see *Measurement of outcomes and quality-adjusted life-years*).

Some of the subgroup and sensitivity analyses included in the original health economic analysis plan (see *Appendix 19*) were not conducted for the following reasons:

- imputation of missing values, as missing values were < 10%
- per-protocol analysis adjusting for adherence; sensitivity analyses in *Chapter 3, Causal effect of adherence with wearing trial garments on primary outcome* showed no evidence of a causal effect of adherence with wearing trial garments on the primary outcome.

- subgroup analysis based on impairment in skin barrier function (*FLG* genotype), as subgroup analysis of the primary outcome suggested no differential effect
- resource use data collected in the observational period (6–8 months) were not included, as there was no overall effect at 6 months.

All statistical analysis was undertaken in Stata 14.

Results

The base-case cost–utility analysis included all participants with complete resource use and ADQoL data at baseline and 6 months ($n = 273$: 134 in the silk garment plus standard care arm and 139 in standard care alone arm). Of the total 300 study participants, 27 (9%) were not included in the base-case economic evaluation because they had discontinued the study or had data missing. In the base case, 58.2% of participants were male and 80.2% were white, and the average age was 5 years.

Baseline health-care costs for eczema over the preceding 4 weeks were £35.60 (SD £69.46) per participant in the silk garment arm and £34.82 (SD £69.14) in the standard care arm (mean difference £0.78, 95% CI –£15.74 to £17.30).

Baseline utility of the child participants (as measured using the ADQoL) was a mean of 0.6879 (SD 0.1418) per participant in the silk garment arm and 0.6959 (0.1288) per participant in the standard care arm (mean difference –0.0081, 95% CI –0.0404 to 0.0241) (*Table 29*).

Resource use and costs

Intervention resource use and costs

In the 6-month period, the mean number of sets of garments (tops and leggings) per participant was 4.15 (minimum 3, maximum 9.5). Sixty-one (45.5%) intervention participants received replacement garments over the 6 months [each participant received, on average, 1.1 extra sets (minimum 0, maximum 6.5)]. The associated mean cost of silk garments, including initial and replacement garments, was £318.52 (SD £136.60; minimum–maximum £198.06–£1167.15) per participant in the base case (see *Table 31*).

Other health resource use and costs

Resource use and costs for all resource items are given in *Tables 30* and *31*. When intervention use was combined with other health resource use, the adjusted mean incremental cost per participant was £364.94 (95% CI £217.47 to £512.42) for those who received silk garments compared with those who did not in the base case (see *Table 31*). The difference in total costs between groups reflects the cost of the intervention; other NHS costs were not significantly different between groups (£48.57 higher per participant, on average, in the intervention group, 95% CI –£105.92 to £203.05).

Productivity costs

On average, parents/carers took off 3.00 (SD 7.90) hours from paid employment in the silk garment arm and 1.79 (SD 5.10) hours in the standard care arm (mean difference 1.21 hours, 95% CI –0.37 to 2.79 hours) as a result of taking care of their child with eczema. Employing a human capital approach, and using a national published gross mean hourly wage rate for men and women of £15.27, resulted in mean estimates of lost productivity of £45.78 (SD £120.61) in the silk garment arm and £27.29 (SD £77.86) in the standard care arm (mean unadjusted difference £18.49, 95% CI –£5.61 to £42.59).

Time off school or nursery

Participants in the silk garment arm missed, on average, 4.17 (SD 10.41) hours off school or nursery as a result of their eczema in the 6-month trial period, compared with an average of 3.57 (SD 8.15) hours in the standard care arm (mean unadjusted difference 0.60 hours, 95% CI –1.62 to 2.82 hours).

TABLE 29 Key findings from the base-case economic evaluation (UK £ 2014/15)

Outcome	Intervention ($n = 134$), mean (SD)	Standard care ($n = 139$), mean (SD)	Mean difference (95% CI)[a]
Health outcomes			
Utility (ADQoL)			
Baseline	0.6879 (0.1418)	0.6959 (0.1288)	–0.0081 (–0.0404 to 0.0241)
6 months	0.7515 (0.1273)	0.7292 (0.1308)	0.0224 (–0.0084 to 0.0531)
QALYs			
> 6 months	0.3598 (0.0561)	0.3563 (0.0562)	0.0036 (–0.0098 to 0.0169); **0.0064 (–0.0004 to 0.0133)**
Costs			
Garments	318.52 (136.60)	0.00 (0.00)	318.52 (295.71 to 341.33)
Primary care visits	36.52 (57.74)	47.01 (73.71)	–10.49 (–26.30 to 5.33)
Secondary care visits	213.09 (604.47)	153.00 (327.13)	60.09 (–55.16 to 175.34)
Prescriptions	119.82 (244.67)	120.86 (243.81)	–1.04 (–105.92 to 203.05)
Total health-care costs (excluding garments)	369.43 (805.88)	320.86 (446.13)	48.57 (–105.92 to 203.05)
Total health-care costs (including garments)	687.96 (809.27)	320.86 (446.13)	367.09 (212.12 to 522.07); **364.94 (217.47 to 512.42)**
Patient additional out-of-pocket costs	65.00 (166.75)	54.96 (128.75)	10.04 (–25.38 to 45.46)
Productivity costs	45.78 (120.61)	27.29 (77.86)	18.49 (–5.61 to 42.59)
Total costs (NHS, patient and employer)	798.73 (970.99)	403.11 (524.10)	395.62 (210.60 to 580.64); **392.98 (216.44 to 569.53)**

NHSBSA, NHS Business Services Authority.
a Values in bold denote adjusted mean differences and those in roman are unadjusted values.
ICER = £56,811 per QALY; ICER taking a NHS/family/employer perspective was £61,385 per QALY.

Out-of-pocket costs incurred by the family

Families paid out of pocket for an average of 10.66 (SD 21.75) items as a result of their child's eczema in the silk garment arm, compared with an average of 9.80 (SD 21.74) items in the standard care arm, over the 6-month trial period (mean difference 0.86, 95% CI –4.33 to 6.04). On average, the additional out-of-pocket costs incurred for these items were £65.00 (SD £166.75) in the silk garment arm and £54.96 (SD £128.75) in the standard care arm over the 6 months (mean unadjusted difference £10.04, 95% CI –£25.38 to £45.46).

Base-case cost–utility analysis

Base-case cost–utility analysis from a NHS perspective

The adjusted mean difference in QALYs per participant was 0.0064 (95% CI –0.0004 to 0.0133) (see *Table 29* for the key findings from the base-case analysis). Combined with adjusted mean cost, the adjusted mean incremental cost per QALY was £56,811 (*Figures 15* and *16*; see also *Table 29*), suggesting that silk garments for moderate to severe eczema 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%.

TABLE 30 Mean (SD) resource use and mean (unadjusted) difference (95% CI) in resource use per participant

Resource use item	Intervention ($n = 134$), mean (SD)	Standard care ($n = 139$), mean (SD)	Mean difference (95% CI)
Intervention			
Silk therapeutic garments (number provided over 6 months)	4.15 (1.55)	0.00 (0.00)	4.15 (3.88 to 4.41)
Primary health care			
GP (per surgery consultation)	0.78 (1.08)	1.06 (1.74)	–0.29 (–0.64 to 0.06)
GP (per telephone consultation)	0.01 (0.09)	0.01 (0.12)	–0.007 (–0.03 to 0.02)
GP (per consultation out of hours)	0.00 (0.00)	0.01 (0.06)	–0.01 (–0.02 to 0.01)
Practice nurse (per consultation)	0.13 (0.40)	0.07 (0.35)	0.06 (–0.03 to 0.15)
Community eczema nurse (per consultation)	0.03 (0.27)	0.01 (0.08)	0.02 (–0.02 to 0.7)
Community nurse (per consultation at home)	0.01 (0.09)	0.00 (0.00)	0.01 (–0.01 to 0.02)
Pharmacist (per contact)	0.00 (0.00)	0.01 (0.08)	–0.01 (–0.02 to 0.01)
Health visitor (per contact)	0.00 (0.00)	0.01 (0.09)	–0.01 (–0.3 to 0.01)
Nutritionist (per telephone contact)	0.00 (0.00)	0.01 (0.08)	–0.01 (–0.02 to 0.01)
Homeopathic (per visit)	0.01 (0.17)	0.07 (0.55)	–0.06 (–0.15 to 0.04)
Blood test (per test)	0.01 (0.09)	0.01 (0.17)	–0.007 (–0.04 to 0.03)
Influenza vaccination	0.00 (0.00)	0.01 (0.06)	–0.01 (–0.02 to 0.01)
Total number of primary care visits	**0.98 (1.17)**	**1.28 (1.87)**	**–0.30 (–0.68 to 0.07)**
Secondary health care			
A&E (per visit)	0.01 (0.17)	0.01 (0.12)	0.001 (–0.03 to 0.04)
Outpatient first visit (dermatology, per consultation)	1.04 (1.69)	0.83 (1.50)	0.21 (–0.17 to 0.59)
Dermatology consultation (per telephone call or e-mail contact)	0.01 (0.17)	0.01 (0.11)	0.001 (–0.03 to 0.04)
Consultant eczema nurse (per telephone consultation)	0.00 (0.00)	0.01 (0.08)	–0.01 (–0.02 to 0.01)
Eczema nurse (per telephone contact)	0.00 (0.00)	0.01 (0.08)	–0.01 (–0.02 to 0.01)
Paediatric assessment unit	0.00 (0.00)	0.02 (0.19)	–0.02 (–0.5 to 0.01)
Children's ward (number of visits)	0.04 (0.36)	0.03 (0.34)	0.01 (–0.07 to 0.09)
Inpatient stay for skin disorder without intervention	0.04 (0.27)	0.02 (0.19)	0.02 (–0.03 to 0.08)
Patch test (per test)	0.00 (0.00)	0.02 (0.25)	–0.2 (–0.06 to 0.02)
Total number of secondary care visits	**1.16 (2.12)**	**0.98 (1.65)**	**0.18 (–0.27 to 0.63)**
Total number of health-care visits	**2.13 (2.79)**	**2.26 (2.55)**	**–0.12 (–0.76 to 0.51)**
Medications			
Prescription items (number)	12.56 (17.97)	12.60 (13.90)	–0.04 (–3.86 to 3.78)
Topical corticosteroid (g)	139.03 (212.49)	169.03 (295.14)	–30.00 (–91.47 to 31.47)

A&E, accident and emergency.

TABLE 31 Mean (SD) cost and unadjusted cost difference (95% CI) per participant over the 6 months (in 2014/15 UK pounds sterling)

Resource use item	Intervention ($n = 134$), mean (SD)	Standard care ($n = 139$), mean (SD)	Mean difference (95% CI)
Intervention resource use			
Silk therapeutic garments (including replacements) (base case)	318.52 (136.60)	0.00 (0.00)	318.52 (295.71 to 341.33)
Primary health care			
GP (surgery consultation)	28.72 (39.98)	39.40 (64.43)	–10.68 (–23.51 to 2.15)
GP (telephone consultation)	0.16 (1.90)	0.32 (2.63)	–0.15 (–0.70 to 0.40)
GP (consultation out of hours)	0.00 (0.00)	0.50 (5.84)	–0.50 (–1.49 to 0.50)
Practice nurse	1.63 (4.89)	0.87 (4.30)	0.76 (–0.34 to 1.85)
Community eczema nurse	4.81 (43.89)	1.16 (13.66)	3.65 (–4.04 to 11.34)
Community nurse	0.28 (3.28)	0.00 (0.00)	0.28 (–0.26 to 0.83)
Pharmacist	0.00 (0.00)	0.11 (1.24)	–0.11 (–0.32 to 0.11)
Health visitor	0.00 (0.00)	0.78 (6.45)	–0.78 (–1.87 to 0.32)
Nutritionist (telephone contact)	0.00 (0.00)	0.59 (7.01)	–0.59 (–1.78 to 0.60)
Homeopathic visit	0.85 (9.85)	4.10 (31.18)	–3.25 (–8.80 to 2.30)
Blood test	0.07 (0.78)	0.13 (1.54)	–0.06 (–0.36 to 0.23)
Influenza vaccination	0.00 (0.00)	0.22 (2.56)	–0.22 (–0.65 to 0.22)
Total primary health-care costs	**36.52 (57.74)**	**47.01 (73.71)**	**–10.49 (–26.30 to 5.33)**
Secondary health care			
A&E	1.39 (16.07)	1.34 (11.12)	0.05 (–3.23 to 3.33)
Outpatients first visit (dermatology consultation)	134.15 (217.53)	107.15 (192.82)	27.00 (–21.94 to 75.93)
Dermatologist consultant (telephone/ e-mail consultation)	0.96 (11.09)	0.92 (7.67)	0.03 (–2.23 to 2.30)
Consultant eczema nurse (telephone consultation)	0.00 (0.00)	0.21 (2.46)	–0.21 (–0.63 to 0.21)
Eczema nurse (telephone contact)	0.00 (0.00)	1.16 (13.66)	–1.16 (–3.48 to 1.16)
Paediatric assessment unit	0.00 (0.00)	6.46 (56.64)	–6.46 (–16.10 to 3.17)
Children's ward (observation with no overnight stay)	11.18 (106.49)	8.62 (101.62)	2.56 (–22.24 to 27.35)
Inpatient stay for skin disorder without intervention	65.42 (401.7)	24.84 (216.39)	40.57 (–35.94 to 117.08)
Patch test	0.00 (0.00)	1.98 (23.36)	–1.98 (–5.96 to 1.99)
Total secondary health-care costs	**213.09 (604.47)**	**153.00 (327.13)**	**60.09 (–55.16 to 175.34)**
Total prescription costs	**119.82 (244.67)**	**120.86 (243.81)**	**–1.04 (–59.25 to 57.18)**
Mean total health-care costs without silk garments	**369.43 (805.88)**	**320.86 (446.13)**	**48.57 (–105.92 to 203.05)**
Mean total health-care costs with silk garments	**687.96 (809.27)**	**320.86 (446.13)**	**367.09 (212.12 to 522.07)**

continued

TABLE 31 Mean (SD) cost and unadjusted cost difference (95% CI) per participant over the 6 months (in 2014/15 UK pounds sterling) (*continued*)

Resource use item	Intervention ($n = 134$), mean (SD)	Standard care ($n = 139$), mean (SD)	Mean difference (95% CI)
Wider societal costs			
Patient additional out-of-pocket costs	65.00 (166.75)	54.96 (128.75)	10.04 (–25.38 to 45.46)
Productivity costs	45.78 (120.61)	27.29 (77.86)	18.49 (–5.61 to 42.59)
Total costs (NHS, patient and employer)	**798.73 (970.99)**	**403.11 (524.10)**	**395.62 (210.60 to 580.64)**

A&E, accident and emergency.

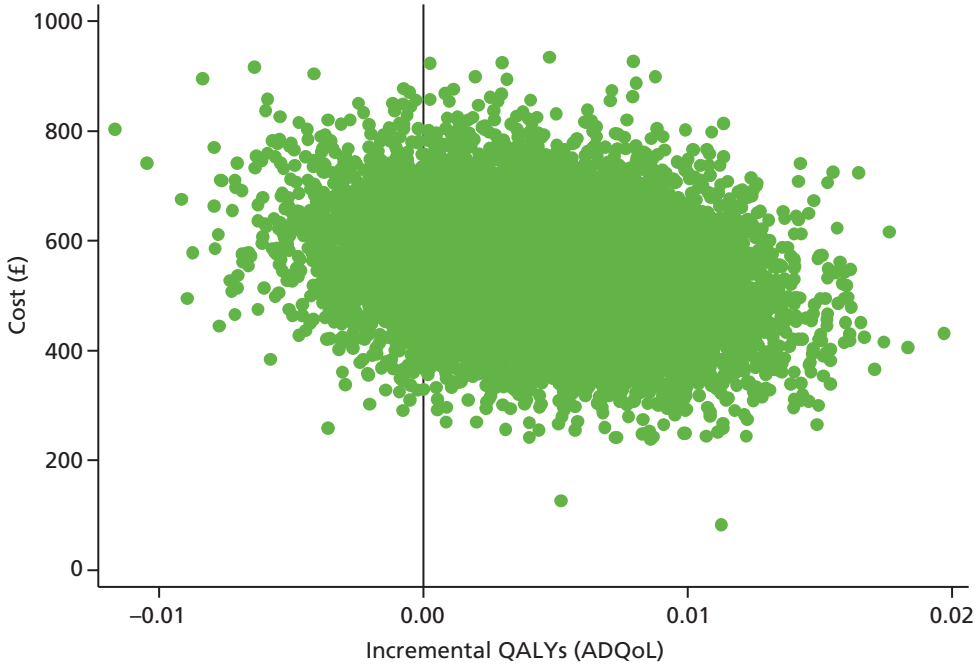

FIGURE 15 Incremental cost-effectiveness plane for the base-case analysis (ADQoL).

Cost–utility analysis taking a NHS and family/employer perspective

In a separate analysis, taking a NHS and family/employer perspective, the unadjusted mean cost per patient for the silk garment group was £798.73 (SD £970.99), compared with £403.11 (SD £524.10) in the control group. The adjusted mean incremental cost per participant was £392.98 (95% CI £216.44 to £569.53) for those who received silk garments compared with those who did not. The adjusted mean difference in QALYs per participant was the same as in the previous analysis taking a NHS perspective only, 0.0064 (95% CI –0.0004 to 0.0132), such that the incremental cost per QALY taking a wider perspective was £61,385.

Cost-effectiveness analysis

Eczema Area and Severity Index

The key results for the cost-effectiveness analysis using proportion of participants achieving a 50% improvement on the EASI as the measure of outcome are shown in *Table 32*. The incremental cost per additional person treated successfully (defined as a reduction in EASI of at least 50% compared with baseline) was £10,425.67.

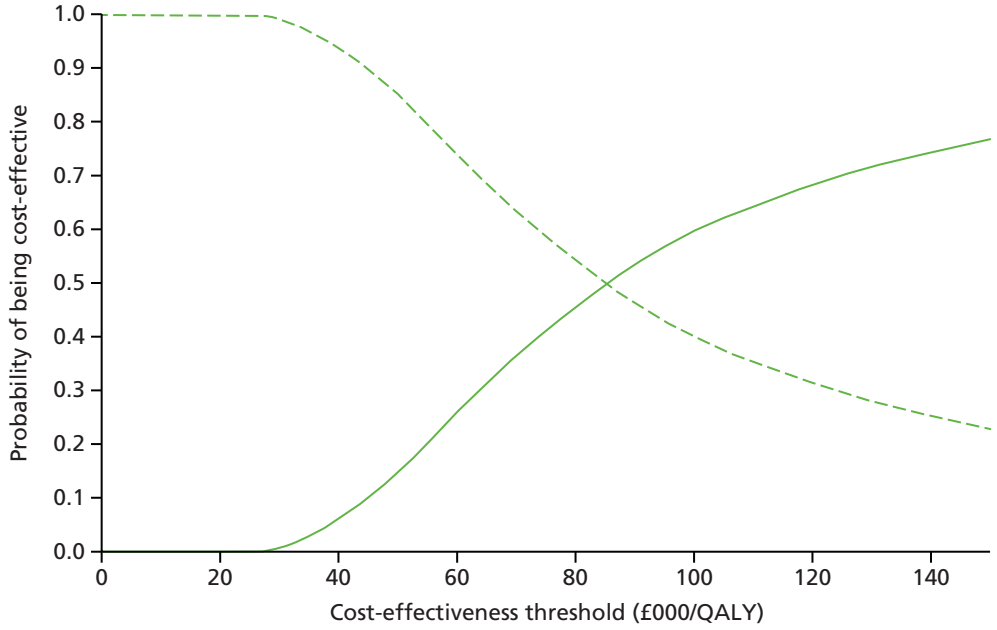

FIGURE 16 Cost-effectiveness acceptability curves for the intervention (solid line) and standard care group (dashed line): base-case adjusted costs and ADQoL utility scores. NICE threshold for willingness to pay per QALY = £20,000–30,000.[69]

Dermatitis Family Impact

The key results for the cost-effectiveness analysis using change in the DFI instrument as the measure of outcome are shown in *Table 32*. The incremental cost for every 1-point improvement on the DFI scale was £435.46.

Cost–utility analysis for main carer EuroQoL-5 Dimensions-3 Levels

The main results for the cost–utility analysis based on main carer quality of life, as measured using the EQ-5D-3L, are shown in *Table 32*. The adjusted mean incremental cost was £369.76 (95% CI £216.02 to £523.51) and the adjusted mean incremental QALY gain was 0.0029 (95% CI –0.0045 to 0.0102) (*Figure 17*), giving an ICER of £251,849 per QALY. At a willingness to pay of £30,000 per QALY, the probability of silk garments being cost-effective was 1.31%.

Uncertainty and sensitivity analysis

Alternative source of unit costs for the silk garments

To test the impact of taking into account the average discount enjoyed by the NHS, we used an alternative approach based on the NHS Business Services Authority formula to estimate the actual cost to the NHS. Using the March 2015 tariff data, where the average discount was 7.43%, the consumables fee £0.0124 per prescription item, the pharmacists' professional fee £0.90 per prescription item, the analysis was re-run (see *Table 32*). This approach reduced the cost of silk garments, but at £53,989 per QALY the estimated incremental cost per QALY was still above the accepted NICE threshold value, such that silk garments would still not be considered to offer value for money to the NHS under this approach. At a willingness to pay of £30,000 per QALY, the probability of silk garments being cost-effective was 10.51%.

Alternative outcome measure: Child Health Utility-9 Dimensions analysis

For the analysis using the CHU-9D instead of the ADQoL to estimate child utility scores, standard care dominates as silk garments were both more expensive and less effective (in terms of QALYs measured using the CHU-9D for utility) (*Figure 18* and see *Table 32*) than standard care. The probability of silk garments being cost-effective at a willingness-to-pay threshold of £30,000 per QALY was 0.06%.

TABLE 32 Incremental cost-effectiveness analyses results for base-case, secondary and sensitivity analyses

Analysis	*n* per arm (intervention; control)	Adjusted incremental health-care costs (including garments) (95% CI)	Adjusted incremental NHS/family/productivity costs (including garments) (95% CI)	Adjusted incremental effectiveness (95% CI)	ICER for NHS perspective	ICER for NHS/family and employer perspective
Base case: cost/ADQoL	134; 139	£364.94 (£217.47 to £512.42)	£392.98 (£216.44 to £569.53)	0.0064 (–0.0004 to 0.0132)	£56,811 per QALY	£61,385 per QALY
Cost/EASI[a]	133; 139	£336.14 (£330.86 to £341.42)	£361.30 (£355.51 to £367.10)	0.0322 (–0.0823 to 0.1468)	£10,426 per additional successful person treated	£11,206 per additional successful person treated
Cost/DFI	133; 138	£354.00 (£204.42 to £503.58)	£383.03 (£204.37 to £561.69)	–0.81 (–2.01 to 0.39)	£435 per one-point improvement on the DFI	£471 per one-point improvement on the DFI
Cost/main carer EQ-5D-3L	132; 138	£369.76 (£216.02 to £523.51)	£401.35 (£217.61 to £585.09)	0.0029 (–0.0045 to 0.0102)	£251,849 per QALY	£273,530 per QALY
Tariff cost/ADQoL	134; 139	£346.46 (£199.08 to £493.84)	£374.50 (£198.04 to £550.95)	0.0064 (–0.0004 to 0.0133)	£53,989 per QALY	£58,488 per QALY
Cost/CHU-9D	61; 61	£593.50 (£338.57 to £848.43)	£667.89 (£357.08 to £978.70)	–0.0061 (–0.0142 to 0.0021)	Dominated	Dominated

a Adjusted using generalised linear models, assuming costs and effects were independent. Costs using the Poisson family and identity link function, and effects using the binomial family and identity link function.

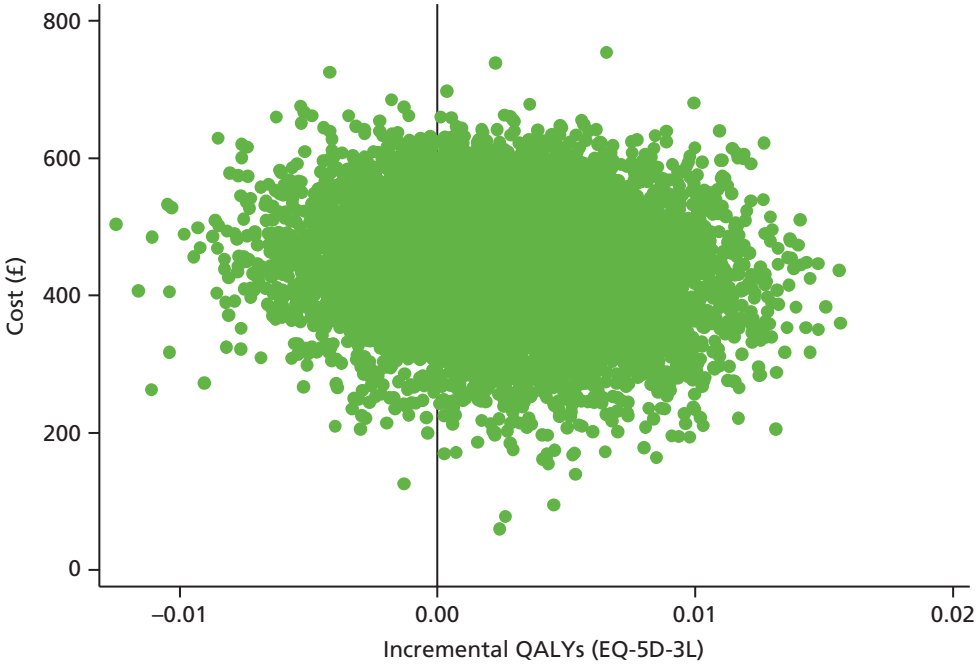

FIGURE 17 Incremental cost-effectiveness plane (main carer EQ-5D-3L).

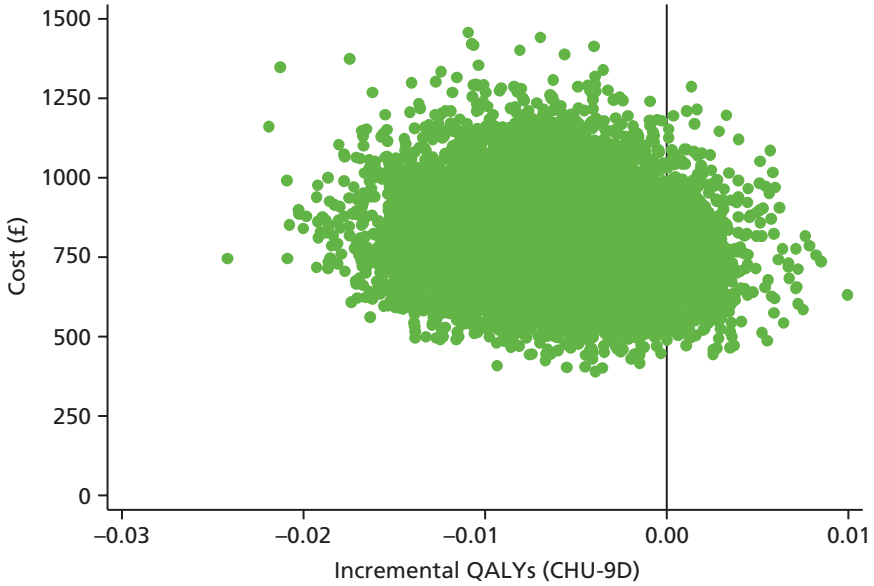

FIGURE 18 Incremental cost-effectiveness plane (CHU-9D).

Discussion and conclusion

Main findings

This is the first economic evaluation of silk therapeutic garment use in children with moderate to severe eczema. The economic analysis extends the clinical analysis to show that silk garments in addition to standard care are unlikely to represent value for money for the NHS. In terms of the costs, the additional costs of providing silk garments to intervention participants were not recouped through cost savings from lower use of wider health-care resource items nor from families in terms of reduced out-of-pocket costs or from employers in terms of reduced time off work by parents caring for their child with eczema. In terms of outcomes (when looking at patient-assessed health-related quality of life), although the ADQoL showed a very small, non-significant, positive benefit in terms of QALYs in favour of silk garments, this was not

sufficient to outweigh the higher costs of providing silk garments. The CHU-9D showed a very small non-significant decrease in QALYs (suggesting worse health) in the intervention arm. When coupled with the higher costs, this suggests that silk garments do not represent value for money for the NHS. The small, non-statistically significant, differences found when estimating QALYs (using the different instruments) suggest that the difference between intervention and usual care groups is negligible and may have been due to chance.

The result of this within-trial cost-effectiveness study also provides an indication of the cost of treating moderate to severe eczema to the NHS. Over a 6-month period, health-care costs were in the region of £345 (SD £647.40) per child (using 2014/15 costs and excluding the cost of silk garments). In addition, the reported personal costs and time lost from work/school as a result of eczema were considerable and, provide important data to inform studies on the societal impact of this condition.

Strengths and weaknesses

Given the clinical result, it could have been argued that an economic evaluation was unnecessary. However, resource use and quality-of-life data were collected alongside the trial, and these results provide useful data to inform future studies and decisions regarding health commissioning.

The study did not explicitly ask families to record how much time they spent applying treatments for their child's eczema. Were a treatment to be effective at reducing disease severity, it could conceivably reduce the amount of time a parent or child spends applying/taking medications and it might be important to capture this effect from a family perspective in future studies.

The study attempted to measure QALYs for the main carer in addition to the child. Our approach had limitations because children may have also lived with another parent or carer in addition to siblings, and we did not seek to capture the health-related quality-of-life effects of these extended family members. It is unclear how best to capture the wider impacts of eczema within a family in an economic evaluation. Further research looking at whose QALYs to capture, how to aggregate QALYs estimated for patients, carers and siblings, and how to present such results is needed.[64] However, given that this study found no difference in effect between treatment arms, the results are unlikely to be sensitive to the assumptions made in relation to such 'beyond the patient' effects.[64]

Conclusion

This economic evaluation shows that in children with moderate to severe eczema, silk garments do not offer value for money to the NHS.

Chapter 5 Nested qualitative study

The value of using mixed qualitative and quantitative research methods in trials is increasingly being acknowledged,[70] particularly when investigating complex health-related topics.[71] In the CLOTHES trial we have been mindful that the qualitative work is more than an adjunct to the main trial; it has been used to elucidate a deep understanding of the 'what', 'why' and 'how come' of participants' beliefs and behaviours.[72] This nested qualitative study was conducted by colleagues at the University of Hull, who were not aware of the treatment allocation of the children involved. The results of this nested qualitative study were collected and analysed separately. The results were not revealed to the rest of the trial team until the data collection and analysis of the main trial results were complete, at which point the results of the qualitative study were used to inform interpretation of the trial findings.

It is now widely accepted that when children are the likely end users of a product under investigation, researchers should consult them directly, rather than depending on second-hand reports from adults.[73] In this chapter we have used the term eczema rather than AE in order to reflect the language used by the parents and children.

The purpose of the qualitative component of the CLOTHES trial was to:

1. qualitatively examine participants' experiences of using silk garments for the treatment of eczema
2. examine barriers and motivators to prescribing silk garments from the perspectives of clinicians and commissioners.

Specific objectives were to:

1. explore factors that might influence the use of silk garments in everyday life
2. examine parent and child views on the feasibility and acceptability of using silk garments
3. explore parent and child experiences of using silk garments
4. examine barriers and motivators to prescribing silk garments from the perspectives of clinicians and commissioners.

This report is divided into three sections:

1. children's focus groups and interviews
2. parent interviews and focus groups
3. clinician and commissioner interviews.

For each of the three elements, a generic qualitative research method was used.[74] The research team comprised three nurse researchers, all of whom were aware of their own potential impact on the study. To ensure rigour, the following steps were taken: preconceived beliefs were acknowledged prior to data collection; each researcher used a reflective log to record their own thoughts; researcher understandings were checked with participants at the end of each episode of data collection; and analysis was conducted independently and then as a team.

The study was approved by Nottingham Health Research Authority East Midlands – Nottingham 1 Research Ethics Committee (13/EM/0255). Ethical guidelines on research with children were followed.[75] All participants gave written or verbal consent or assent depending on their age and on whether the data collection was in person or over the telephone.

Views of children in the CLOTHES trial

Data collection

Interviews and focus groups with children were completed from February 2015 to May 2015. Children were recruited using a convenience sampling strategy[76,77] via the study research nurses. They represented all of the recruiting centres and had all completed the trial before participating. Ten semistructured, audio-taped face-to-face or telephone interviews were conducted by the researcher (EW). The children in the interview group ranged in age from 9 to 15 years. There were three focus groups in total, comprising two groups of 7- and 8-year-olds, each with two participants, and a further group of 5- and 6-year-olds, with four participants. Parents and siblings accompanied the children during data collection according to age and personal preference. The demographic details of the children are presented in *Appendix 20* (see *Table 59*). The researcher (EW) used a wide range of developmentally appropriate, child-friendly techniques, such as drawing, collage, photography, storytelling, stickers and a puppet. The activities were adapted to the needs and interests of individual children. The resources chosen were sex and ethnicity neutral. The activities were selected with sensitivity; for example, the use of stickers and foam people allowed children to illustrate their point without the added pressure of having to be a 'good drawer'. Care was taken to enable children to express their views through whatever medium they preferred. A broad topic guide was used as a basis for interactions with the children (see *Appendix 20*). This was shared with the children so that they understood what would happen next. At the end of each interview and focus group the researcher summed up her understanding of the responses and checked with each child that this was correct.

All data collection focused on finding out from children what it is like to have eczema, what they thought of the silk garments and of being in the trial, and whether or not other children with eczema should be given the garments. All interviews were audio-recorded and transcribed in full. Photographs were taken of artefacts produced during the sessions, as most children wanted to take these home. The children enjoyed taking photographs of what they had made and while they were doing this the researcher used the opportunity to verify her understanding of their thoughts. This was documented alongside the photographs in preparation for data analysis.

Data analysis

The analysis of the data required a sound understanding of children's physical, cognitive, emotional and social development. This contributed to ensuring that the analysis reflected the children's voices as faithfully as possible. Interpretation of drawings, collages and craft work was undertaken with the children at each stage.

The data from the interviews and focus groups were analysed using the three methods of holistic, selective and detailed data analysis of Van Manen:[78] (1) data were viewed as a whole, (2) phrases or illustrations that seemed to represent the experience under study were identified and (3) written data were reviewed line by line in order to identify themes.[79] The aim was to be attentive to the voices of children and recognise subtle significations.[80] This was achieved through prolonged and intensive engagement with the totality of the data.

Data analysis yielded six key themes: (1) living with eczema, (2) expectations of the garments, (3) wearing 'silks' (a term often used by the children to describe their silk garments), (4) did they help?, (5) thoughts about the garments and (6) being part of the study. A description and analysis of each theme, together with supporting illustrations, is provided with a tabulation of each theme containing exemplar data extracts.

Theme 1: living with eczema

This theme comprises two subthemes: (1) health aspects of living with eczema and (2) social and emotional implications of living with eczema (*Table 33*).

TABLE 33 Views of children: theme 1 – living with eczema

Health	Social and emotional
Itchy and hot, hands and feet sore. Eczema keeps me awake at night	*It makes me feel sad and grumpy*
My skin on my back feels like fire, like rocket fire	*It's . . . like poo. I itch all the time and it's just not fair*
It hurts a lot . . . when water touches it, it burns	*I beat myself up for it because like I really want to get rid of it*
	You can't do as many things as you want to and even the sports you want to do, you can't do it because it irritates or makes it worse
	People say I am ugly

Health aspects of living with eczema

All children portrayed a negative view of living with eczema; they particularly suffered with itching, heat, and flaking and dry skin, all in different areas of their bodies and with differing severity. A picture by an 8-year-old boy depicts how burning, red and sore the eczema on his back felt (*Figure 19*). Many said that eczema affected their sleep at night and that this impacted on their daytime activities, particularly school and play.

Social and emotional implications of eczema

Several children spoke of the emotional effect that eczema had on their lives, including frustration with the condition and how it affected their general well-being. The children spoke of how eczema affects their ability to fit in with their peer group and the limiting effects the condition could have; for example, most did not like exposing their skin to others and did not enjoy sporting activities for this reason.

Theme 2: expectations of the garments

This theme has three subthemes: (1) use of other treatments, (2) garments and (3) hopes. Many participants had preconceptions about the garments (*Table 34*).

FIGURE 19 Photograph showing depiction of eczema by an 8-year-old boy.

TABLE 34 Views of children: theme 2 – expectations of the garments

Use of other treatments	Garments	Hopes
Still have to use cream	*[Silks] made me feel hotter, I thought it would make me cooler*	*I was a bit dubious because nothing's ever really worked that well for me*
During the day we use the silk suits, put the cream on underneath	*I had a lovely silk long-sleeved top and it was really comfy to wear, very easy, forgot you had it on, and I think that was what I thought it would be. If it had been pure silk and not with all of these holes . . . that would have worked for me but . . . it was a bit like a washing machine bag*	*I had all these expectations built up . . . I was really hopeful as well. I was really willing to wear them to start with, and then I got them for the start and everything just turned negative for me*
I have to put cream on every day	*If the trousers had been proper silk and that skin-colour tights, I'd have definitely worn them a lot longer because I think that would have really helped me*	*I just put them on because I think they're going to help*
		I was a bit confused because I thought it was meant to be really good and I thought it was meant to be really soft . . . I wasn't too happy with it

Use of other treatments

One particularly strongly held belief was that the silk garments would mean that other treatments, especially creams, would no longer be needed or would at least be reduced. This was also an expectation that parents had, and so it became a shared belief, and was a significant factor for some children agreeing to take part in the trial. Children were disappointed when this proved not to be the case. In fact, for some, cream use actually increased when using the garments.

Garments

Children also had ideas about what the garments would be like; because the garments were silk, the childen were expecting a soft and luxurious product, and many were surprised by the 'roughness' of the material. This reinforces the need for practitioners to be mindful of children's cognitive understanding when ascribing labels to products. A number of children had expected the silks to be cooling, but for many the effect was the opposite, with the garments making them hot and uncomfortable.

Hopes

Many of the children were excited to try the garments and had very high hopes that they would really help their eczema. Others were much more cautious, having previously tried so many treatments that they thought of as failures.

Theme 3: wearing silk garments

This theme recounts when the children chose to wear the silk garments. There are two subthemes: (1) day versus night and (2) school versus home, leisure and play (*Table 35*).

Day versus night

Figure 20 is an example of how a child conveyed the times at which he wore the garments. Few children of any age wore their silks during the day; a majority of the children preferred to wear them at night and only when at home.

School versus home, leisure and play

Children reported not wanting peers to see the garments for fear of attracting unwelcome questions or comments. There was a seasonal element to garment wear, particularly not wanting the garments to be visible when wearing shorts and t-shirts in the summer. There were many issues with being able to wear

TABLE 35 Views of children: theme 3 – wearing silk garments

Day vs. night	School vs. home, leisure and play
Always wear them at night	*I wore them to school but not PE [physical education] days . . . people would laugh*
During the day we use the silk suits, put the cream on underneath, then put all the suits on . . . and that sort of stops my clothes rubbing against my skin. Wearing the tights day and night	*Poor fit trousers so not worn to school/don't fit under tights*
I prefer to wear them during the day rather than the night because the silk is really comforting on my skin	*One of the problems was that at school – because they're quite strict on uniform – that's a problem*
Wearing them at night because some people ask like what's that and it's a bit annoying	*Yes I wore them to school but it was a bit weird when like everyone was like 'What is that?'*
I wear them mainly at night	*I did the upper body one once at school . . . but everyone kept on asking about it and I just didn't like it*
	I usually just wear them at home
	I wouldn't wear them at a sleepover just because I would find that really embarrassing, because no offence, it didn't really look that good

FIGURE 20 Photograph showing a child's depiction of times garments were worn.

them for school, ranging from fit, uniform-requirements, physical education issues and the reactions of other school children. Peer groups and friendships were very important for all children; only those with very secure friendships felt that they could openly speak about their eczema and the garments.

Theme 4: did they help?

This theme has three subthemes: (1) getting better, (2) getting worse and (3) no difference but liked them anyway. There was a real mixture of perceived success of the garments, ranging from a perceived complete cessation of eczema to no effect at all, to worsening of symptoms (*Table 36*).

Getting better

Some children reported that the silks had improved their sleep, whereas others felt that the silks had made them more comfortable in bed but had not improved their eczema per se. Improved sleep was linked with better well-being at school and at home the following day. A few children stated that the clothing improved their mood.

TABLE 36 Views of children: theme 4 – did they help?

Getting better	Getting worse	No difference but liked them anyway
It made it feel better but the crusty is still there	*I stopped wearing them as soon as I realised they were making [my] eczema worse. It helped the cream absorb better but it did make it all inflamed and more itchy*	*It was comfy. Top and bottoms were smooth*
Better, the itch goes away	*It kind of got worse. It just got more dry and really red*	*Feels nice on my skin*
At night I got to sleep through for the first time. It made me feel good inside	*[At] night, it wakes you up because it is scraping at my skin and because you have got loose bits of dead skin . . . it catches and it rips it*	*They feel nice, I like wearing them. They . . . helped me be less annoyed*
It's kind of helping the eczema go away. Less sore		

Getting worse

Other children were disappointed in the effect of the garments, which affected their self-esteem. Some children suggested that it was their own fault the garments had not worked for them.

No difference but liked them anyway

Some children liked wearing the garments, even if they had no perceptible effect on their eczema. This was predominantly because they were comfortable, although some parents reported that the garments made their child feel special. *Figure 21* shows what an 8-year-old girl thought other children should know about what was 'good' and 'bad' about the silks. The blue-stamped areas represent where the garments were hot and uncomfortable.

Theme 5: thoughts about the garments

This theme comprises three subthemes: (1) quality and cost, (2) fit and fabric, and (3) design and appearance (*Table 37*).

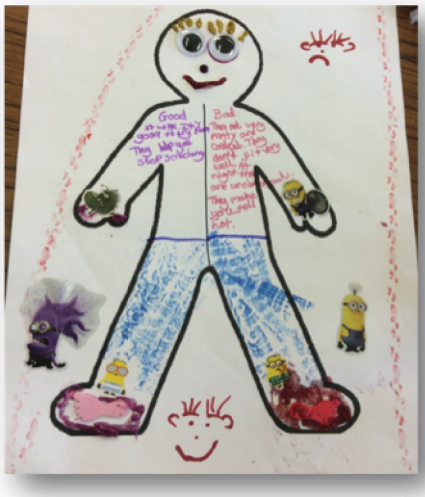

FIGURE 21 Photograph of an 8-year-old girl's thoughts on garments.

TABLE 37 Views of children: theme 5 – thoughts about the garments

Quality and cost	Fit and fabric	Design and appearance
Looked like a trial clothing rather than a purchase	*'Random sizing' poor fit. Uncomfortable – too tight*	*[Didn't like] that you could see through them*
I've got massive holes gaping wide	*I would make them a bit tighter, problem with the elastic, and they bunch at the bottom*	*It's not . . . that private to be wearing something basically see-through . . . like wearing cling film*
Get hot . . . and they can tear	*I just found them really, really uncomfortable. They were tight. There wasn't the give in them*	*Gap between trouser and top untreated and elastic waistband itchy*
I think the best thing about them is that they are 100% silk and they don't have any . . . elastic	*Kind of transparent – needed to wear pants under*	*No good for summer – long sleeves*
We didn't think they were going to be as expensive		*They look really grubby*
		They are not very pretty

Quality and cost

Children were remarkably aware of cost and quality issues. Many thought that the garments were quite poor quality in fit, appearance, design or the fabric itself, especially given the cost. They were disappointed in the shape, size and colour. The cost was an issue for further purchase for a few, with older children (and their parents) feeling that the garments should be available on prescription from a GP.

Fit and fabric

Many felt that the sizing and fit, especially of the trousers, were poor. Children were aware that the garments did not always wash well, turning baggy and grey, and affecting fit over time as illustrated in *Figure 22*. Most children used the garments with creams, which made the silks sticky and oily, and, in some cases, smelly. Some felt the texture was rough and actually irritated their skin more; some also felt that the silks actually made them hotter.

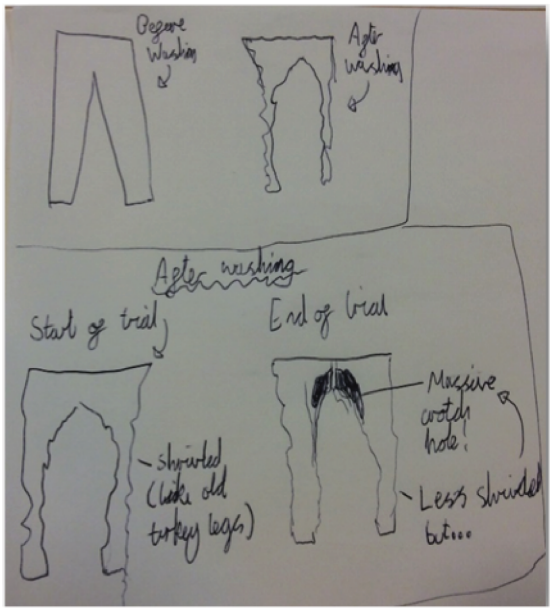

FIGURE 22 Child's illustration of garments over time.

Design and appearance

The fact that the silks were see-through was an issue for many; this limited their use to the home, and many children had to wear another layer of clothing over the silks. At night, the garments tended to be worn under pyjamas or onesies. Issues of fit, appearance and smell compounded children's sense of being 'different' from their peers. Children commented that, although three sets of garments were provided, these did not reflect sex differences in relation to puberty nor the normal varied physical growth spurts experienced at this time.

Children suggested a range of improvements to the garments, including using smoother and more closely woven fabric, resembling 'proper' silk. Some wanted the garments to be tighter, but others preferred the looser fit. A few thought that different colour options would be good, especially the youngest and oldest children. In terms of design, a 'onesie' was seen as a positive option, as were short-sleeved tops and shorts for summer. Others felt that additional protection for hands and feet would be beneficial, as these areas were not covered by the trial garments (except for those aged < 2 years) and were often troublesome. Children suggested that a few changes would make the garments more wearable in the daytime provided that this was under normal clothing, including school uniform, in the colder winter months. All except one participant felt that they would recommend other children to try the garments, even if they had not been particularly successful personally. Many of the children recognised that everyone's experience of eczema was different and that they would respond differently to different treatments, and they seemed keen to ensure that other children did not miss any opportunity to improve their eczema.

Theme 6: being part of the study

This theme comprised two subthemes: (1) helping others and (2) the research process (*Table 38*).

Helping others

Many of the children were really pleased to be taking part in the trial. Indeed, the majority of children demonstrated a significant level of altruism, wanting to be part of the trial particularly if it would help other children.

The research process

All children relished the opportunity to be with others with eczema and to talk about their experiences. Many were disappointed that the data collection was a one-off event. Most enjoyed the whole research process, and younger children valued the small gifts they received and enjoyed charting their progress. A few of the older children reported that they would 'give the garments another try', having had the opportunity to talk about them with the researcher.

Children engaged readily in the interviews and focus groups. Older children appreciated the chance to discuss their experience of eczema and the garment trial. In addition to the activities outlined in previous sections, all children were encouraged to feed back to the researcher throughout the process. All children in focus groups and face-to-face interviews chose to 'mark' the researcher's work in a similar way to

TABLE 38 Views of children: theme 6 – being part of the study

Helping others	The research process
Happy to know I am helping everyone in the world, who has eczema probably in the world	*It felt quite good because I was doing it in a trial*
It felt like I was helping the other people who had it as well so then they got some research. It felt quite good	*[The focus group was] lots of fun it gives you a chance to talk to others about your feelings . . . you get to do lots of fun stuff at the end!*
I didn't mind wearing them because I knew it was for a trial to see if it could help people with eczema	

their experience of their schoolwork being marked by a teacher. The researcher's understanding and performance, including whether or not she had asked all of the pertinent questions and understood their answers, were assessed by the children 'ticking' the work with carefully selected coloured pens.

Children took home all their artwork and checked the final photographs for use by the researcher, which gave them a sense of achievement and accomplishment. Children were asked how the findings of the project would best be communicated: most advocated either posters or a website, which they felt should be fun and incorporate activities. *Figure 23* shows a dissemination poster designed in one of the focus groups.

Child participants presented a range of views about the silk garments. All had high hopes when they entered the trial and, with few exceptions, their expectations were not realised. Some found the garments comfortable but many did not like the look, feel and fit of them. Even those children of a relatively young age were aware that the garments were expensive. Patterns of use varied, but most children reported wearing the garments fairly regularly at night. Although the children tended to report a limited effect on their skin condition, they almost universally recommended that other children should 'give the garments a try', perhaps exemplifying their experience of trying different treatment options and recognition of individual differences and needs.

Views of parents of children taking part in the CLOTHES trial

Data collection

A series of in-person focus groups and telephone interviews with the parents of children in the trial was conducted between November 2014 and August 2015. A convenience sample of parents was recruited via trial information leaflets and invitations, and with the support of the research nurses.[76,77] All participants had reached the end of the trial prior to participating and they represented all recruiting centres. In total, 28 mothers and five fathers participated, representing 11% of all trial participants. The age range of their children was 2–14 years and the sex split was 19 boys and 13 girls; 17 of the children were allocated to the standard care group and 15 were allocated to the intervention group. The demographic details are summarised in *Appendix 20* (see *Table 60*).

FIGURE 23 Dissemination poster designed by a child.

The researcher (FC) conducted the semistructured focus groups and telephone interviews using a prepared topic guide (see *Appendix 20*). The four focus groups had between two and four participants and lasted between 42 and 95 minutes. Telephone interviews lasted between 18 and 50 minutes. All data were audio-taped and transcribed verbatim.

Data analysis

Data were analysed using the five-stage Framework Analysis process.[81] The five stages comprise (1) familiarisation with the data through reading full transcripts; (2) development of a theoretical framework through identification of recurring and important themes; (3) indexing and pilot charting; (4) summarising data in an analytical framework; and (5) synthesising data by mapping and interpreting. In line with usual qualitative research practice, the researcher completed a reflective account and this was used to inform the analysis process. Stages 1–3 of the framework are illustrated in detail in *Appendix 20* and stages 4 and 5 are documented below. The analysis process yielded four key themes: (1) despair and hope, (2) fit, durability and care, (3) perceived impact of the garments and (4) engaging in the trial. A total of 13 subthemes were identified. A description of each theme is provided below, and this includes a tabulation of each theme and subtheme with exemplar data extracts.

Theme 1: despair and hope

The theme concerning despair and hope comprises four subthemes: (1) treatments, (2) adjustments, (3) quality of life and (4) hopes for the trial (*Table 39*).

Treatments

Participants presented differing accounts of the various treatments used through the course of their children's eczema. Virtually all had used emollients, often working their way through the 'full gamut' of products to find one that suited their child, and topical steroids of different potencies. Smaller numbers had been prescribed wet wraps, oral steroids, protopics, antihistamines or bleach baths, or offered photochemotherapy. Complementary therapies and specialised clothing (non-silk) had been used by some. Parents appeared to relish having the opportunity to have time to recount the ups and downs of their child's eczema treatment; for many it was a long and challenging attempt to find the best regimen. In the focus groups there was a tangible sense of relief that their stories were typical of others. Parents tended to minimise the use of topical steroids because of concerns about side effects and long-term impact on the skin condition. They also described the development of 'immunity' to treatments, which resulted in the need for periodic changes of medication. Faith in the medical profession was variable, with some parents recounting excellent experiences and others less so, particularly those receiving only primary care services. There appeared to be different approaches to treatment escalation across study sites. A small number of parents felt the need to stop treatments for a day or two before a medical consultation to ensure that the doctor saw the eczema at its worst and so would take the problem more seriously.

Adjustments

Adjustments to life had been made in a number of ways and to varying degrees that did not always obviously correlate with the described disease severity. At one extreme, one parent who received Disability Living Allowance had employed a carer to accompany her child to playgroup to apply emollients and change his nappy every hour. This mother had prepared an individual ladder of care to guide the actions of the carer and this had allowed the mother to continue with her own job and ensure that her child lived as normal a life as was possible. Many parents made adjustments such as buying only cotton clothing for their children, using natural fibre bedding, often laundered very frequently, and avoiding soft toys. Many children had sensitivities or allergies; most of these had been medically diagnosed, but some were based on the observations of parents. This led to modifications to lifestyle and diet that caused varying levels of disruption; these ranged from accepted changes, such as replacing carpets with wooden flooring, to constantly monitoring diet and living in fear of anaphylaxis. It was notable that some parents and children had managed to adapt effectively even to seemingly major lifestyle changes. For some parents, eczema care, more than quality of education, influenced the choice of their child's pre-school and school.

TABLE 39 Views of parents: theme 1 – despair and hope

Treatments	Adjustments	Quality of life	Hopes for the trial
We've probably tried every cream that can be prescribed	*We have really invested heavily into our property . . . we invested quite a lot in everything to help her with her eczema*	*It's really bad head to toe at the moment it's gone mental . . . we can't get control of it at all . . . it's a bit of a nightmare*	*Really I was hoping, you know, praying that it was going to be the answer*
Medication wise he's used everything under the sun literally	*Limited soft toys, changing all his bedding, washing his bedding at a higher temperature*	*It has affected all of us, all of our lives, totally*	*I would do anything for my daughter not to have eczema . . . I would pay anything if it meant she didn't have to suffer . . . I am desperate now, I am at my wits' end now . . . I'm praying that someone somewhere can do something for her*
She's on a rigmarole of steroids, protopics and emollients and there's a whole bathing regime . . . basically we've never really won the battle . . . the only thing that ever might keep it at bay is really strong steroid cream and even that stings . . . I've got real issues covering her in steroids	*I wouldn't let her go to anyone else's [friend's houses]*	*It doesn't really, really affect his life too much. He's just used to being itchy and uncomfortable*	*Trying to look for the miracle cure really*
[Steroids] we don't like to use them too much for too long they just thin the skin	*[At school] she has a space she can go where she can keep her cream, she's got a health plan*	*She just wants to be normal, she doesn't want to stand out in any way*	*But you would love to have the magic answer . . . that's why you just try anything. You're always searching for answers aren't you*
Time consuming doing all the creams and treatments and if she doesn't want to do them	*He lives with it, he just seems to get on with it . . . there are times when he's had to come home from school, sometimes he'll take a shower and go back in again*	*When he was scratching at his most he would be red, he would be bleeding, he would get frustrated, but it never stopped him doing anything . . . I think it's more down to our attitude because we didn't want him to stop doing things because he had this illness*	*At first we thought . . . brilliant, brilliant, we've got something, it's kind of what we've been looking for*
Hated being creamed . . . would run away			

They generally reported that care in the early years was excellent, but provision from Year 1 upwards was much more unpredictable; this provoked concern or even fear in some parents.

Quality of life

Eczema and the treatment required had a mixed impact on the quality of life of both children and their families. Every parent mentioned the scourge of itch and the disruption of sleep, with a few reporting that the whole family was disturbed by the child with eczema during the night. Listening to some parents, it was evident that they were struggling with their perceived inability to care for their child. They reported the challenges of applying topical medication regularly, in terms of both the child disliking application and the time taken to apply it. Several spoke of having tried 'everything' and conveyed their feelings of despair each time another treatment failed. Others appeared to feel this burden less and again this was not necessarily related to the described disease severity. Parents of children from the age of 5 years upwards talked about concerns regarding self-consciousness; some had deliberately encouraged their children to simply explain their condition to others and this had generally proved to be an effective strategy.

Hopes for the trial

Parents had a range of hopes for the trial. A few had very low expectations, but many had reached a point of desperation and were hoping for a 'miracle cure'.

Theme 2: fit, durability and care

Participants expressed a range of views on the garments encompassing the subthemes of (1) look, fit and feel, (2) durability and (3) laundry care. Many parents and children awaited the arrival of garments with a sense of optimistic anticipation. Positive comments on the aesthetics of the garments were not forthcoming. Some suggested that they would be more attractive to children if they were coloured or decorated; however, they understood the hazards of introducing dyes to the fabric (*Table 40*).

Look, fit and feel

Fit was an issue for many participants. On the whole, the garments fitted reasonably well for the youngest children. The exception to this was the styling of the neck, which was so loose on some that it slipped over their shoulders and gave easy access for scratching; some parents resorted to partially sewing up the neck seams. Garments for older children often bore no relation to their size or age range (despite actual height measurements being used to guide size selection); this was rectified by provision of alternative sizes by the trial team. There was marked uncertainty about how the garments should fit, although several parents commented that this information was provided. A snug fit was the preference for some, as this was viewed as an effective way to keep topical medications on the skin. Others favoured a looser fit on the assumption that this would make the garments cooler and more comfortable to wear.

'Soft' was a frequently used descriptor of the garments, although some parents were surprised by the texture as they had expected a feel more akin to normal silk. Parents who returned garments for replacement noticed that the texture of fabric was not consistent and, although some reported that softness was maintained over time, others suggested that the garments quite quickly became 'crispy' and 'rough'. A few reported that their children found the garments scratchy and that they had a tendency to stick to their skin.

Durability

The issue of durability was raised regularly, seemingly more so for younger children, particularly boys. Although a few parents reported that the garments had lasted for the full 6 months of the trial, more recounted signs of wear and tear occurring after only a few days. Specifically, the garments were prone to the fabric pulling away from the seams, laddering and developing holes in areas of persistent scratching. This was managed by either returning the garments for replacement or, by some, creative methods of repair including the removal of the feet of the garments and the concoction of new garments from parts of damaged ones.

TABLE 40 Views of parents: theme 2 – fit, durability and care

Look, fit and feel	Durability	Laundry care
[Daughter said] they're just horrible . . . ugh, they're just vile	*They started off really nice . . . might as well have been putting dish rags on him by the end of it, they had holes in them*	*Mine fell apart because I was washing them so much*
To be honest they are very clinical looking aren't they, they are very basic	*They start off like holes and they'd ladder round the edge almost*	*I couldn't get the stains out*
They weren't tight enough . . . they're a little bit baggy . . . in some places they were tight and in other places, the arms and that, were loose	*Fabric's just really . . . it just pulls apart . . . the material just disintegrates*	*[Three sets] . . . nowhere near enough, you're always washing*
The trousers won't stay up so that's why I had to do the top up under, to keep the trousers up	*I cut the feet out because of the holes, they used to get holes in the toes where he used to scratch*	*[He wore them] as often as I could . . . unless I got behind in washing . . . it was all the time basically*
He's quite a skinny, tall lad but yes, they fitted quite well	*They were getting trashed, you know, little boys outside*	*Three sets make sense but I could have done with a couple of extra . . . they get muddy or the odd explosive nappy*
Actually after 6 months they still felt as they did at the beginning . . . they were still soft	*They've been quite hard wearing*	*Three garments were fine, because he always had at least one fresh pair at any stage . . . they didn't deteriorate at all*
They didn't feel right . . . they felt twisted . . . felt really awkward	*They wore very, very quickly . . . and in the end we had holes in them and they were all pulled and grey*	*They went from white to grubby yellow-grey at the end of it*
He thought they were really comfortable	*. . . they have shrunk quite significantly . . . he'll wear his underpants over the top of it . . . because it doesn't stay up*	*I'd probably have three sets so I didn't have to do the washing every day*
She calls it her scratchy clothes	*. . . they are totally worn . . . I think they are very badly made . . . they just tore from the seams . . . we sewed them up and we did everything we could to the last set*	*[Washing] was a struggle . . . I would only want her to wear them like one set for the day and one set for the night . . . because she shed so much skin*
She didn't find them particularly comfortable . . . they stuck really badly to her skin . . . it was like putting on clothes when you are wet		*They are a funny sort of shape after washing . . . the tops go sort wide and the trousers were a bit shorter*
Because it was silk he could feel the coolness on his skin		

Laundry care

Parents adopted habits for washing the garments ranging from daily hand-washing using non-biological products to washing them every 2–3 days in a mixed family load. It appeared that washing was not a problem for parents who already laundered small loads separately, but it was burdensome to others and sometimes resulted in children missing wear for brief periods. The garments' quick drying time was universally commended. There were reports of shrinkage after washing and some reported gradual discolouration over time. Many parents found that three sets of garments was insufficient; this was predominantly, but not exclusively, the case among younger children and those wearing them both day and night.

Theme 3: perceived impact of the garments

As seen in theme 2, parents had differing views on the look, feel and fit of the garments and this, combined with their commitment to being in the trial (subtheme 2 of theme 4), influenced patterns of usage, which forms the first subtheme of theme 3. Subsequent subthemes are the effect of the garments and intentions regarding continued use post trial (*Table 41*).

TABLE 41 Views of parents: theme 3 – impact of the garments

Patterns of usage	Effect of the garments	Continued use post trial
He started asking for it 'cos I think they kept him quite cool	*We noticed a difference very quickly . . . within the first month . . . we don't know if that's why it's cleared up or are we consciously putting the cream on more often*	*So the silks have actually retired to the drawer now . . . they are getting a bit small and tight now I think I just need to throw away my love affair with them and forget about them, which is a shame*
. . . she wore them at school . . . [friends] just asked her what they was and she just told them	*It made an immediate impact . . . this is the first time in 8 years that we've had a full nights sleep from him and this has absolutely 100% broken it [itch–scratch cycle], do you know this is the thing I've been waiting for, it's brilliant . . . once we got the silk clothing, literally, it was like the light switched off*	*I wouldn't recommend the clothes to anyone based on my experience . . . very, very disappointed*
He was quite excited about [wearing the garments] we told him they were special clothes, his 'whites'	*A little bit better but not massively better*	*I've since bought them, I buy them now, because they do work for us*
. . . she didn't do very well wearing them . . . because it hurt so much to pull them off . . . in the night when she does her damage the most and claws at herself then by the morning it's stuck to the wounds she's made . . . I just thought I can't do this, it's not worth getting her stressed out trying to get the garment on	*I wouldn't say they medically helped her and made it better, they just make her more comfortable and more bearable with the itching and stuff*	*We were looking at buying it . . . the cost of it! So I thought I can afford to buy a couple of pairs . . . I asked them to prescribe a couple of pairs and they did*
She felt embarrassed because she said they were too see-through	*I think it has contributed but it didn't have an instant effect . . . it's hard to pinpoint one thing*	*Would you ever consider buying them . . . no, not worth the money, no . . . if I could get them on prescription I'd definitely have them*
She didn't actually like wearing them . . . she had just come out of hospital and she had wet wraps . . . because they were white she thought I was going to wet wrap her . . . she got a bit wary of them	*Well I think her skin improved, but I have to say that I couldn't say that was because of the silk, but I do think . . . I think it has helped . . . I can't 100% say that the clothing had definitely cured and fixed it, I think it has aided the whole process*	*If I had to pay . . . I probably wouldn't invest in them . . . if the doctor would prescribe them, then yes, I'd definitely have some*
	To be honest they made no difference at all to her eczema	*Yes, even if I had to pay for them I think I would in the long run, just for his comfort*
		I thought that was just too expensive . . . I would probably say I would not because of the cost

Patterns of usage

Patterns of usage varied enormously, from children wearing the garments virtually 24 hours per day throughout the trial, to the other extreme where one teenage girl could be persuaded to wear them for one night only. Parents reported differing thoughts from children about their family and friends seeing them in the garments; this appeared to be loosely related to developmental stage. Younger children quite enjoyed the attention of having something different, whereas older children preferred to wear them only at home, often covered with other clothing, partly because of their see-through nature. Most children wore the garments each night and a smaller proportion chose to wear them in the daytime. Garment usage is summarised in *Appendix 20*.

Effect of the garments

The reported effect of garments was wide ranging and not necessarily linked to frequency or consistency of wear. A minority stated that the garments had had a significant positive impact on skin condition. The most frequently cited benefits were comfort and coolness, sometimes leading to improved quality and quantity of sleep and providing an effective barrier to scratching. A few were very disappointed to find that the garments had no impact whatsoever.

Generally, those parents who reported improvements in their child's skin condition or quality of life found it difficult to assess whether or not this was wholly a result of garment usage. Parents often suggested that the garments were just one element of a complex mixture of influencing factors. Other reasons for improvement in the eczema were suggested as being the usual waxing and waning nature of eczema, seasonal change, holidays in the sun and greater concordance with other treatments prompted by weekly reporting for the trial.

Continued use of garments

Parents were generally equivocal about continued use of the garments after the trial. A minority stated that they already had or definitely intended to buy further garments; for some this was because of a tangible improvement in the skin condition, whereas for others it was predominantly for comfort. Several parents had investigated the cost of garments and found this prohibitive, particularly because they were so quickly damaged or outgrown. In some cases parents continued to use garments that had become very tatty and in need of repair or were too small to the absolute end of useful life. A few parents considered requesting the garments on prescription, but did not have high hopes of success; although one parent had managed to obtain a GP prescription.

Theme 4: engaging in the trial

Participants were forthcoming about their engagement with the trial. This theme comprises three subthemes: (1) experience of participation, (2) commitment to the trial and (3) important outcome measures (*Table 42*).

Experience of participation

Experiences of participation in the trial were almost universally positive. Parents were complimentary about the organisation of the process. In particular, they commented on the quality of information provided, the ease of communication with the trial team when required and the friendliness of the research nurses. The only minor negative was the need to return damaged or outgrown garments before new ones could be issued, sometimes leading to a break in wear for a day or two. All found the questionnaires and diaries quick and easy to complete, and appreciated the e-mail reminders. Several commented that the completion of the questionnaires had been useful in prompting more regular use of usual eczema treatments. Three issues were raised by a minority of parents. First, online questionnaires were available for only a finite time and this meant that they were occasionally missed. Second, in some cases the worst areas of eczema were on the hands and face, which were not covered by the clothing; parents suggested that this could lead to an unfairly negative evaluation. Third, parents thought that they were repeating themselves each week and that this may not be helpful. Older children sometimes completed information with parents and some parents were pleased to

TABLE 42 Views of parents: theme 4 – engaging in the trial

Experience of participation	Commitment	Important outcome measures
I think the way the trial was run is fantastic . . . it was always made very, very easy for us. The nurses were always so lovely with her	*I was incredibly compliant to the enth degree*	*How his general well-being is, within himself*
He loved getting the card . . . they made it special, a fun thing rather than a chore . . . he loved the fact that when we came here he couldn't tell the lady	*I busted a . . . because I thought if I'm doing this I'm doing it properly . . . I wanted it to be my magic cure*	*Well for me, it was just being avoiding having to use the steroid cream. That would be the ultimate goal*
It is good to be involved and learn whilst the research has actually been taking place . . . we have really been excited to have been part of that	*She was too embarrassed to wear them to school, so I didn't overstress her . . . I don't get into battles with her*	*A bit calmer and not be so itchy*
I was always glad of the reminder email . . . it was good, it wasn't too much . . . 5 minutes	*Well we sort of discussed it with him and said look, there is really no point in saying you are going to do the trial if you are not going to be prepared to wear it all the time . . . he was quite on board with that*	*One hope really was for his eczema to get better and reduce the reliance on the steroid creams . . . you don't want to keep putting toxic chemicals all over your child do you?*
We had to send them back [and were told] we can't send you some more until we've received the old ones back . . . and for us they were working so well I didn't want him not to have them	*The more we can invest in research, I think it's the better. And if I can help that, then that benefits everybody doesn't it?*	*Itching and flares*
It's easier to kind of forget about it . . . it only takes a few minutes . . . it's more about remembering to fill in the form	*I'm curious about this . . . I guess I'm quite scientifically minded so I wanted it to be a good result*	*How he looks*
Going to the appointments was fine. Obviously I was able to pick times and days what suited me so that was fine	*I just felt we were trying to make a difference so I didn't mind . . . I realised that in order to maybe get better results from the study you would need to talk to people and it is like only a few minutes out of my time*	

keep a personal copy of progress through the trial. Appointments were routinely made at convenient times and several parents were particularly grateful for home visits by the research nurses. Younger children were reported as having enjoyed being in the trial, particularly liking the sticker charts (see *Appendix 8*) and gifts. One boy objected to being undressed to be examined. Parents of older children reported that they were quite content to take part. Unsurprisingly, both parents and children allocated to the standard care group felt a great sense of disappointment on hearing their treatment allocation.

Commitment to the trial

Commitment to the trial revealed some insights into individual beliefs about levels of participation and about future recruitment, specifically to nested qualitative studies. All parents agreed that it was important to complete questionnaires and diaries. However, views on wearing the trial garments varied from wholehearted commitment to others who, not unreasonably, left the choice to their child. Parents who spoke of their engagement in the qualitative study reported that this opportunity was revealed right at the end of the study,

and that this may have been detrimental to recruitment as some parents may have considered that the trial had already finished for them. Telephone calls from the research nurses who already had a relationship with parents were by far the most effective method of recruiting to focus groups and interviews. Some parents who were willing to take part struggled with the time and location of the focus groups, despite the variety of times and places offered. Those who did participate offered two major reasons for this: (1) they tended either to feel a sense of duty to give something back having been involved in the study or (2) they had some knowledge or interest in research and could therefore see the value of their contribution.

Important outcome measures

Parents unexpectedly found it difficult to talk about outcome measures that were important to them. On discussion, the most important success factors identified were comfort, improved sleep and general well-being, and reduced itching. Reduced medication usage, specifically steroids, was important to a fair proportion of parents. A few parents mentioned appearance and even less reduction in flares or disease severity per se.

Overall, the 34 participants in these focus groups and interviews presented mixed views on the usefulness of the silk garments. Many had struggled for years to effectively care for their child's eczema and had tried an array of treatments, both prescribed and over the counter. Only a few had tried any type of garments. Most had very high hopes for the garments and were particularly enthusiastic about this non-pharmacological intervention. Patterns of wear varied enormously, as did views on the fit and durability of the garments. Many reported that the garments were of poor quality. Although a few parents reported unequivocal success in using the garments, many more were more circumspect about their impact, suggesting that they may have been helpful as part of a broader treatment regimen. In common with clinician and commissioners, parents had little knowledge about the silk garments and many were dubious about whether or not they represented value for money, particularly if they were purchased rather than prescribed.

Views of clinicians and commissioners

Data collection

Interviews with clinicians and commissioners in England were completed from June 2014 to January 2015. A purposive[76,77] sample of participants was recruited via advertisements on health professional and dermatology websites, and snowballing. This approach yielded a range of dermatology specialist and primary care generalist participants from across the country. Some had dual roles, for example GP and commissioner, so they have been categorised by their stated primary role, and included dermatology specialist nurses ($n = 9$), dermatologists ($n = 4$), GPs ($n = 3$), pharmacists ($n = 3$) and health-care commissioners ($n = 2$). All clinicians had a minimum of 5 years' experience of caring for people with eczema. Demographic information about the 21 participants is summarised in *Appendix 20* (see *Table 63*). Semistructured telephone interviews using an interview guide (see *Appendix 20*) were conducted by the researcher (FC) lasting from 9 to 24 minutes. Interviews were audio-recorded and transcribed verbatim.

Data analysis

Data were analysed using the five-stage Framework Analysis process, described in *Data analysis*, and the researcher's reflective account was used to inform the analysis process. Stages 1–3 of the framework are illustrated in detail in *Appendix 20* and stages 4 and 5 are documented below. The analysis process yielded four key themes: (1) knowledge base, (2) reasons to use silk garments, (3) reasons for not using silk garments and (4) outcome measures. A total of 14 subthemes were identified. A description and analysis of each theme is provided below, and this includes a tabulation of each theme and subtheme with exemplar data extracts.

Findings

Theme 1: knowledge base

The theme concerning knowledge base comprises three subthemes: (1) lack of evidence base, (2) information from manufacturers and (3) treatment protocols. Participants presented differing views on the level of evidence available and the quality of evidence they required prior to prescribing silk garments (*Table 43*).

Lack of evidence base

The majority agreed that there was a significant lack of high-quality evidence and reported that until this was produced they would not consider prescription of silk garments. There was universal agreement on the need for the CLOTHES RCT, and many participants indicated that the outcome of this trial and of subsequent studies would influence their future practice. Participants noted that many treatments currently used are underpinned by very limited research evidence, citing the example of wet wraps, which are commonly used in childhood eczema. It was noted that lack of empirical evidence does not mean that a treatment does not work.

Information from manufacturers

A very limited number of participants were aware that more than one brand of silk garments is available, and most had received information from only one company representative; several could name individual representatives, but were hazy in their recollection of the product name. Views on the value of manufacturer information varied. Several participants stated that it was limited and potentially biased and that they largely discounted it; some suggested that, as this was virtually all that was available, it should be considered. Others took a more pragmatic view and were willing to base their treatment decision on this imperfect information combined with clinical need and personal experience.

Treatment protocols and guidelines

Treatment protocols and guidelines were raised predominantly by commissioners and GPs, some of whom stated that there were clear protocols in their local area. However, it was evident that the existence of such guidance was patchy, which led to a 'postcode lottery' on prescribing practice. The majority of participants implied the need for robust protocols that provide clear information about when and in what circumstances silk garments should be prescribed. Clarity about who should prescribe and in what quantity was also considered essential to ensure equity of provision. On the whole, participants favoured silk garments being part of a clear ladder of treatment and something to be used when other treatment options had been exhausted. This subtheme is allied to the first subtheme of theme 2 (failure of other treatment regimens); however, this subtheme refers to population-wide protocols, whereas failure of other treatment regimens applies more to decision-making in relation to individual patients.

TABLE 43 Views of clinicians and commissioners: theme 1 – knowledge base

Lack of evidence base	Information from manufacturers	Treatment protocols
There isn't actually much evidence out there	*I had contact with a rep[resentative] some while ago and was given some leaflets*	*There is a description of an appropriate place in treatment*
There's not enough big studies . . . to convince prescribers	*I've got some of the manufacturers' product information*	*A lot of CCGs [Clinical Commissioning Groups] will have issued guidance on the prescribing of silk products*
But because there isn't any evidence doesn't mean that something doesn't work	*Rep[resentative]s have visited and given us evidence*	*We would expect them to go through all the NHS treatments first*
I'm not keen until research evidence has been proven	*You don't just take the rep[resentative]'s word for it*	

Theme 2: reasons to use silk garments

Participants cited a number of reasons that silk garments may be used as a treatment option, and this theme comprises four subthemes: (1) failure of other treatment regimens, (2) greater concordance, (3) avoiding referral to secondary care and (4) cost-effectiveness. Around one-third of participants had prescribed, or recommended prescription of, silk garments in practice, but none claimed to be an expert in the use of these products or prescribed them on a regular basis (*Table 44*).

Failure of other treatment regimens

All participants agreed that silk garments were not a first-line treatment, but rather that they were considered to be a 'last resort' for children who had already used emollients, topical steroids and sometimes also specialist cotton clothing and wet wrapping.

Greater concordance

Participants highlighted the challenges of treatment adherence with traditional eczema regimens. Several mentioned the acceptability and ease of use of silk, and proposed that this may lead to greater concordance with treatment plans.

Avoiding referral to secondary care

Participants, particularly nurses, suggested that, based on their clinical experience, silk garments had a value for children who were 'hot', 'miserable' and 'itchy' with their eczema, and that these symptoms were more likely than an objective measure of eczema severity to lead them to prescribe silk garments. An alternative reason for prescription, more commonly mentioned by GPs, was avoidance of costly referral to secondary care.

TABLE 44 Views of clinicians and commissioners: theme 2 – reasons to use silk garments

Failure of other treatment regimens	Greater concordance	Avoiding referral to secondary care	Cost-effectiveness
It's not a first-line treatment	*If they were motivated because they liked something . . . then I would certainly carry on recommending it*	*If I saw a person was struggling . . . even to the point of considering secondary care referral . . . I'd probably feel confident in considering that prescription*	*It might potentially be a cost-effective option . . . don't say cheaper*
At the moment silk would be the last option	*The goal of eczema treatments to give patient as much control as possible*	*I mean . . . it costs enough to refer them (to secondary care)*	*When they use the silk garments they need less steroid creams and obviously emollients*
Once we've exhausted the usual treatments of emollients and topical steroids	*It certainly gets rid of the wet wrap business*	*The most attractive place to use it is an alternative to secondary care referral*	*We are sometimes short-sighted in the way we look at costs . . . we should look at overall costs*
It's like a last resort	*Compliance is obviously the biggy isn't it . . . we do have some patients with cupboards full of stuff that hasn't been used*		*. . . they don't need as many visits . . .*
I tend to reserve it for the most severe cases			*It's a cost saving in the long run*
More likely to prescribe if I can say we have tried this and it didn't work			

Cost-effectiveness

Some were able to quote the cost of both silk garments and secondary care referral, and considered that the choice of silk garments may be more cost-effective. In these cases cost alone was the dominant feature of decision-making. The price of silk garments was raised on many occasions. Some participants took a literal view of cost per item and this is discussed in more detail in the second subtheme of theme 3. In this subtheme participants took a far broader view. They acknowledged that the silk garments were 'expensive', but when set within a context of potential reduction in use of topical medication, alternative clothing, wet wraps and medical consultations, participants proposed that they could be a cost-effective option. In this group, participants also took into account the impact that these products may have on the health and well-being of both the child with eczema and his or her family.

Theme 3: reasons for not using silk garments

As seen in theme 2, many practitioners suggested that there was a place for silk garments in the armoury of childhood eczema care, but equally they were cautious and balanced this view with a number of reasons why these products should not be used at present. Theme 3 was generated from the following subthemes: (1) lack of familiarity or experience, (2) cost, (3) contentious prescription and (4) quality of product (*Table 45*).

Lack of familiarity or experience

All participants stated that they were not particularly familiar with silk garments and none prescribed them regularly. Some GPs believed that they would never have sufficient expertise or confidence to prescribe them, but a small number suggested that nurses, either dermatology specialist nurses or practice nurses, would be better placed to be experts in practice.

TABLE 45 Views of clinicians and commissioners: theme 3 – reasons for not using silk garments

Lack of familiarity/ experience	Cost	Contentious prescription	Quality of product
We haven't used them a lot . . . so we haven't got a lot of experience	*We don't want to see a sort of explosion [of prescriptions] . . . because that's to no-ones benefit*	*Well there's absolutely no doubt, this is a primary care prescribing thing*	*Within a couple of washes very dirty, look grey and have gone very baggy*
As a GP many of us would struggle to have the time and the expertise	*I mean it's not that massive . . . it would be a manageable cost*	*More for secondary care I feel to prescribe it*	*Rep[resentative] says 'oh they'll wash for about a year' . . . their knees get very thin and sometimes they only last about half of that time*
I would never prescribe them by myself	*It would worry me . . . we're going to get inundated wanting all these little garments*	*Should be initiated by dermatology clinics and then obviously continued by GPs*	*They rip very easily*
	The problem with GPs initiating this is that you get creep prescribing . . . it escalates	*Patients should be clinically assessed . . . and then it's down to accountability and clinical confidence*	*Impractical in terms of current construction and surprisingly undesirable for teenage . . . patients*
	Very good idea but practically rather expensive	*Some GPs will and some GPs won't [prescribe]*	*They get discoloured [parents] didn't like the look of them*
	My fear would be that I prescribed some very expensive item and they	*There has to be some regulation here because pushy parents are going to get what they want*	

Cost

Silk garments were generally perceived as an expensive treatment option. The estimates of cost per set of top and leggings varied from around £40 to £100. The assumed cost of the garments, together with lack of familiarity, led to robust beliefs about responsibility for prescription.

Contentious prescription

There was a balance of views that prescriptions should be either from primary or secondary care, or be initiated in secondary care and continued by GPs. There was uncertainty from some participants about whether or not they were 'allowed' to prescribe these garments. Discussion of nurse prescribing was scant, and nurse participants generally reported that they advised medical colleagues to prescribe rather than undertaking the process themselves. Views on who should prescribe did not necessarily correlate with the participant's job role; so, for example, not all GPs suggested that secondary care should prescribe and vice versa. A minority of participants suggested that the key factor in successful prescription was competent and thorough clinical assessment, preferably by a clinician who provides the most dermatology care for the patient. Commissioner and GP participants had concerns that if GPs began to prescribe silk garments this may open the floodgates to a widespread, costly and ineffective prescribing practice.

In practice, most prescriptions involved secondary care providers writing to GPs recommending silk garments; however, such requests were fairly regularly rejected on personal and unpredictable whim, rather than a clear clinical reason. Concerns were expressed that this could lead to treatment inequity, as 'pushy', 'middle-class' parents were more likely to persist with requests until they were met, whereas less affluent and less vocal parents were likely to give up.

Quality of product

The few participants who were relatively familiar with silk garments commented that there were quality issues, particularly considering the expense. They suggested that the garments did not wear well and that they looked unattractive and 'grubby' after several washes. A few participants reported that they were not acceptable to patients, particularly older children, and that if not used would lead to valuable resources being wasted; clearly, this argument could be applied to any treatment.

Theme 4: outcome measures

Participants acknowledged the need to measure outcomes of all treatments; however, the value they placed on different measures was notable. Theme 4 comprises three subthemes: (1) existing measures, (2) clinical improvement and (3) patient/parent reports (*Table 46*).

Existing measures

Participants generally talked in the abstract about what they considered to be best practice in measuring outcomes. None used an objective measure of disease severity, although one participant suggested that the use of EASI[31] would be useful. Others raised the importance of patient/parent-based symptom or experience measures. Specifically, they advocated POEM[34] and the Dermatology Life Quality Index (including child and family measures). No participants had used POEM with this patient group and a very small number had used formal quality-of-life measures. A few participants alluded to the need for measures but were not familiar with those already available.

Clinical improvement

Subjective measures of practitioner-assessed clinical improvement were much more commonly suggested. The constituents of clinical improvement included the child being more 'settled' and 'comfortable', and specifically less 'hot', and experiencing improved sleep and a reduction in itching, scratching and episodes of infection. A reduction in the use of topical medication was also used as a measure of effective treatment. Several participants suggested that parent and patient reports of improvement were every bit as valuable as clinicians' views, and some stated that these alone would be sufficient for them to advise the continued use of silk clothing. The impact on family as well as children was particularly highlighted by nurse participants.

TABLE 46 Views of clinicians and commissioners: theme 4 – outcome measures

Existing measures	Clinical improvement	Patient/parent reports
I assess . . . using a child or infant DLQI	*Clinical improvement . . . a little bit hard to quantify*	*What the parent or child thinks . . . a description of severity*
Eczema severity . . . we can do some kind of scoring tool	*It's clinical judgement . . . you'd be assessing social factors as well*	*In reality on the ground I would just say how have they improved? Mums and dads know pretty promptly whether it has*
I suppose initially we would carry out an EASI score and a DLQI, that's kind of like a measurable thing . . . we'd probably reassess every 3–4 months	*Reduction in use of other treatments such as emollients and steroids*	*I would probably go by what the parents say*
POEM . . . It's easier to understand	*Amount of flare ups they're having*	*If the parent thinks it's helping I'm okay with that*
POEM is nice because you can share it with the patient	*Are they sleeping better, are they feeling more comfortable, are they less itchy, scratching less*	*All the ones that had used them have had very positive results*
You want two measures . . . quality of life and severity of the eczema . . . there must be some sort of graded . . .	*The child is more relaxed because they're sleeping and they're not scratching all the time*	*Certainly the ones who've used them regularly do find them beneficial*
	Much more settled, that there's not as many flares, that it's not got infected	*The parents said they thought they had helped*
	How much distress the family suffers . . . you can't necessarily gauge that by looking at the skin	

DLQI, Dermatology Life Quality Index.

Patient/parent reports

The few participants who had prescribed silk garments reported positive, but not overwhelming, feedback from parents. They reported that children found the garments 'cooling' and that they did not adhere to the skin and could be used even in the presence of infection.

Overall, the 21 participants in this study had limited experience in the use of silk garments for childhood eczema, and anecdotally this is a fairly typical picture across the country. It was stated that there is a dearth of evidence about the effectiveness of these garments, a position that participants were keen to see rectified through the CLOTHES trial and subsequent studies. On the whole, silk garments were perceived as expensive, although when put into a wider context many participants suggested that they may provide value for money. The prescribing of silk garments was contentious, with participants holding firm beliefs about whether this should be the responsibility of primary or secondary care. There was consensus that use of these products should be monitored and evaluated, although there was little agreement on the preferred outcome measures to be used.

Conclusion

In this nested qualitative study children and parent participants have provided insights that correlate closely with the quantitative results in that there was some limited improvement in eczema for some children, but the hoped-for 'miracle cure' did not transpire. On the whole, clinicians and commissioners had limited

knowledge and experience and were reluctant to prescribe garments that they perceived as costly and lacking in robust evidence of effectiveness. Collectively, the qualitative component of the CLOTHES trial illustrates a very mixed picture of knowledge, beliefs and experiences of using the silk garments.

Limitations

There are two limitations to this nested study. First, participants were essentially self-selecting and may therefore not be representative of the trial cohort. Second, the recruitment of children from recruitment centres in prescribed age bands was difficult and we would have preferred to recruit more children. We considered recruiting to wider age bands for the focus groups, but made the decision not to do this as it would have compromised the value of using age-appropriate activities to enable children to convey their thoughts and feelings.

Key learning points

Implications for interpretation of trial results

- Children's responses were particularly helpful in providing additional detail on possible reasons for non-adherence in wearing the garments.
- Parents and children portrayed mixed views on the garments. Few, if any, reported the longed-for 'miracle cure' and there was a significant sense of disappointment in relation to effectiveness and the quality, fit and durability of garments.
- Some parents found the weekly questionnaires useful in prompting more regular use of their child's usual eczema care.
- Clinicians and commissioners were generally equivocal about the use of silk garments. Most wanted a robust evidence base to inform treatment decisions and were eager to see the results of the CLOTHES trial.
- Results of the qualitative studies were in line with the quantitative trial data, suggesting that important differences between the groups had not been missed.

Added value of qualitative studies within trials

- The added value of the qualitative work is that it has provided a deeper, richer and more detailed understanding of the 'what', 'why' and 'how come' underpinning participant's beliefs and behaviours. It has uncovered understandings, which help to inform interpretation of the results of the study.
- Parents who participated were universally positive about having an opportunity to talk with a researcher who was interested in their child's condition, but, perhaps more importantly, focus group participants relished meeting other parents in the same situation.
- Likewise, children wanted to talk with the researcher and were very able to express their views with clarity, given age-appropriate means of communication.

Lessons for conduct of nested qualitative studies

- Recruitment to qualitative studies nested within RCTs can be challenging. Research nurses who had personal contact with participants were crucial to successful recruitment. Participants in some centres were geographically widespread and the ages of children completing the trial at a time suitable for involvement in the focus groups meant that many participants were unable to take part.
- Early awareness of the forthcoming focus groups may help to boost recruitment.
- Child data added a valuable dimension to our understanding of childhood eczema and the use of silk garments. However, these were time-consuming to collect as there was a need for pre- and post 'playtime'. Recruitment was particularly challenging, as the groups were age banded to ensure the appropriateness of data collection methods.

Chapter 6 Involvement of patients and the public

Public and patient involvement (PPI) in research has been strongly encouraged for many years,[82] but, until recently, the evaluation of PPI activities and the impact that they may have on the design, conduct and delivery of clinical trials has been limited.[83–85]

In this chapter, we aim to summarise the breadth and depth of PPI involvement that has taken place throughout the lifetime of the CLOTHES trial, and to share our experiences in documenting the likely impact of this activity.

Aims

1. To evaluate the impact of PPI on the design, conduct and dissemination of the NIHR HTA-funded CLOTHES trial.
2. To add to the literature on PPI and its potential impact on research.

Methods

This report synthesises various strands of activity that have taken place over a period of many years, spanning October 2009 until now. Diverse methodologies have been employed according to the stage of the research and the types of PPI input required. In line with INVOLVE guidance,[82] specific ethical approval was not required for the majority of the described engagement activities.

Throughout the study, we adopted the eight core principles framework identified by Telford *et al.*,[86] as outlined in *Table 47*. Documentation of impacts throughout the stages of the research from prioritisation of the topic through to dissemination of the findings has been presented using the framework proposed by the Public Involvement Impact Assessment Framework Study Group[87] and reported according to the Guidance for Reporting Involvement of Patients and Public guidelines.[85]

For the purposes of this report, we define PPI as being inclusive of all relevant stakeholders and users of the research. As well as focusing primarily on involvement of patients, their carers and the general public, we also include examples of involvement with other key stakeholders including health-care professionals, commissioners, providers of health information, guideline writers and researchers.

Patient and public information activities were logged on an ongoing basis throughout the trial using a dedicated PPI log that all members of the trial team had access to.

Results

Contextual factors relating to patient and public information involvement

Many factors contributed to ensuring strong PPI in the CLOTHES trial.

Funding body

The CLOTHES trial was funded by the NIHR HTA programme. This public funding body was one of the first in the world to recognise the importance of PPI, both at an organisation level (with PPI members on funding panels and PPI reviewers) and through the research projects that it funds. This strong endorsement by the funding bodies meant that PPI was embedded within the prioritisation process in identifying the topic area for research, encouraged the involvement of a patient representative as a co-applicant on the grant, and allowed the inclusion of costs and time to facilitate PPI input.

TABLE 47 Summary of core principles for PPI involvement in the CLOTHES trial[86]

Core principles	How evidenced in CLOTHES trial
Principle 1: the roles of the consumers are agreed between the researchers and the consumers involved in the research	The role of the PPI representatives was documented in the funding application, protocol and final report
Principle 2: researchers budget appropriately for the costs of the consumer involvement in research	PPI costs were included in the budget (0.6–1.6% of total budget) and PPI representatives were reimbursed for their travel and child care (and in some instances, their time)
Principle 3: researchers respect the differing skills, knowledge and experience of consumers	Contribution of PPI representatives' skills, knowledge and experience has been included in research reports and papers
Principle 4: consumers are offered training and personal support to enable them to be involved in research	Support and training in research methodology and understanding of key terminology was provided by the Centre of Evidence-Based Dermatology's Patient Panel, and by a dedicated member of staff who is responsible for co-ordination of PPI and engagement activities within the research group
Principle 5: researchers ensure that they have the necessary skills to involve consumers in the research process	Researchers involved in the design and conduct of the CLOTHES trial attended the Centre of Evidence-Based Dermatology's Patient Panel training events and were encouraged to attend conferences and workshops addressing the importance of PPI involvement in research
Principle 6: consumers are involved in decisions about how participants are both recruited and kept informed about the progress of the research	PPI representatives involved in meetings to discuss trial design and conduct and were involved in amending paperwork in response to potential difficulties with recruitment. PPI representatives were involved in writing and communicating updates about the trial and helping with trial updates via social media and websites
Principle 7: consumer involvement is described in research reports	PPI contribution and analysis of its impact included in the final report and written up as a separate paper
Principle 8: research findings are available to consumers, in formats and in language that they can easily understand	Trial disseminated widely with the help of PPI representatives, including lay summaries, contributions to patient support group newsletters, social media, websites and podcasts

Research group

The trial was developed by a research group with a strong track record of conducting AE research (thus allowing ready access to patient partners and relevant networks, to facilitate speedy engagement with users). This group had organisational structures in place prior to starting the CLOTHES trial, including an established patient panel whose members receive training and support through face-to-face workshops, newsletters and attendance at relevant training courses/conferences. The panel is supported by a dedicated member of staff (PPI manager) who maintains regular newsletter communication with members of the panel and signposts members to upcoming projects requiring PPI input.

Sponsor organisation

The School of Medicine at the University of Nottingham places strategic importance on the involvement of patients and the public in both teaching and research activities across the school. It funds a PPI co-ordinator post to support researchers in developing PPI initiatives and runs regular training workshops to ensure that researchers have the necessary skills to engage effectively with PPI partners.

Patient support groups

The research team had strong pre-existing links with two active patient support groups (National Eczema Society and the Nottingham Support Group for Carers of Children with Eczema). Both support groups were very familiar with our research activity, had participated in the James Lind Alliance Eczema Priority Setting Partnership[6] and were keen to support the trial.

Stages of research and opportunities for patient and public information impact

A summary of the stages of research that provided opportunities for PPI engagement are summarised in *Table 48*, along with details of the PPI activities and their impact.

Research agenda setting

The CLOTHES trial was developed in response to a commissioned call by the NIHR HTA. This pre-dated our formal James Lind Alliance Priority Setting Partnership, in which patients and health-care professionals identified the most important areas of treatment uncertainty.[6] Nevertheless, results of the Priority Setting Partnership confirmed patients' strong interest in non-pharmacological interventions for the treatment of AE.

TABLE 48 Summary of PPI methods used and likely impacts (framework adapted from Public Involvement Impact Assessment Framework Study Group recommendations)[88]

Stage of the research	Methods used in CLOTHES trial	Measures of impact
Research agenda setting	• James Lind Alliance Priority Setting Partnership for eczema,[6] which included PPI representation on the steering group, identified non-pharmacological interventions as an important area of interest for patients • Trial discussed by the UK Dermatology Clinical Trials Network's prioritisation group and presented at the Steering Group meeting in October 2009 – provided feedback from patients and other health-care professionals involved in delivering AE care	• Prioritised trial confirmed to be an important topic and one that both patients and health-care professionals would like to see addressed • Informed choice of comparators, the need for feasibility work and consideration of implementation issues
Research design and delivery	• Patient representative co-applicant and member of Trial Management Group (mother of two children with severe AE, previous participant in an AE trial, member of the CEBD patient panel). Contributed to meetings during design phase of the trial (both before and after funding) • Patient online survey ($n = 475$) to gather patients' views on issues relevant to the design and conduct of the CLOTHES trial (see *Table 47* for details). Survey designed with input from patient partners • HOME initiative developing a core outcome set for AE trials. Patients are active partners in the HOME initiative and provide vital insight into the face validity of chosen outcome instruments • Workshop discussion group at CEBD patient panel event to discuss how to encourage patients to participate in the trial, choice of comparator, the needs for specific washing instructions and barriers to adherence • Engagement with patients support groups (National Eczema Society and Nottingham Support Group for Carers of Children with Eczema) to support awareness of the trial (through websites and social media) and help with distribution of online survey • Members of CEBD patient panel provided advice in developing appropriate washing guidance that would be acceptable to participants	PPI input informed multiple trial design decisions including: • Choice of comparator (no clothing, cotton clothing or other 'placebo' garment) • Eligibility criteria (use of wet-wrap dressings in the previous month, concurrent use of other specialist clothing) • Understanding likely adherence in wearing the garments. This informed our stopping rules and analysis plan for reporting adherence • Barriers to participation, particularly the need to provide garments to all participants after 6 months in order to limit differential drop-out in the control group • Choice of outcome measures (selected HOME-approved core outcomes) • The need for clear washing instructions that were not too onerous for families to implement

continued

TABLE 48 Summary of PPI methods used and likely impacts (framework adapted from Public Involvement Impact Assessment Framework Study Group recommendations)[88] (*continued*)

Stage of the research	Methods used in CLOTHES trial	Measures of impact
Ethics and oversight	• Patient co-applicant and members of the CEBD patient panel helped to produce and comment on patient-facing materials, especially the information sheets and online questionnaires • PPI member of the Trial Steering Group provided patient-focused oversight of the trial and facilitated links with the National Eczema Society and the HOME initiative (both of which this PPI member is an active member of)	• Resulted in amendments to wording and introduction of more detailed information on what participants would be required to do when participating in the trial. For the online questionnaires, PPI members recommended improved signposting throughout the questionnaire and amended the wording • Ethics committee feedback on the trial was that the team were to be commended for the quality of the patient information leaflets provided • Patients' views were voiced during Trial Steering Group meetings and was particularly helpful when we experienced supply problems with one of the brands of garments
Recruitment	• PPI members contributed to media broadcasts about the trial to boost recruitment: PPI co-applicant (and her son) agreed to be interviewed for BBC local TV news, Nottingham Evening Post and BBC local radio. Another patient (and parent) agreed to be interviewed for ITV local news, and a parent was interviewed on local radio in Cambridge • Feedback from some trial participants suggested that those children allocated to the control group felt extremely disappointed. We worked with our PPI members and the Medicines for Children Research Network, to redesign some of our participant information sheets, retrained our research nurses to ensure that they explained fully the importance of the control groups during the recruitment process and introduced a 'welcome' pack for all children, which reinforced the importance of all participants in the trial, regardless of group allocation	• Resulted in a considerable boost to recruitment, which ensured that the CLOTHES trial was ahead of its recruitment targets throughout the trial, and was delivered on time and budget • Videos and podcasts also used on the trial website and continued to provide awareness of the trial[89] • Feedback from participants was that the children appreciated the 'welcome packs' and felt less upset about being allocated to the control group • Parents were able to communicate the importance of the 'control group' in language that both they and their children could understand • **Children of our PPI co-applicant were unable to take part in the trial because of a conflict of interest** Reflections from PPI partner: *It was disappointing for my son, who wanted to be part of the trial after helping to raise the profile of the trial through a TV report and newspaper article. However the training provided to the PPI partner in previous years had explained the issues around 'conflict of interest'. The research team managed this sensitively by sending a written letter of appreciation with a voucher and framed picture from a local newspaper article*
Data collection	• PPI members commented on the data collection tools (especially the online questionnaires) to ensure that they were easy to use and not confusing for participants	• Completion of the weekly questionnaires was excellent – 85% of participants completed ≥ 12 of the weekly questionnaires over the trial period
Data analysis and interpretation of results	• Patients have contributed to our understanding of the minimum clinically important difference in the EASI and POEM scores through patient involvement in the HOME initiative • Two PPI members attended the results reveal meeting, where interpretation of the trial results was discussed. Their input was vital in helping to understand how best to present the results to the general public	• Understanding what is considered to be clinically important improvements in the EASI and POEM scales was vital to the overall interpretation of the trial results. This was particularly important for the CLOTHES trial, where a statistically significant, but small, between-group difference was observed in the secondary outcome (POEM) –this was not felt to be clinically meaningful for patients

TABLE 48 Summary of PPI methods used and likely impacts (framework adapted from Public Involvement Impact Assessment Framework Study Group recommendations)[88] (*continued*)

Stage of the research	Methods used in CLOTHES trial	Measures of impact
	• Nested qualitative study involving 34 parents of children taking part in the trial, 17 children and 20 health-care professionals and commissioners. This qualitative study provided vital information to help in interpreting the trial results and planning for dissemination and implementation of the trial findings	• The nested qualitative study provided greater insight into the expectations of trial participants prior to entering the trial (which informed our interpretation of the results – especially in relation to subjective patient-reported outcomes that were more likely to be susceptible to expectation bias) • Interviews with health-care professionals and commissioners enabled us to prepare documents that would address their needs and be more likely to inform clinical decisions
Writing up	• PPI members contributed to trial write-up of the main report (including the *Plain English summary*), academic publications, news items, tweets and podcasts	• Patient-facing materials were created in a variety of engaging formats
Dissemination	• PPI members used their existing networks and social media channels to help in disseminating the trial results • Contact details of trial participants who were willing to talk to the media in each of our five recruiting regions were prepared in advance, ready for speedy uptake once results were released	• We were in a position of readiness to engage with media interviews and able to develop a patient-friendly video to convey the results • Engaging through existing networks (patient support group, professional networks and links with guideline writers and patient information resources) meant that the results were rapidly disseminated and taken up • Ongoing engagement with commissioning groups during the trial meant that many were waiting the results of the CLOTHES trial prior to making prescribing recommendations
Time and cost	• PPI costs were included in the CLOTHES budget (0.6% of total award, 1.6% including costs of nested qualitative study) • Procedures for claiming expenses were in place to ensure timely payment. In addition, non-pay gifts were sent to PPI partners in recognition of their input at Christmas and for special birthdays or milestones in the project • Existing infrastructure was utilised to support PPI members and provide training – this meant that it was easier (and less time-consuming) to engage effectively with our PPI partners. It also meant that we were able to access a range of experienced PPI partners quickly if timely responses were required or there was a need for multiple perspectives • Our PPI co-applicant was paid for time spent working on the trial, and had travel and child care costs reimbursed. All other PPI contributors received travel expenses and costs of printing where applicable, but did not receive recompense for time spent contributing to the project	• Having a dedicated patient panel and PPI manager to support many research projects was a big advantage for the CLOTHES trial and made PPI engagement easier for the trial team (who had less experience of managing PPI contributions). It also meant that PPI input was available in a timely manner, thus minimising delays in the research timelines • **Although money had been allocated within the budget to recompense our PPI co-applicant for her time on the project, she was very reluctant to accept the payment and felt uncomfortable in doing so** • **Payments made in this way are subject to tax and it is the responsibility of the PPI partner to submit relevant tax returns**

BBC, British Broadcasting Corporation; CEBD, Centre for Evidence Based Dermatology; HOME, Harmonising Outcome Measures for Eczema; ITV, Independent Television; TV, television.
Bold text denotes potentially negative impacts.

Trial design

In order to inform trial design from an early stage (pre-funding), we conducted an online patient survey (Survey Monkey™, SurveyMonkey, Palo Alto, CA, USA) that was designed with the assistance of PPI members of our patient panel. The survey consisted of 25 questions, took approximately 10–15 minutes to complete and was open from January to April 2012. Links to the survey were distributed via the National Eczema Society and the Nottingham Support Group for Carers of Children with Eczema [which has a Twitter (Twitter, Inc., San Francisco, CA, USA) following of 5600] to patient participants of the James Lind Alliance Priority Setting Partnership, to AE patients who had taken part in previous AE trials conducted at the Centre of Evidence Based Dermatology, and through social media and other personal and professional networks.

Participants were asked to complete the survey if they were a parent of a child with AE. A total of 475 parents completed the survey [296 (62%) completed all 25 questions]. All responders were included in the analysis regardless of completeness of individual questions.

The survey confirmed that having AE influenced parental choice of clothing for their children (69% quite a lot, 26% a little and 5% not at all) and 293 out of 454 (65%) participants said that they had bought special clothing because of their child's AE. Factors parents considered important when choosing clothing to be used next to the skin were natural fibres (85%), avoidance of wool or scratchy fabrics (79%), softness (56%), cost (43%), fit (42%) and ease of washing (41%).

Specific issues relating to trial design and the impact of PPI input are summarised in *Table 49*.

Trial delivery and recruitment

Following publication of a press release announcing the start of recruitment into the CLOTHES trial, the trial team received considerable interest from media outlets including television, radio, newspapers and magazines. Having access to PPI partners who were willing to give interviews about the impact that AE has on their lives ensured that the news stories were widely distributed and engaging. In total, three parents, two children with AE and a representative from the National Eczema Society gave media interviews (*Figure 24*).

As a result of this media coverage, the trial team received 492 expressions of interest from potential participants in the space of 3 months. This resulted in a surge in recruitment at the start of the trial and meant that the trial was consistently ahead of recruitment targets throughout the study (*Figure 25*).

Interpretation of results

The nested qualitative study involving health-care commissioners, health-care providers and participants of the trial was extremely useful in providing additional contextual information to aid interpretation of the trial result, in guiding how best to disseminate the trial results to ensure speedy uptake and in helping to understand potential barriers to the use of silk clothing in children with eczema (see *Chapter 5*).

Reflections from our patient and public involvement partners

> *As a member of the CEBD [Centre for Evidence Based Dermatology] panel I was part of the initial priority-setting research which led to this trial and have felt privileged to be given the opportunity to play such an active role in this research, which is close to my heart.*
>
> *Early mainstream media interest in this trial has made me to feel more involved than I may have had in other projects, making it a pleasant and rewarding experience. Throughout the research process I feel my contribution has been valued and treated with professionalism and the team have made a conscious decision to drive inclusive behaviours through the use of 'simple' plain English versus technical jargon.*
>
> *Amina (PPI co-applicant)*

TABLE 49 Design issues informed by PPI input

Design issue	Why decision required PPI input	PPI feedback	Design decision
Eligibility criteria			
Should age of participants be limited to children aged ≤ 5 years?	• AE is most common in children aged ≤ 5 years • Possibly easier to ensure adherence in wearing the trial garments in younger children • Less influenced by peer pressure (as pre-school) • Fewer sizes of garments needed (so logistically easier)	48% of children who expressed an interest in taking part in a trial of specialist clothing were aged > 6 years (35% were aged 6–11 years and 13% aged 12–16 years)	Eligibility criteria were broadened to include all children up to the age of 15 years in order to be as inclusive and generalisable as possible
Should patients who routinely use wet wraps be excluded?	• Patients who use wet wraps frequently would not be able to benefit from the intervention clothing (as the skin would not come into contact with the clothing) • Occasional use of wet wraps may be possible within a pragmatic trial, but unclear what 'cut-off' to use in defining 'regular users of wet wraps'	Of those currently using wet wraps ($n = 89$), 46% used wet wraps < 10 times in the previous 6 months, but 38% used them > 30 times in the last 6 months	Exclusion criteria were defined to exclude participants who used wet wraps very frequently (≥ 5 times in the previous month) – equivalent to 30 times in the last 6 months
Definition of intervention			
How should clothing be prescribed for use (wear 24 hours per day, night-time only, or as preferred)?	• Needed to ensure sufficient exposure to the intervention in order to test its efficacy • Wanted to reflect what might happen in normal practice (pragmatic trial)	Of 269 responders, 52% said their child would be willing to wear the clothing only at night, while 46% said that their child was willing to wear the clothing day and night; 19% would wear the clothing during the day, but not during PE/games lessons	Children were asked to wear the clothing as often as possible, and as a minimum every night
Trial design: impact on trial delivery			
Should participants allocated to standard care receive silk clothing after the randomised allocation follow-up is complete?	• Concerned that high expectation around the use of silk clothing would result in differential loss to follow-up in the standard care group	Of 298 responses, only 59% said they would still be willing to take part if they were allocated to standard care	Trial design amended to allow participants allocated to standard care group to receive the silk clothing after 6-month primary outcome assessment was complete
Trial analysis			
How much would parents be willing to pay for specialist clothing?	• Useful information to inform health economic analysis and interpretation of trial results	• 361/422 (86%) of responders were willing to pay only £20 or less for special clothing • 10% would use the clothing only if it was provided free of charge on prescription	• Therapeutic silk garments typically cost £60–75 per set, depending on size and type • Willingness to pay used to inform interpretation of results

PE, physical education.

FIGURE 24 Patient and public involvement co-applicant Amina being interviewed with her son Tahmid about the trial for BBC local news. BBC, British Broadcasting Corporation.

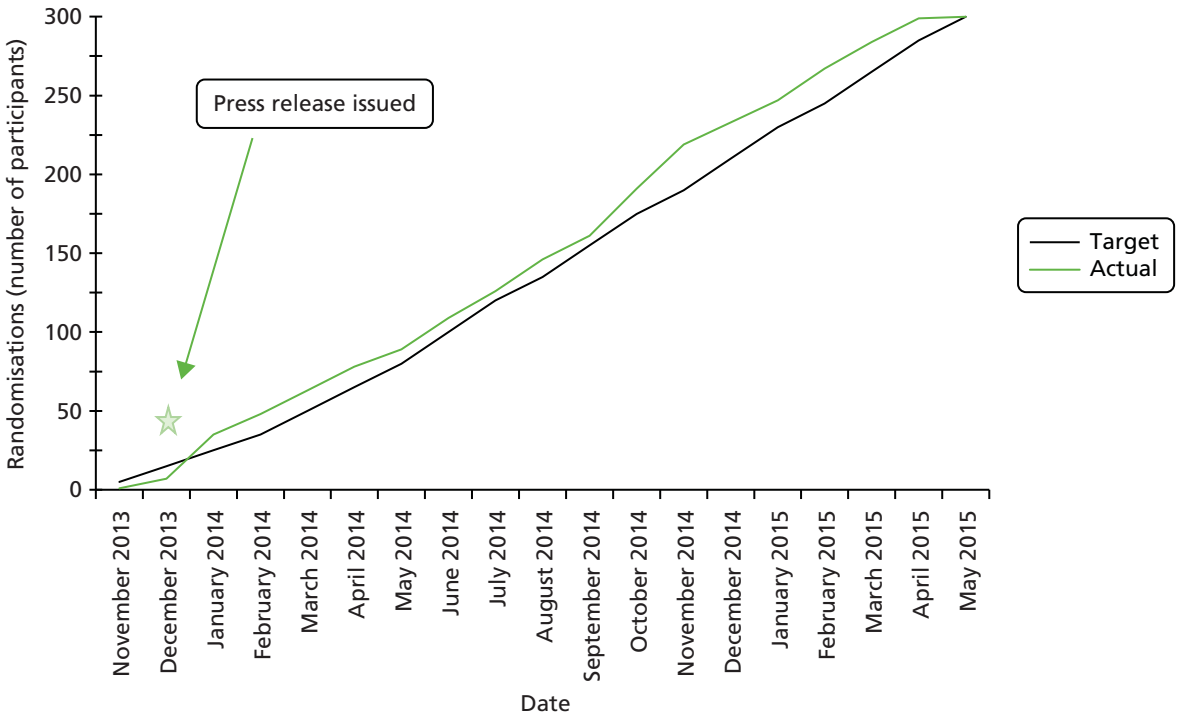

FIGURE 25 Recruitment graph for the CLOTHES trial showing impact of initial media interest.

As an attendee at the original Centre of Evidence Based Dermatology Patient Panel where the concept for the CLOTHES trial was first aired, I have been delighted to be involved at various stages of this well-run trial. I know the result will be of use and interest to the followers of the Nottingham Support Group for Carers of Children with which I am involved.

Amanda (member of CEBD patient panel and main contact for Nottingham Support Group for Carers of Children with Eczema)

As the lay member of the Trial Steering Committee I did not have as active a role as the other PPI members, but took part in all the meetings and kept up to date with the progress of the trial. I also liaised with the National Eczema Society and took part in the CLOTHES Collaborators meeting in June 2015. I am impressed with the interest in non-pharmacological interventions for the treatment of AE shown by the patients and carers in this trial and with the PPI input at all stages of the trial.

Rosemary (PPI member of Trial Steering Committee)

Discussion

This chapter documents the breadth and diversity of PPI experience that has contributed to the success of the CLOTHES trial. PPI was an integral element throughout the research life cycle of this national, multicentre RCT. It involved engagement with both children and their families, thus presenting additional challenges and opportunities for engagement. We have demonstrated how the contribution of PPI to this study has resulted in measurable impact, and hope to have inspired future researchers to think creatively about how best to engage with patient partners and the wider community to improve research.

By necessity, we have worked extremely closely with some of our patient partners and these individuals have now become skilled researchers in their own right. This phenomenon of 'professional patients' has been documented previously[90,91] and requires awareness of the shifting roles of members of the team as time progresses. We sought to limit the impact of this effect by reaching out through social media to as many patients as possible at crucial times; to ensure that diverse views were captured (in particular through online surveys and the nested qualitative study). Wider engagement is often particularly important while setting research priorities, in finalising the trial design, and during dissemination and implementation of the results.

Documenting evidence of impact of PPI is a constant challenge and one that requires a systematic approach involving all members of the research team. It is the responsibility of the lead researcher to ensure that all members of the trial team understand the importance of PPI and how to record it. The documentation of negative impacts of PPI remains a particular challenge, and may well require different methods to elicit feedback and documentation of such effects.

Involvement in teleconference conversations that involve multiple people can often be particularly challenging for new PPI partners. Special efforts should be made by the chairperson of such meetings to ensure that PPI partners feel supported and able to voice their opinions freely.[92] It is often advisable to provide specific training prior to participation in such meetings, or to have a pre-meeting conversation with PPI members so that they have an opportunity to clarify the proposed agenda items and to ask any questions that they might feel uncomfortable in asking in the wider group.

Conclusion

The NIHR-funded CLOTHES trial was a successful trial for many reasons. Having strong PPI embedded within an environment that values PPI input was just one aspect of a strong multidisciplinary team with experienced CTU support. However, the benefits of PPI far outweighed any potential negative impacts and contributed in diverse ways throughout the lifetime of the project.

Chapter 7 Experiences of working with clothing suppliers

Background

Collaboration between academia and industry in delivering clinical research has been given high priority within the UK's research agenda.[93] The advantages of collaboration can be multifaceted, bringing mutual benefits to all parties. However, working together with industry partners to deliver publicly funded research can also be challenging as a result of the differing expectations and priorities.

Industry partners often have varying levels of engagement with the research process, depending on the needs of the individual project. Having previously collaborated with industry to successfully deliver the NIHR HTA-funded SWET,[61] the CLOTHES trial team sought to draw on lessons from this previous experience in establishing a successful collaborative relationship.

Delivery of the CLOTHES trial was supported by two silk garment suppliers (Espère Healthcare Ltd, UK distributor of DermaSilk, and DreamSkin Health, manufacturer of DreamSkin). These two companies donated the silk garments for use in the trial free of charge. This donation was made on the basis that the companies had no input into the trial design, conduct, analysis or interpretation of the trial results (other than to inform logistics of trial delivery, and to advise on appropriate use and care instructions for the garments).

This chapter describes the role that the clothing suppliers played in ensuring the success of the CLOTHES trial and reflects on lessons learned for future trials.

Priorities and responsibilities

Working with industry can highlight differences in culture between the private and public sector, as the needs and drivers for both parties are necessarily different. For the public sector, the primary aim is to provide better quality evidence to inform medical decision-making and health commissioning, as well as academic drivers ensuring the need to publish in high-impact scientific journals. For the private section, any commercial venture clearly relies on making a financial profit to pay their employees and to satisfy shareholders.

For the companies involved in supplying garments for the CLOTHES trial, there were many benefits of being involved in such a high-profile, publicly funded clinical trial. However, there were also considerable financial risks, should the study show that the products were not effective.

For the trial team, the benefits of having the garments donated from the two participating companies meant that trial set-up was expedited with regard to negotiation of treatment costs with participating NHS trusts. Under the terms of research funding within the UK, these costs are not covered from within the research budget and are negotiated with participating health-care providers prior to starting the trial. The main risk for the trial team was the potential for perceived lack of independence in conducting and reporting the trial, and potential risks over continued supply of the interventional product throughout the trial.

We sought to build a working relationship between the trial team and the clothing suppliers that was fair to all parties, and ensured that any perceived or actual influence from the clothing suppliers was minimised (*Box 2*). This approach was taken in order to protect the core principle of research independence and to

BOX 2 Responsibilities of clothing suppliers and the trial team

Responsibilities of the clothing suppliers were to:

- supply silk garments for the trial
- provide replacement garments for any worn-out or outgrown garments
- provide guidance to the trial development team on appropriate use of the garments
- establish a system for supplying garments as required
- advertise support for the trial in a responsible manner.

Responsibilities of the CLOTHES trial team were to:

- design and conduct the trial according to a pre-defined and registered protocol
- secure ethics and R&D approvals as needed, and to conduct the trial in line with local and national governance requirements
- pre-define the statistical analysis plan before locking the data set
- maintain independence and clinical equipoise in relation to the trial results
- clearly communicate with clothing suppliers over progress of the trial and the rationale for design and analysis decisions.

R&D, research and development.

ensure validity of the results. To achieve this, a number of processes were put into place, based on the trial team's previous experience and the recommendations laid out in Maskell *et al.*[94] (*Table 50*).

Involvement of the clothing suppliers in trial design and set-up

The original NIHR HTA commissioning brief did not specify any particular brand of silk garment to be used in the trial. At the time of trial design, two CE-marked brands of commercially produced silk garments were available on the NHS formulary (DermaSilk and DreamSkin). The suppliers of these two brands agreed to support the trial and supplied a letter of agreement to donate the garments to support the funding application.

At the trial design stage, engagement with industry representatives was most helpful in four key aspects:

1. Helping to secure NIHR funding. Having letters of support from each of the clothing suppliers was helpful in demonstrating to the funders (NIHR HTA) that the clothing suppliers were fully committed to the trial.
2. Informing correct use of intervention. Advising on appropriate use of the silk garments (e.g. washing instructions, concurrent use of AE medications, number of garments required, best ways of measuring the size of the child to ensure the correct size of garments).
3. Facilitating site set-up. Having donations of the garments meant that our planned recruiting sites were opened quickly and with minimal difficulties in negotiating NHS treatment costs. However, one potential recruiting centre was unable to open as a result of unwillingness on the part of the NHS trust to agree to the low risk of paying for the silk garments, should the clothing companies be unable to fulfil their offer of donation.
4. Trial conduct and logistics of supply. The trial team worked closely with company representatives to establish appropriate systems for ensuring delivery of the product in a timely manner, as well as minimising the requirement to hold multiple sizes and styles of garments at the co-ordinating centre.

TABLE 50 Summary of recommendations for successful delivery of academic research in collaboration with industry partners (adapted from Maskell *et al.*[94] and reflections from our previous NIHR HTA-funded trial[61])

Recommendation	Implementation within the CLOTHES trial
Provision of regular written reports for the industry partner	• Clothing suppliers were regularly updated on trial progress via e-mail and sent newsletter updates
Continual monitoring and prompt resolution of concerns	• The central trial management team at Nottingham CTU monitored garment stock control and flagged up any issues with the companies (e.g. sizing queries, participant concerns)
Basic research practices education for industry partners	• We held face-to-face meetings between members of trial management group and the clothing suppliers before start of recruitment, after database lock and after completion of the final report, to clarify key aspects of the trial design and implications for interpretation of the results • The meeting at the beginning of the trial included a presentation of the protocol, explanation of the reasoning behind key decisions regarding trial design and clarified the use of the intervention according to manufacturers' instructions • The meeting held after data collection was complete and the database had been locked, was used to explain the statistical analysis plan, and key aspects of trial design were re-emphasised (e.g. pragmatic design of the trial; the need for an objective primary outcome measure). We also emphasised the need to maintain independence during the analysis and write-up of the trial, and clarified timelines for release of the results • A final meeting after analysis and write-up was complete was used to clarify the results and to address any remaining questions regarding trial design and interpretation. We were careful to ensure that this meeting did not take place until after the final report was complete and had been submitted to the funders
Minimisation of industry partner contact with participants	• The trial participants had no contact with the clothing suppliers
Clear roles and responsibilities of all stakeholders	• The need for trial independence was emphasised by the trial team in early contacts with the clothing suppliers and throughout the trial • Prior to commencing the trial, written agreement was sought from both clothing suppliers to confirm that they would supply the garments for the trial, although there were no penalty clauses for failure to comply with this agreement as the garments were being donated free of charge • Trial team committed to providing the clothing suppliers with regular updates about trial progress and to give them advanced notice of when the results were to be released
Clarify and have a clear understanding of roles and responsibilities of research governance departments and ethics committees to avoid confusion and potential disagreements	• Clothing suppliers had no contact with the research ethics committee that reviewed the trial • Clothing suppliers had no contact with research governance departments in the recruiting centres
Communication through an independent third party if possible[a]	• Independent arbiters were chosen to manage communication between the chief investigator, trial team and the two clothing suppliers
Engage with multiple partners to ensure generalisability of findings and to limit commercial advantage to any one company[a]	• Two suppliers of silk garments were approached to support the trial

a Recommendations from the CLOTHES trial team based on previous experience of working with industry on academic trials.

Involvement of clothing suppliers during the trial

Trial logistics

Both clothing suppliers were supportive and were responsive in addressing questions or concerns about use of the silk garments. They worked closely with the trial co-ordinators at the Nottingham CTU to ensure efficient supply of the garments and development of an audit trail.

The central team at the CTU acted as the distribution hub for all trial garments to increase efficiency of stock supply, to maintain blinding of local site staff and to act as an intermediary between participants and the clothing companies (in the event that questions arose regarding the clothing). A detailed inventory of stock was kept so that supplies could be ordered weekly, providing accountability of garment usage and serving as a reordering system. Any returned stock (because of ill fit, excess wear or child growth) was returned to the manufacturers for them to see how the clothing held up with regular use.

Although three sets of garments were supplied to all participants, the need for replacement garments during each participant's 6 months' involvement in the trial was underestimated during our planning phase. This presented an increased financial burden on the companies, which remained supportive and supplied the additional garments after discussions with the trial team about why they were required. In this regard, it was helpful to work with two companies, so that the financial burden could be shared.

Having two companies involved in the study was also particularly beneficial when one of the companies experienced supply problems partway through the recruitment period. Each supplier remained supportive of the trial, doing all they could to allow the trial to continue. The company that experienced stock shortages kept back reserves of their dwindling stock for the trial, leaving them with fewer to sell on the market. The other company provided cover for their commercial competitor, providing more garments to the trial than originally intended.

Independence from the trial team

As outlined in *Table 50*, we attempted to replicate the model of engagement with commercial companies through an independent third party, as was successfully achieved in our previous NIHR HTA-funded SWET. To achieve this, we asked a representative of the lead NHS trust and the local lead for the comprehensive research network to be independent arbiters between the companies and the Trial Management Group. However, despite initial agreement from all parties, this approach did not work well in reality. This was largely because the nature of the ordering and stock control system meant that it was necessary for the trial management team to have weekly contact with representatives from the clothing suppliers. As a good working relationship developed, the majority of trial communication inevitably involved the trial manager. Nevertheless, this situation ensured that any concerns were resolved quickly, which was beneficial for delivery of the trial, and direct contact with the rest of the Trial Management Group (including the chief investigator) was kept to a minimum.

Training in trial design and interpretation

Given the importance of this trial to the financial concerns of both companies, we strove to ensure that the rationale for our trial design was clearly explained before, during and after the trial, so that the clothing suppliers had a good understanding of the trial design and conduct. In particular, we explained our approach to controlling for bias and the implications of running a pragmatic RCT.

As outlined in *Table 50*, we conducted face-to-face meetings to discuss these issues prior to start of recruitment, and again prior to data analysis, to ensure that the clothing suppliers understood the reasoning behind trial design decisions. In particular, these meetings focused on explaining the following key aspects:

- what a pragmatic trial is and implications for the design of the trial
- importance of the primary outcome and the need for an objective primary outcome

- interpreting unblinded trials
- understanding *p*-values and CIs
- individual versus group mean effects
- the need for transparent reporting of results
- timelines and availability of the findings
- ownership of the data and write-up of study results.

Involvement of clothing suppliers after completion of the trial

Given that the CLOTHES trial failed to find any clear benefit of silk clothing for improving eczema severity, it is perhaps not surprising that the final dissemination stage of the project has also been the most challenging to manage. Both suppliers are passionate about their products and about the potential health benefits that the garments could bring to patients. Their passion is reflected in the significant investment both suppliers made in the trial. This belief in their product based on earlier, smaller, sponsored, studies and testimonies from satisfied customers undoubtedly led to an expectation, both implicit and explicit, that the trial would show the garments to be beneficial.

The need to ensure academic independence until the data had been fully analysed and interpreted, and the trial report had been subject to peer scrutiny was a difficult balance to achieve in a manner that was acceptable to all parties. Our two clothing suppliers were understandably eager to receive the trial results and to ask questions, but it was important that we did this in a transparent and accountable way, and without allowing them an opportunity to change any of the pre-planned analyses or the interpretation of the results. Both companies received a copy of the full report after it had been through peer review, but prior to publication. The companies provided reflections to the trial team that were incorporated into the report at the team's discretion. The feedback included notification that a mistake had been made in applying the unit costs of the garments in the health economic analysis, which resulted in the analysis being corrected and re-run prior to publication. Other minor amendments to the report at this stage are listed in *Appendix 21*.

Of particular concern to the companies was the desire to explore the results specific to their individual brands (in addition to the combined results). This was potentially problematic as the trial was not powered to look for such comparisons, although those allocated to receive the intervention were randomised to the two brands, which allowed exploration of brand effects in tertiary analysis.

Discussion

This chapter has provided brief reflections on our experiences of delivering a large, independent trial with support from clothing suppliers in the form of donation of the trial intervention. This co-operative partnership has brought many benefits, but also challenges, particularly as the commercial needs of the companies are at odds with the overall findings of this trial. A summary of our key reflections on completion of the CLOTHES trial is presented in *Box 3*.

Despite our best efforts to maintain independence between the trial team and the companies involved, the need to work together over the past 3 years has meant that a relatively close relationship has been established for some members of the team (especially those at the co-ordinating centre). However, contact with research nurses and investigators at recruiting centres was successfully limited.

Our agreements with the clothing suppliers took the form of letters of agreement to supply the garments. At the time, this was felt to be sufficient to document the agreement between the University of Nottingham and the clothing suppliers. However, a formal contract that outlined key responsibilities for all parties, defined expectations and clarified ownership of intellectual property may have been useful, and we would recommend this approach for future trials.

BOX 3 Top tips for conducting academic trials in collaboration with industry colleagues

- Ensure roles and responsibilities are documented for both parties from the outset – particularly in relation to continuity of supply, when and how the results will be shared, and intellectual property.
- Ensure sign-off of the trial protocol by all stakeholders prior to commencing the trial.
- Be aware of the benefits and potential difficulties of using multiple brands to represent one randomised intervention.
- Early engagement with suppliers to establish 'how to use their product' can help to avoid claims of inappropriate use at a later date.
- If planning a pragmatic clinical trial to establish effectiveness of an intervention in normal practice, special efforts should be made to ensure that all industry colleagues understand the concept of a pragmatic trial (sometimes referred to as a comparative effectiveness trial), and the implications for trial analysis and interpretation.
- Keep detailed notes of what is discussed during meetings – this can be helpful in preventing debate at the end of the study as to what was agreed and when.

For the CLOTHES trial, there were benefits of working with two suppliers:

- better generalisability of study results
- security of supply (not reliant on a single supplier for the success of the trial)
- reduced financial burden for individual companies.

However, for non-drug trials, where the comparability of the interventions may be less clear than in drug trials, there is also a risk to the trial integrity, particularly if different products, which were assumed to be functionally similar, prove to be different in terms of treatment response. Thankfully, for the CLOTHES trial, this was not the case and the ability to generalise from one branded product to a class of products is helpful for informing clinical decision-making.

Alternative models of industry involvement in academic trials are available and these may warrant further consideration. In particular, our relationship with the companies may have been very different had the garments been supplied at a reduced cost rather than free of charge. However, in such a scenario, the delays in negotiating NHS treatment costs with each participating site would still have been present, potentially delaying the start of the trial and choice of recruiting centres. We would be pleased to see further consideration of appropriate funding models to address excess treatment costs within the UK funding landscape, as this currently represents a considerable source of delay and wasted resource.

Chapter 8 Discussion

Main findings

This trial found no evidence of any 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. Sensitivity analyses (imputing missing values, adjusting for baseline imbalances and exploring the impact of adherence in wearing the garments) supported the primary analysis.

Subgroup analysis based on *FLG* genotype showed no evidence of differential treatment response in children with an inherited impairment in the skin barrier function. A post hoc analysis exploring the impact of baseline severity on the primary outcome also showed no effect, suggesting that children with more severe disease were unlikely to benefit from the clothing more than children with milder disease.

It is possible that silk garments could prove beneficial in the absence of a change in disease severity if the garments resulted in a sparing effect on topical corticosteroid use. However, the proportion of days on which topical corticosteroids or calcineurin inhibitors were used did not differ between the groups.

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

Of the seven unblinded secondary outcomes, only POEM and PGA showed differences in favour of the silk garments. However, the observed differences in POEM and PGA were small, making them unlikely to be clinically meaningful for patients.[40] These effects appeared to be most prominent during the first 3 months of the trial, when belief in the effectiveness of the garments was most likely to influence responses.
It is possible that these effects occurred by chance, as many secondary outcome variables were assessed. However, a previous AE trial of non-pharmacological interventions has reported similar differences between blinded and unblinded outcomes.[61] The nested qualitative study highlighted the high hopes that both children and parents placed on the trial intervention from the outset and would suggest that risk of bias for participant-reported outcomes is likely to be high in a trial of this kind.

Relevance to existing literature

There have been no further RCTs on the use of silk garments for AE since the CLOTHES trial began (search updated 13 April 2016) and meta-analysis of the four existing silk trials (including CLOTHES) is not possible because of the heterogeneity of designs. Additional brands of silk garments have since become available for use in AE (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 in England alone. By 2015, this amount had risen to £2,039,575 per annum.

Strengths and limitations

This was an adequately powered, independent RCT, with high follow-up rates and good adherence to the trial intervention. The trial placed special emphasis on objective outcome measures in order to minimise detection bias and 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.

It is possible that our emphasis on objective AE 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 recorded in POEM), may be important drivers in determining whether or not parents choose to purchase silk garments for their children. However, the magnitude of any such benefits was small, and we found no evidence of improved quality of life among trial participants using a range of validated quality-of-life scales.

It is also possible that treatment effects were masked by enhanced adherence to standard AE care, which may have resulted from participating in a study such as this in which AE activity and treatment usage were monitored weekly.

It is also possible that the effects of silk garments are best realised during a period of AE flare rather than wearing the garments all the time (day and night). Daily use of the garments in the CLOTHES trial could have led to more rapid degradation of the product than might have been seen if the garments were worn occasionally when the AE was at its worst.

Generalisability

The study has good external validity as it was pragmatic in design, recruited children with a range of AE severities and reflected normal clinical practice in the UK. Participants were able to use existing AE treatments alongside their allocated trial intervention, as would be the case if used in practice.

Participants were recruited from five UK centres covering a range of urban and rural settings. The mix of ethnic groups was broadly representative of that in the UK.

This trial included children with moderate to severe AE on the grounds that these were the patients most likely to receive silk garments from their health-care providers. However, some children in the trial had milder disease on the day of recruitment as AE severity was assessed over the previous year for eligibility. Although AE is most common in children aged < 5 years, we included children of all ages to improve the relevance of the study results to all children with AE.

Chapter 9 Conclusion

Main conclusions

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

It is hoped that these trial results provide health commissioners with a better evidence base on which to make informed decisions about the use of silk garments for AE.

Implications for clinical practice

- Although patients are keen to identify non-pharmacological interventions to help in the management of AE, it would appear from this trial that silk garments provide false hope for the majority of patients and high costs for health-care providers.
- In a world where health-care resources are finite, the use of silk therapeutic garments for the management of AE appears to represent poor value for money. Whether or not parents feel that the small benefits identified in some of the secondary outcomes are sufficient to justify purchasing these garments for themselves is something for individuals to consider on a case-by-case basis.

Implications for research

- Although this trial proved negative, patient interest in the role of non-pharmacological interventions for AE remains high, and priority areas for future research have been identified in a James Lind Alliance Priority Setting Partnership.[6] Prioritised topics relating to non-pharmacological interventions include:

  i. What role might food allergy tests play in the management of AE.
  ii. What is the best psychological treatment for itching/scratching in AE?
  iii. Which is the best way for people with AE to wash: frequency of washing, water temperature or bath versus shower?
  iv. What are the best and safest natural products to apply to the skin for AE?
  v. How much does avoidance of irritants and allergens help people with AE?
  vi. What is the role of diet in treating AE: exclusion diets and nutritional supplements?
  vii. Which is more effective in the management of AE: education programmes, GP care, nurse-led care, dermatologist-led care or multidisciplinary care?

- The CLOTHES trial has evaluated just one of many types of garments that have been purported to be effective in the management of AE. Some, such as silver-impregnated fabrics, are available on prescription and are currently recommended in clinical guidelines in some countries, whereas other fabrics and products are still experimental; none have been well evaluated.

It remains entirely possible that wearing soft, smooth fibres next to the skin can prove soothing for AE patients, and further trials of other fabric types are needed.

As with many areas of research, outcomes remain a challenge for the evaluation of AE treatments. Although the HOME initiative[95] has made much progress with regard to development of a core outcome set for AE,[96] further work is still required in establishing how best to capture long-term control and quality of life in AE trials. In this respect, it is important for researchers throughout the world to work together and to share data sets, such as the CLOTHES data set, to allow further validation of outcomes and testing of their performance in different clinical settings and types of patients.

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The trial was sponsored by the University of Nottingham, was co-ordinated from the Nottingham CTU and was supported by the NIHR Clinical Research Network and the UK Dermatology Clinical Trials Network.

Contributors to the CLOTHES trial:

- Independent Trial Steering Committee: David Paige (chairperson), consultant paediatric dermatologist, Barts Health NHS Trust; Nick Francis, GP/senior clinical research fellow, Cardiff University; Caroline O'Leary, senior statistician, IMS Health; Rosemary Humphreys, patient representative
- Nottingham CTU: Lelia Duley, Director of Nottingham CTU and advisor on trial design; Andrew Jadowski, trial administrator; Jennifer White, trial co-ordinator; Sarah Walker, data co-ordinator; Tessa Clarke, senior trials manager; Trish Hepburn, senior medical statistician; Justin Fenty, senior statistician; Lucinda Murphy, data manager; Daniel Simpkins, information technology (IT) and data manager; Chris Rumsey, IT programmer
- Other support staff at recruiting centres: Sharon McCready, research nurse lead; Rachel Watson, clinical trials assistant; Gill Glasbey, research study co-ordinator
- Contributors to the qualitative study: Rachel Harding, paediatric nurse; Jo Aspland, research associate
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Contributions of authors

Kim S Thomas (Professor of Applied Dermatology Research and Co-Director of the Centre of Evidence Based Dermatology) contributed to the conception and design of the study, trial oversight (as chief investigator), interpretation of the data, and drafted and critically reviewed the report.

Lucy E Bradshaw (Medical Statistician) contributed to the design of the study, was responsible for the statistical analysis plan, carried out the statistical analyses, contributed to interpretation of the data, and drafted and critically reviewed the report.

Tracey H Sach (Reader in Health Economics) contributed to the design of the study, carried out the health economics analyses, contributed to interpretation of the data, and drafted and critically reviewed the report.

Fiona Cowdell (Reader in Wellbeing in Long-Term Conditions) contributed to the design of the study, was the lead for the nested qualitative evaluation, contributed to interpretation of the data, and drafted and critically reviewed the report.

Jonathan M Batchelor (Consultant Dermatologist) contributed to the design of the study and interpretation of the data, and drafted and critically reviewed the report.

Sandra Lawton (OBE, Nurse Consultant) contributed to the design of the study and interpretation of the data and critically reviewed the report.

Eleanor F Harrison (Clinical Trial Manager) managed the trial, contributed to interpretation of the data, and drafted and critically reviewed the report.

Rachel H Haines (Clinical Trial Manager) managed the trial, contributed to interpretation of the data, and drafted and critically reviewed the report.

Amina Ahmed (patient representative) contributed to the design of the study and interpretation of the data, and critically reviewed the report.

Taraneh Dean (Dean of the Science Faculty) contributed to the design of the study, was responsible for oversight of the trial at the Isle of Wight centre (as principal investigator), contributed to interpretation of the data and critically reviewed the report.

Nigel P Burrows (Consultant Dermatologist) contributed to the design of the study, was responsible for oversight of the trial at the Cambridge centre (as principal investigator), contributed to interpretation of the data and critically reviewed the report.

Ian Pollock (Consultant Paediatrician and Paediatric Allergist) contributed to the design of the study, was responsible for oversight of the trial at the London centre (as principal investigator), contributed to interpretation of the data and critically reviewed the report.

Hannah K Buckley (Consultant Paediatrician) was responsible for oversight of the trial at the Portsmouth centre (as principal investigator), contributed to interpretation of the data and critically reviewed the report.

Hywel C Williams (Professor of Dermato-Epidemiology and Co-Director of the Centre of Evidence-Based Dermatology) contributed to the design of the study, was responsible for oversight of the trial at the Nottingham centre (as principal investigator), contributed to interpretation of the data and critically reviewed the report.

Joanne Llewellyn (Research Nurse) recruited participants and conducted assessments, contributed to interpretation of the data and critically reviewed the report.

Clare Crang (Research Nurse) recruited participants and conducted assessments, contributed to interpretation of the data and critically reviewed the report.

Jane D Grundy (Research Nurse) recruited participants and conducted assessments, contributed to interpretation of the data and critically reviewed the report.

Juliet Guiness (Research Nurse) recruited participants and conducted assessments, contributed to interpretation of the data and critically reviewed the report.

Andrew Gribbin (Research Nurse) recruited participants and conducted assessments, contributed to interpretation of the data and critically reviewed the report.

Eileen V Wake (Paediatric Nurse Lecturer) contributed to the data collection, analysis and interpretation of the nested qualitative evaluation, and drafted and critically reviewed the report.

Eleanor J Mitchell (Senior Trial Manager) contributed to the design of the study, contributed to interpretation of the data and critically reviewed the report.

Sara J Brown (Professor of Molecular and Genetic Dermatology) contributed to the design of the study, contributed to interpretation of the data, and drafted and critically reviewed the report.

Alan A Montgomery (Professor of Medical Statistics and Clinical Trials) contributed to the design of the study, was responsible for the statistical analysis plan, carried out the statistical analyses, contributed to interpretation of the data and critically reviewed the report.

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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**:390.

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Data sharing statement

Non-identifying data will be made available, as appropriate, for research purposes following an application to the corresponding author.

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Appendix 1 Additional studies on therapeutic garments

TABLE 51 Summary of RCTs investigating therapeutic clothing (other than silk) for AE

Type of clothing	Reference	Participants	Interventions	Main results
Silver textile	Juenger *et al.* (2006)[17]	30	Group 1 ($n = 10$): silver textile undergarments Group 2 ($n = 10$): silver-free textile undergarments Group 3 ($n = 10$): prednicarbate ointment For phase 1 (days 1–14) the three interventions were applied. For phase 2 (days 14–28) all groups wore undergarments made with silver textile. In phase 3 (days 28–56) all treatments were withdrawn except for prednicarbate ointment	Median SCORAD at 14 days was 29.9 in group 1, 48.2 in group 2 and 24.0 in group 3 Change in scores between day 1 and 14 in groups 1 and 3 differed significantly compared with the change in score in group 2 between day 1 and 14 ($p = 0.03$ and $p = 0.14$, respectively)
Silver textile	Gauger *et al.* (2006)[16]	68 (57 analysed)	Group A ($n = 37$): silver-coated textile consisting of micromesh material (82% polyamide, 18% lycra) with woven silver filaments with a silver content of 20% in total Group B ($n = 31$): placebo pure cotton textile of equal size Both interventions worn day and night next to the skin (except for consultations) for 2 weeks	Reduction in SCORAD index after 2 weeks: 27.4% in silver group and 16.3% in placebo. No significant differences between the two groups
Cellulose fibres with seaweed enriched with silver ions	Araújo *et al.* (2013)[18]	19	Group A ($n = 12$): clothing made with a biofunctional textile consisting of 70% cotton fibres, 20% cellulose fibres with algae extracts and 10% silver-activated algal cellulose fibres. The textile contains about 6000 p.p.m. (0.6%) silver Group B ($n = 7$): 100% cotton clothing, woven similarly to the trial textile From day 0 the clothes were worn continuously 24 hours a day until day 7 when intermittent use of the clothing started. The clothes were worn only at night until the end of the study (day 90)	In group A at 90 days, mean SCORAD was 24.0 (SD ±12.5) compared with 24.2 (SD ±12) in the cotton clothing group, with no difference between the groups ($p = 0.97$)

continued

TABLE 51 Summary of RCTs investigating therapeutic clothing (other than silk) for AE (*continued*)

Type of clothing	Reference	Participants	Interventions	Main results
Cellulose seaweed fabric with silver	Park *et al.* (2012)[19]	14 (12 analysed)	Garments (top and leggings) consisting of two parts: one half made from silver-loaded cellulose fabric made from seaweed (SkinDoctor®, Ventex Co. Ltd, Korea), and the other half 100% cotton, so participants were exposed to both interventions at the same time Garments worn during the day and night for 4 weeks	SCORAD decreased from 30.8 (SD ±8.4) to 19.5 (SD ±6.3) on Skin Doctor side, and from 30.7 (SD ±8.8) to 25.33 (SD ±8.2) on cotton side after 4 weeks ($p < 0.001$, 95% CI 3.60 to 8.43)
Cellulose seaweed fabric with silver	Fluhr *et al.* (2010)[20]	37	Group A: silver-loaded seaweed-based cellulose fibre garments (SeaCell® Active, SeaCell GmbH, Rudostadt, Germany) ($n = 19$) Group B: cotton garments ($n = 18$) Long-sleeved t-shirts worn for 8 weeks	Change in *Staphylococcus aureus* colonisation after 8 weeks was 10 participants in silver group compared with four participants in the cotton group ($p = 0.0120$)
Cellulose fibre	Love and Nedorost (2009)[21]	15 with AE and 15 control (27 analysed)	Intervention A: cellulosic fibre (lyocell, Lenzing AG, Lenzing, Austria) garments Intervention B: 100% cotton garments Short sleeved t-shirts, long-sleeved pyjama tops and trousers and bedding were provided. Participants were randomised to use either the lyocell or cotton for 1 week. Following this, all used their normal clothes for a 1-week wash-out period and then crossed over to the other intervention for 1 week	Atopic participants' average itch score was lower during the week they used lyocell (2.08) than the week they wore cotton (2.67). Both lyocell and cotton produced a lower itch score then usual clothing (3.42)
Anion textile	Kim *et al.* (2012)[22]	52 (44 analysed)	Intervention A ($n = 30$): undergarments made from an anion textile (constructed from pure polyester filaments containing nanosized, fine-crusted tourmaline powder) Intervention B ($n = 22$): undergarments made from pure cotton Participants were instructed to wear the undergarments at all times during the 4-week study period	Mean SCORAD decreased from 47.2 (SD ±14.0) to 36.1 (SD ±16.5) in the anion group, and from 41.8 (SD ±16.3) to 37.7 (SD ±17.2) in cotton group at 4 weeks. A significant difference was detected between the groups ($p = 0.03$)

TABLE 51 Summary of RCTs investigating therapeutic clothing (other than silk) for AE (*continued*)

Type of clothing	Reference	Participants	Interventions	Main results
Ethylene vinyl alcohol (EVOH) fibre	Ozawa *et al.* (2008)[23]	30	Group A: EVOH copolymer fibre underwear (MEDIELE®) Group B: Cotton underwear Both groups wore the intervention for 4 weeks, and then crossed over to the other intervention for 4 weeks	No difference in local SCORAD between groups
EVOH fibre	Yokoyama *et al.* (2009)[24]	21	Group A ($n = 10$): EVOH fibre underwear (short sleeved) Group B ($n = 11$): cotton underwear Followed up for 4 weeks	Mean SCORAD decreased from 22.1 (SD 19.1) to 10.7 (SD 12.1) in EVOH group, and from 21.4 (SD 17.0) to 15.1 (SD 14.3) in the cotton group at follow-up
Borage oil-coated cotton	Kanehara *et al.* (2007)[25]	32	Group A: cotton undershirt coated with borage oil ($n = 16$) Group B: non-coated cotton undershirts ($n = 16$) Garments worn for 2 weeks	In the borage oil group, itch improved from 1.44 (SD ±0.51) to 0.94 (SD ±0.57) and erythema from 0.81 (SD ±0.83) to 0.31 (SD ±0.48) after 2 weeks. No changes observed for papules, erosion, scaling or lichenification in borage oil group. No differences in clinical symptoms observed in the non-coated cotton group after 2 weeks
Chitosan-coated cotton	Lopes *et al.* (2015)[27]	78 (69 analysed)	Group A: chitosan-coated cotton ($n = 43$) Group B: cotton ($n = 35$) Long sleeved pyjama tops and trousers worn at night for 8 weeks	SCORAD improved in both groups after 8 weeks: 44.2 (95% CI 34.5 to 53.9) to 29.4 (95% CI 21.4 to 37.4) in chitosan group and 41.4 (95% CI 34.3 to 48.6) to 25.7 (95% CI 18.3 to 33.1) in cotton group, with no significant difference observed between the groups
Cotton and synthetic fibres	Diepgen *et al.* (1990)[26]	86 participants (55 with AD and 31 healthy controls)	Intervention A: cotton shirts Interventions B–D: shirts made of synthetics with different fibre structure	Intensity of itching/discomfort with synthetic shirts higher in patients with AD. Cotton shirts were best tolerated

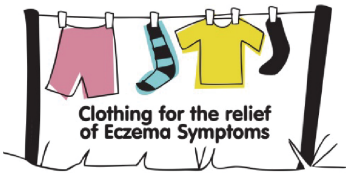
AD, atopic dermatitis; EVOH, ethylene vinyl alcohol; p.p.m., parts per million; SCORAD, SCORing Atopic Dermatitis.

Search strategies used to identify studies

- Global Resource for Eczema Trials (GREAT) database was searched on 18 May 2016. The full search strategy used for the GREAT database can be found at www.greatdatabase.org.uk/GD4/Home/Strategy.php (accessed 18 May 2016).
- PubMed (www.ncbi.nlm.nih.gov/pubmed) was searched on 11 May 2016 using the following terms: ('dermatitis, atopic' [MeSH Terms] OR 'eczema' [MeSH Terms] OR 'eczema' [All Fields] OR 'atopic dermatitis' [All Fields] OR 'neurodermatitis' [All Fields]) AND (clothes OR clothing OR 'clothing' [MeSH Terms] OR fabric OR fabrics OR textile OR textiles OR 'textiles' [MeSH Terms] OR silk OR 'silk' [MeSH Terms] OR garment OR garments).

Appendix 2 Parent/guardian information sheet

The University of Nottingham



CLOTHES Trial

Parent/guardian information sheet
(Final version 2.0. 3 Feb 2014)

Title of study: **A clinical trial to see if using silk clothing helps in the relief of eczema symptoms**

Name of Chief Researcher(s): Professor Kim Thomas
Name of Local Researcher(s): Local details to be added

Where the word "parent" is used, please read parent/guardian i.e. those who have parental responsibility, which may include a legal representative such as a grandparent.

Your child is being invited to take part in a research study. Before you decide if you wish your child to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

What is the purpose of the study?
It has long been understood that clothing can cause irritation to the skin, and current guidelines recommend the use of loose cotton clothing and the avoidance of wool and other itchy or synthetic materials next to the skin. In recent years, new silk clothing products have been developed for the management of eczema symptoms, but there is no firm evidence to suggest that they work.

In order to decide whether silk clothing is a useful addition to the treatments currently available for children with eczema, 300 children with eczema will be asked to take part in this study: 150 children will be asked to wear the clothing straight away, and 150 children will be asked to wear the clothing in 6 months' time. This will allow us to compare if the clothing has any effect on the eczema

Why has my child been invited?
Your child has been invited to take part in this study as they are between 1 and 15 years old and has been diagnosed as having quite bad eczema.

Does my child have to take part in this study?
No. It is up to you and your child (where possible) to decide whether or not to take part. Your decision will not affect the standard of eczema care your child receives.

You are both free to withdraw from the study at any time without giving a reason. This will not affect the standard of eczema care your child receives or their legal rights.

What will happen to my child if s/he takes part?
The study will last for 8 months and your child will be asked to come into clinic at the hospital four times in total. A contribution towards reasonable travel expenses will be offered.

Screening
On your first visit to the nurse, the study will be explained to you and your child (if appropriate). If you are happy for your child to take part, you will be asked to sign a consent form. If your child is old enough, they can sign the form too, if they wish.

They will then be examined by a research nurse to make sure that they are suitable to take part in the study. If they are suitable, your child's eczema will be examined by the research nurse and you will be asked some questions about the eczema, the treatment they use and whether they experience many skin infections. You will also be asked to complete some short questionnaires.

This first visit will be between 60 and 90 minutes.

Group Allocation

In order to find out if silk clothing (bodysuits, leggings and vests) alongside normal eczema treatment is effective in the long term management of children with eczema, the children in this study will be split into two groups: one group will wear the clothing from the onset of their participation in the study, the other group will continue with their normal eczema treatment.

Clothing for babies / infants

Clothing for older children

The decision as to which group your child will be allocated to will be done randomly by a computer and they will have an equal chance of being in either group. You will be sent a letter from the unit who are running the study, soon after your first visit with the nurse, that outlines what group your child is in and what to do next.

It is important to realise that we currently do not know if the silk clothing will have any effect on the eczema so there is nothing to lose, or gain, by being in either of the two groups.

Clothing Now Group

For the first 6 months of the trial this group will be given the clothing to wear whilst continuing with their normal eczema care.

Three sets of garments will be sent after the first visit with the nurse, and you will be able request replacement clothes in the first 6 months if the clothing starts to wear out or becomes too small. You will be asked to return the clothing you would like replaced.

Over this first 6 months you will be asked to complete a short questionnaire each week to record information about your child's eczema, whether they saw any healthcare professionals about their eczema, whether they had any prescriptions for their eczema, and how many days and nights they actually wore the clothing that week.

This questionnaire can be completed either on-line or by post. If you choose to complete it on-line, we will ask for your e-mail address.

You will be given a diary card and a wall chart (with stickers if your child would like!) to help you remember this information from one week to the next.

Clothing Later Group
This group will continue with their normal eczema care over the first 6 months of the study.

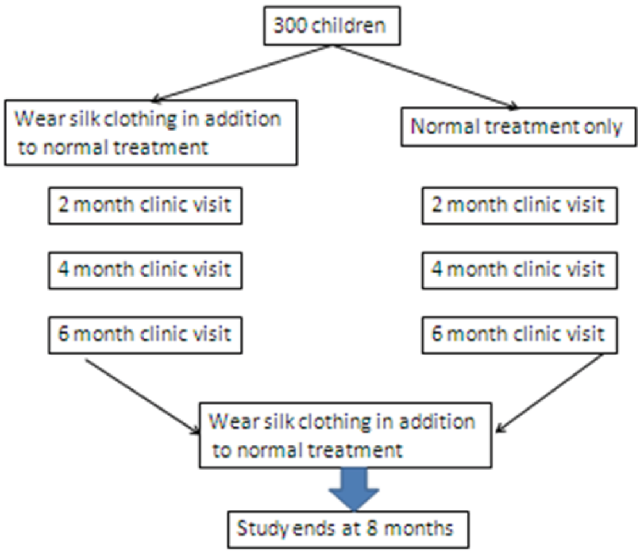
Over this first 6 months you will be asked to complete a short questionnaire each week to record information about your child's eczema, whether they saw any healthcare professionals about their eczema, and whether they had any prescriptions for their eczema.

This questionnaire can be completed either on-line or by post. If you choose to complete it on-line, we will ask for your e-mail address.

You will be given a diary card and a wall chart (with stickers if your child would like!) to help you remember this information from one week to the next.

Nurse Visits
Your child will need to visit the nurse 3 times: at 2, 4 and 6 months. Your child will be examined by the research nurse and you will be asked about the eczema treatments they have used (not including the silk clothing) and if they have had any skin infections. You will also be asked how you think your child's eczema is by completing a short questionnaire. These three visits should take no longer than 30 minutes.

It is important that the research nurse looking after your child doesn't know whether your child is wearing the clothing or not. If the nurse knew this information it might mean that assessments of your child's skin might be influenced by this knowledge. This is called bias. We would ask that your child does not wear the clothing to any clinic visit or talk to the research nurse about the clothes.



Last two months of the study
For the last two months of the study, all children in the study will wear the clothing. The children who wore the clothing for the first 6 months will continue to wear the clothing they already received.

For the group who receives the clothing after the 4th visit with the nurse, 3 sets of garments will be sent to you at this point. If they do not fit when you receive them you will have an opportunity to send them back immediately and receive a replacement set in the correct size.

All children should continue wearing the clothing for the next two months of the study. At the end of the 8 month mark, a short questionnaire will be sent to you, and this will mark the end of the trial.

After the end of the trial, all children get to keep the clothes they were given during the trial, to wear as often or as little as they choose.

Saliva (spit) sample
During a clinic visit you will be asked if you are willing for your child give a saliva (spit) sample. If you don't want your child to give the sample, that's fine – they can still take part in the main study. Please just say that you would rather not take part in this.

If you choose for your child to give a sample, we will ask them to spit into a small pot, or if they are too young to spit, the nurse will collect some saliva on an absorbent cotton bud. .

What are the alternative treatments for my child?
This study does not restrict your child's current or future treatment and your child will still receive all their normal eczema treatments while in the study. The wearing of the clothes being tested is in addition to their normal treatment.

What are the possible disadvantages and risks of taking part?
Since your child will be receiving their normal eczema treatment throughout the study, no major risks or disadvantages to their eczema is expected. It may be that your child finds the clothing uncomfortable or that it makes them too hot. This can be addressed by checking that the size is correct for your child and perhaps using lighter clothing on top of the silk trial clothing (or wearing them as pyjamas at night).

Are there any possible side effects?
There are no known side effects to wearing the clothing but we will be collecting the information on the number of skin infections experienced by the children, just in case this is affected.

What are the possible benefits of taking part.
There are no direct benefits to you or your child from taking part in this study, although you may feel that visits to the research nurse is helpful. Some past study participants have said that they found regular monitoring of their eczema at home useful.

It is possible that your child's skin may improve through wearing the clothing, but we do not know if this is the case, and it is possible that the clothing may have no impact or make the eczema worse.

What happens when the research study stops?
When your child completes their 8 months in the study, the results of the study will not be known so we cannot make any recommendations for their future treatment at that time. You

will be able to keep the clothing at the end of the study. You can also speak to your child's doctor about their future eczema treatment.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the local researchers (their contact details are at the end of this sheet) who will do their best to answer your questions. If any questions remain you can contact the Chief Investigator of this study Professor Kim Thomas (kim.thomas@nottingham.ac.uk). If you remain unhappy and wish to complain formally, you can do this by contacting NHS Complaints via the Patient Advisory and Liaison Service (PALS). The details are at the end of this leaflet.

In the event that something does go wrong and your child is harmed during the research study there are no special compensation arrangements. If they are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my child taking part in this study be kept confidential?

Yes. We will follow ethical and legal practice and all information about your child will be handled in confidence.

If your child joins the study, some parts of the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to your child as a research participant and we will do our best to meet this duty.

All information which is collected about your child during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about your child which leaves the research centre will have your name and address removed (anonymised) and a unique code will be used so that your child cannot be recognised from it.

All research data will be kept securely for seven years. After this time your child's data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your child's confidentiality. Only members of the research team will have access to their personal data.

In order to be able to contact you about how your child is getting on, your child's name and contact details will be made available to the researchers running this study. These details will be kept securely, with access restricted. Your child will not be named or otherwise identified in any study publication.

You will be asked to consent to your child's identifiable details being registered with the NHS Information Centre. These may be used to help us keep in touch with you and to follow up your child's health status. We will have confidentiality and security agreements in place to ensure your child's details are dealt with in the strictest confidence.

With your permission we will inform your child's GP that they are participating in this research study.

We have a mailing list to inform parents and guardians about skin research that is being carried out. If you would like to be added to that list you can indicate this on the consent form. The contact email address you provide will be held in a separate secure database.

What will happen if I don't want to carry on with the study?
Your child's participation is voluntary and they are free to withdraw at any time, without giving any reason, and without your or your child's legal rights being affected. If your child withdraws then the information collected so far cannot be erased and this information may still be used in the project analysis.

Will any genetic tests be done?
If you agree, the research nurse will collect some saliva from your child's mouth to test for a gene which may play a part in childhood eczema. The sample will be sent to a genetics laboratory at the University of Dundee for analysis.

We will only test for a gene that may be relevant to childhood eczema and we will not do any other genetic testing. Current guidelines suggest that you should not be informed of the results of this test as the findings will not be used to influence your child's clinical care. The research nurse can explain why this is if you would like to know more.

The results from this testing will be sent securely back to the Nottingham Clinical Trials Unit (the co-ordinating centre).

What will happen to any samples my child gives?
Any remaining samples may be stored and used to test for other genes found to be associated with eczema in the future – this is optional (please indicate you agree to this on the consent form). The samples will be stored with a code unique to your child and securely at the Centre for Dermatology & Genetic Medicine of the University of Dundee (Ethics number 12/ES/0083). The samples will only be made available to the existing study team.

Any samples or data will be anonymised, and your child will not be identified in anyway. You do not have to agree to store your child's sample to be able to take part in the genetics study. If you do not agree to this, any remaining samples will be disposed of in accordance with the Human Tissue Authority's codes of practice.

What if relevant new information becomes available about the topic being studied?
Sometimes during the course of a research project new information becomes available about the topic being studied. If this happens, a member of the research team will tell you and your child (if applicable) about it and discuss whether you want your child to continue in the study. If you decide that you wish your child to continue in the study you will be asked to sign an updated consent form, which your child may also sign if they wish. Also, on receiving new information the research team might consider it to be in your child's best interests to withdraw them from the study. If this happens, they will explain the reasons why. If the study is stopped for any other reason, you will be told why.

What will happen to the results of the research study?
When the study has been completed, the data will be analysed and the results published in a medical journal and presented at medical meetings. You will be sent a copy of the results unless you tell us that you would prefer not to receive them. The results will allow a recommendation to be made to doctors and nurses about whether silk clothing is useful in the treatment of eczema in children.

Who is organising and funding the research?
This research is being organised by the University of Nottingham and is being funded by the National Institute of Health Research (NIHR) Health Technology Assessment Programme. The clothing being used in the study has been donated by the clothing suppliers for these garments.

Who has reviewed & approved the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by [NAME] Research Ethics Committee.

Further information and contact details
Contact Details of your local Research team

Name_____ and Telephone Number_____

Contact details for any questions about the clothing

Name_____ and Telephone Number_____

If you have any general queries about participating in research you can contact the Patient Advisory and Liaison Service (PALS) *Local PALS details to be added*.

THANK YOU FOR READING THIS INFORMATION SHEET

Appendix 3 Child information sheet (for age 1–5 years)

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Clothing for the relief of Eczema Symptoms

The CLOTHES Trial

An information sheet for children aged 5 and under

Sometimes you get itchy and your skin gets sore.
This can make you sad.

Your mummy or daddy may put cream and bandages on you to make you feel better but sometimes it doesn't work and you get itchy and sore again.

The doctors and nurses here are looking for ways to stop your skin getting sore. They would like to see if wearing some special clothes after your mummy or daddy puts your cream on, helps you.

You can wear these during the day and when you are asleep.

You can wear your other clothes on top.

The postman or postlady will either bring your special clothes right away or later on.

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To help the doctors and nurses to know if your skin is getting better, your mummy and daddy will be asked to answer some questions. You can help them by telling them how you feel

You could even draw them a picture or put stickers on a special chart. And you could help your mummy or daddy type some things into the computer too.

The nurse will look at your skin when you come to visit them.

They aren't allowed to know if you have been wearing the clothes or not so please don't tell them!!

If we find out that the special clothes do help children like you, then we can give them to more children to make their skin better.

If they don't really help then we can keep looking for ways to help everyone.

You can chat more to your mummy or daddy or the doctors or nurses about this.

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Appendix 4 Child information sheet (for age 6–10 years)

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Clothing for the relief of Eczema Symptoms

The CLOTHES Trial

An information sheet for children aged 6 to 10

Sometimes your skin gets red and itchy and this can be sore and make you feel miserable or grumpy.

You may put on creams and lotions and bandages but sometimes they don't help very much.

Doctors and nurses are investigating whether wearing special clothes after you have put your normal creams on, will help your skin. We do not know if they help, but we want to find out.

We are looking for 300 children like you to help in this investigation!

To know if the clothes work, half of the children wear the clothes right away, and the other half will wear them a little later.

VS

We will compare these two groups.

After your visit with the nurse, a computer will decide which group you will be in:

Clothes Now

Clothes Later

All children who help us in the study, whether they wear clothes right away or later, are very important to helping us in our investigation!

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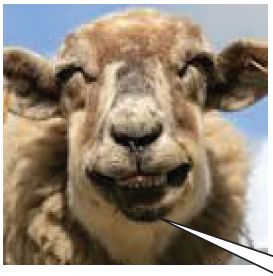
When the special clothes arrive at your house, you can wear them:

during the day under your normal clothes,

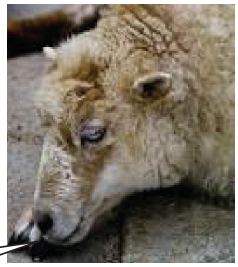
and at night.

You will be asked to see the nurse 4 times and they will look at your skin. They aren't allowed to know if you have been wearing the clothes or not so please <u>don't tell them</u>!!

Your mummy or daddy will be asked to fill in some information about you and how you have been getting on. You can help them with this by telling them how you feel and completing a sticker chart. Some of the information can be filled in on the computer and they may let you help them.



It would be really good if you could tell your mum or dad what you think about the clothes. You don't have to say that they are good if they aren't.



When everyone finishes wearing their clothes, the doctors and nurses will look to see if the clothes have helped.

If the clothes have helped, then they can try to make sure that all children like you are able to wear them so that their skin can get better. If they haven't helped, then they can tell people that the special clothes don't help and try to think of new ways to help.

If you would like to chat about this or have any questions then please ask your mum or dad, or one of the doctors or nurses.

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Appendix 5 Child information sheet (for age 11–15 years)

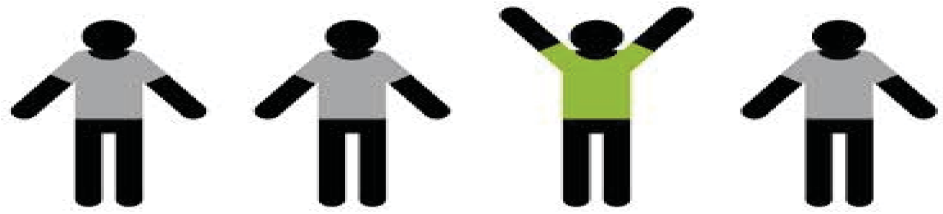
The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Clothing for the relief of Eczema Symptoms

The CLOTHES Trial
An information sheet for children aged 11 to 15

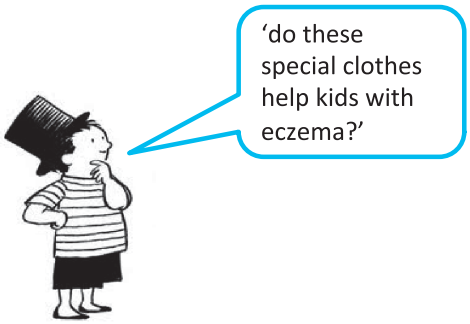
Eczema can be a horrible condition sometimes making your skin red, itchy and sore. This can be both painful and embarrassing. As you know it can be treated with creams and you may have been advised to wear loose cotton clothing and avoid having wool and other rough fabrics next to your skin.

Some companies have developed special silk clothing which might help children with eczema, like you. However, there is no proof that these clothes work, but we would like to find out.



We would like to investigate whether wearing silk clothing under your normal clothes can help your eczema. To do this we need 300 children like you to take part in a 'clinical trial'. 150 children will be asked to continue with their normal eczema treatment and start wearing the silk clothing right away, and 150 children will be asked to continue with their normal eczema treatment for 6 months and then to wear the silk clothing after that.

We need to have these two groups so that we can compare, over time, the skin of children who wear the clothes right away to the skin of the children who wear the clothes a little bit later. Having these two groups is the only way we can answer the question:



Answering this question could maybe help us treat a lot more children like you in the future, but we would not be able to answer our question if we did not have both groups: **all children who help us in the study, whether they wear clothes right away or later are very important to helping us in our investigation!**

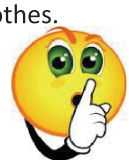
ChildInformationSheet_11-15_Final2.0_7 Feb 2014

In order to make the study as scientific as possible, a computer will decide who will wear the clothes right away and who will wear them after 6 months. You would have an equal chance of being asked to start right away or start after 6 months.

150 children to start wearing clothing now

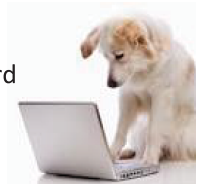
150 children to start wearing clothing in 6 months

If you agree to take part, you would be asked to come to the clinic 4 times – once at the start of the trial and then 2, 4 and 6 months later. At the clinic you would have your eczema examined by a research nurse. The nurse would not be told whether you had been wearing the silk clothing so that they would not be swayed by knowing that you had or had not been wearing the clothes. **It is important that you do not to tell the nurse and not to wear the clothes to your appointment!!!** This will make the results far better.



At these appointments your parent or guardian would also be asked some questions and asked to complete some short questionnaires which you could help with.

During the study, you (or your parent/guardian) would be asked to record information about your eczema and its treatment in a diary card each day and also in a short questionnaire each week which can be completed either on-line or by post. You (or your parent or guardian) would also be asked to note when you had worn the silk clothing.



When everyone has completed the study, the data will be analysed. We will compare eczema in children who wore the clothes for the first six months and those who didn't. We will also look at the children who started to wear the clothes later to see if there were any changes in their eczema after they started to wear the clothes.

VS

The results will be used to help doctors to understand if silk clothing is useful for children like you who have eczema. If you don't want to take part in this clinical trial, it will not affect any of the treatments you receive now or in the future.

Please ask your parent/guardian and research nurse if you have any questions.

Thank you for reading this!

ChildInformationSheet_11-15_Final2.0_7 Feb 2014

Appendix 6 Statistical analysis plan

Randomised controlled trial of silk therapeutic clothing for the long-term management of eczema in children

FINAL Statistical Analysis Plan

Version 1.0 (15th December 2015)

Based on Protocol version 3.0 (dated 11 February 2014)

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
Name	**Role**	**Signature**	**Date**
Lucy Bradshaw	Author		
Prof Alan Montgomery	Trial Statistician		
Caroline O'Leary	Independent Statistical Reviewer (TSC statistician)		
Prof Kim Thomas	Chief Investigator		

Abbreviations

Abbreviation	Description
ADQoL	Atopic Dermatitis Quality of life preference based index
AE	Adverse Event
CHU-9D	Child Health Utility 9 dimensions
CI	Chief Investigator
CRF	Case Report Form
DFI	Dermatitis Family Impact Questionnaire
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EASI	Eczema Area and Severity Index
IGA	Investigator Global Assessment
NCTU	Nottingham Clinical Trials Unit
NESS	Nottingham Eczema Severity Scale
PGA	Participant Global Assessment
POEM	Patient Orientated Eczema Measure
RCT	Randomised Controlled Trial
RN	Research Nurse
SAE	Serious Adverse Event
TIS	Three Item Severity Scale
TMG	Trial Management Group
TSC	Trial Steering Committee

Amendments to versions

Version	Date	Change/comment	Statistician

1. INTRODUCTION & PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the HTA funded randomised controlled trial of silk therapeutic clothing for the long-term management of eczema in children.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses is appropriate.
2. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence.

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

2.1. Trial aims and objectives

The purpose of this study is to establish whether silk therapeutic clothing is effective in the long-term management of eczema in children.

2.1.1. Primary objective

To assess whether silk therapeutic clothing, when used in addition to standard eczema care, reduces eczema severity in children over a period of six months.

2.1.2. Secondary objectives

1. To estimate the within trial cost-effectiveness of silk therapeutic clothing with standard care, compared to standard care alone, from an NHS and a family perspective.
2. 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 (assessed in qualitative component)
3. To examine prescribers /commissioners views of the use of silk garments (assessed in qualitative component)

2.2. Trial design and configuration

This is an assessor-blind, multicentre parallel group randomised controlled trial over 6 months followed by a 2 month open follow-up period where the control group will also receive the therapeutic clothing. There is an optional qualitative component 8 months post randomisation.

2.3. Trial centres

Participants will be recruited from 5 centres in the UK:

1. Nottingham
2. Barnet and Chase Farm
3. Cambridge
4. Isle of Wight
5. Portsmouth

Additional centres may be added during the recruitment period.

2.4. Eligibility criteria

2.4.1. Inclusion criteria

- Children aged 1 to 15 years at baseline.
- Diagnosis of moderate or severe eczema (atopic dermatitis). Presence of eczema will be confirmed using the UK Diagnostic Criteria for Atopic Eczema and eczema severity judged using the Nottingham Eczema Severity Scale (NESS).
- Resident within travelling distance of a recruiting centre.
- Children with at least one patch of eczema on the trunk or limbs.
- Parent/legal guardian able to give informed consent.

2.4.2. Exclusion criteria

- Children who have taken systemic medication (including light therapy) or oral steroids for eczema within the previous three months.
- Children who have started a new treatment regimen within the last month.
- Children who have used wet/dry wraps ≥5 times in the last month.

- Children who are currently using silk clothing for their eczema and are unwilling to stop using the clothing during the trial.
- Children who are currently taking part in another clinical trial.
- Children who have expressed a wish not to take part in the trial.

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 eligibility criteria above.

2.5. Description of interventions

Standard care

All participants will continue with their standard eczema care in line with NICE guidance [1][1]. This includes emollients, topical corticosteroids and topical calcineurin inhibitors. No efforts will be made to intervene or change a child's standard eczema care. Standard advice about what clothing to use for a child with eczema will be provided but specific products will not be recommended.

Silk therapeutic clothing

The medical device under investigation is a knitted, sericin-free silk therapeutic garment with a CE mark for use in eczema. The silk clothing will be worn at night, and when possible during the day. Participants will receive three sets of garments (long-sleeved vest and leggings, or body suits and leggings depending on the age of the child). Clothing will be replaced as required during the six-month RCT. Two different brands of clothing, Dermasilk and Dreamskin, which are currently available on prescription, will be used although participants will not be aware of the brand of clothing they receive.

2.6. Randomisation procedures

Randomisation is conducted by research nurses at the baseline visit, after eligibility for the trial has been established, via a remote internet based randomisation system developed and maintained by Nottingham Clinical Trials Unit (NCTU). The randomisation schedule is based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by NCTU in accordance with their standard operating procedure (SOP) and held on a secure University of Nottingham server. Children are randomised to either receive standard care and silk therapeutic clothing or standard care alone. The randomisation is stratified by recruiting hospital and by child's age: <2years; 2 to 5 years; and >5 years. Children randomised to therapeutic clothing are then further randomised to one of the two brands of silk clothing. A further randomisation for children randomised to standard care alone determines the brand of clothing which they will be sent at 6 months for the 2 month open follow-up period.

The sequence of treatment allocations will be concealed until interventions have all been assigned and recruitment, data collection, and all other trial-related assessments are complete.

After each allocation, the Nottingham CTU co-ordinating centre is notified so that participants can be informed by letter of their treatment allocation, and receive their supply of therapeutic clothing if appropriate.

2.7. Sample size and justification

Three hundred participants provides 90% power, at the 5% significance level (two-tailed) to detect a difference of around 3 points between the groups in mean EASI scores over 2, 4 and 6 months using a repeated measures

analysis of covariance, assuming a standard deviation of 13, a correlation between EASI scores at different time points of 0.6 and loss to follow up of 10%.

A 3-point improvement in EASI represents a small but still clinically meaningful difference between groups, and we are keen to ensure that the study is sufficiently powered to detect this magnitude of difference since it is unlikely that a trial like this will be done again. A small treatment response could still be worthwhile to the NHS since this non-pharmacological treatment is assumed to have no adverse effects, and because eczema affects so many people. It is also likely that a relatively small response on the objective primary outcome will be reflected in larger, more clinically meaningful treatment effects in the patient-reported outcomes.

2.8. Blinding

The table below summarises the knowledge of group assignment for participants, research nurses, trial management team and statistician during the study.

	Blinding status	Comments
Participants	Not Blinded	It is not possible to blind participants. Efforts will be made to minimise expectation bias.
Research nurses and PI	Blinded	Participants will be reminded in their clinic appointment letters not to wear the clothing when they attend the clinic or to mention the clothing in any way when talking to the research nurses. Instances where research nurses become unblinded will be recorded.
Trial staff at Nottingham CTU	Not blinded	NCTU staff will be the main point of contact for participants wishing to contact the research team, will package and post the clothing to the participants according to the randomisation schedule, and will provide general advice.
Statistician	Blinded	The analysis plan will be finalised prior to database lock and release of the treatment codes. Any reports required for TSC split by treatment group will be run by an NCTU statistician not working on the Clothes study.

2.9. Trial committees

A Trial Management Group (TMG) and a Trial Steering Committee (TSC) will be assembled for the study. No Data Monitoring Committee (DMC) will be assembled due to the low safety risk of the clothing.

The TMG will be responsible for the day-to day running of the trial and will meet regularly to review the progress of the trial and to address any issues arising.

The TSC will be set up with an independent chairperson and will monitor, review and supervise the progress of the trial at least once a year.

2.10. Outcome measures

2.10.1. Primary outcome

The primary outcome is eczema severity measured by the objective Eczema Area and Severity Index (EASI) [2] at baseline 2, 4 and 6 months. Assessments will be made by research nurses who have been trained in using

the EASI tool and who are blinded to group allocation. The same research nurse will assess the skin at each time point for each participant in order to minimise inter-observer variability.

The head and neck, upper limbs, trunk and lower limbs are assessed separately for key signs of erythema (E, redness), induration/papulation/oedema (I, thickness), excoriation (Ex, scratching) and lichenification (L, lined skin) and rated on a scale of 0 (none) to 3 (severe) in steps of 0.5. Each sign is assessed for the entire body region – for example a patient may have grade 1 erythema in some areas, but grade 3 erythema in others. If that is the case, then the "average of the two" is taken and so the score becomes 2. Likewise, if they have some areas that are grade 2 and others that are grade 3, then the score becomes 2.5. Within each body area, a different representative site can be chosen for each sign. The percentage area affected within each body region is also assessed and scored as in the table below.

% area	No eruption	< 10%	10-29%	30-49%	50-69%	70-89%	90-100%
Area category	0	1	2	3	4	5	6

An EASI score for each body area is then calculated as:

(E + I + Ex + L) x area category

The total EASI score is a weighted sum of the four EASI scores for each body area, where the weights are determined by the child's age at randomisation as shown in the table below. The final EASI score ranges between 0 and 72.

Body area	Aged 7 years or less	Aged 8 or more
Head & neck	0.2	0.1
Upper extremities	0.2	0.2
Trunk	0.3	0.3
Lower extremities	0.3	0.4

Research nurses were trained in how to use the EASI prior to using it for study assessments. Nurses from the different sites also assessed the EASI in pairs on between 5 and 10 participants. The aim was for the total EASI scores for the two nurses to be within 3 points.

2.10.2. Secondary outcomes

a) Global assessment of the eczema

Assessed by research nurses (Investigator Global Assessment: IGA) and by participants (Participant Global Assessment: PGA) at baseline, 2, 4 and 6 months and rated as either clear, almost clear, mild, moderate, severe, or very severe.

b) Three Item Severity scale (TIS)

Assessed by the research nurses at baseline, 2, 4 and 6 months and used to assess eczema severity.

Erythema, oedema/papulation and excoriation are rated as absent (0), mild (1), moderate (2) or severe (3). The TIS score is the sum of the scores for each sign and ranges between 0 and 9. One representative body site is chosen to assess all three signs. This site should be in an area covered by the clothing and be the area that, in the view of the parent/participant, is most bothersome. The representative body site may change from visit to visit.

c) Use of topical treatments: use and potency of topical steroids and topical calcineurin inhibitors, use of emollients and frequency of wet / dry wrapping throughout the trial.

The weekly questionnaires will ask about the number of days in the previous week that emollients, topical steroids, topical calcinuerin inhibitors and wet/dry wraps were used. For each participant, the proportion of days that each of these topical treatments were used will be calculated:

total number of days topical treatment used/(total number of questionnaires completed*7)

Change in eczema treatment is assessed at each clinic visit and is categorised as no change, neutral change, reduction or escalation. Potency of topical treatments will be assessed at baseline and at the 6 month visit in clinic.

d) Self reported eczema symptoms using the Patient Oriented Eczema measure (POEM) [3]

This can be completed by the parent/guardian or child and asks about the frequency of seven signs of eczema (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking and dryness) in the previous week (no days, 1 to 2 days, 3 to 4 days, 5 to 6 days, every day). The responses to the seven items are scored to create a total score ranging from 0 to 28.

The POEM questionnaire is included in the 2 monthly clinic visits and also in the weekly questionnaires (online or postal) due to the fluctuating nature of eczema. It is recommended for a consistent approach to questionnaire completion that the parent and child complete the questionnaires together if the child is old enough.

e) Health Related Quality of Life at baseline and 6 months

This will be assessed for the children with eczema and for the rest of the family/parents using the assessments below.

a. Dermatitis Family Impact Questionnaire (DFI) [4]

This is completed by the child's parent/guardian and assesses the impact of the child's skin problem on family life over the previous week. There are 10 questions assessing different aspects of family life which are summed to create a total score ranging from 0 to 30.

b. EQ-5D-3L

This is a generic instrument to measure health related quality of life and will be used to provide a utility score for the main carer [5]. A score from a visual analogue scale ranging from 0 (worst imaginable health status) to 100 (best imaginable health status) is also collected.

c. Atopic Dermatitis Quality of life preference based index (ADQoL) [6]

This will be used to provide an eczema specific utility score for the child from the 16 possible health states from the index for the day the questionnaire is completed. The utility value is anchored so that 0 represents a health state which is perceived as being dead and 1 represents a health state representing perfect health.

d. Child Health Utility 9 dimensions (CHU-9D) [7]

This is a generic measure of health related quality of life for children on the day that the questionnaire was completed and can be completed by either the child or the parent/guardian. A utility score for each child is derived from the responses to 9 dimensions of QoL assessed. The

index will be completed by the children themselves if they are aged 7 or over, together with the parent or guardian for children aged between 5 and 7 and will not be completed for children under 5.

f) Durability of the garments, adherence and acceptability of use (as assessed by children and parents/carers)

For participants allocated to the intervention group, the number of days and the number of nights that the clothing has been worn in the previous week is completed on each weekly online/postal questionnaire. Participants are given a sticker chart to use as an aide memoir to help complete these questions. For each participant, the proportion of days/nights that the clothing has been worn will be calculated as:

total number of days(nights) clothing worn/(total number of questionnaires completed*7)

The adherence and acceptability of the clothing is assessed on the 6 month online/postal questionnaire for participants allocated to the intervention group and for all participants at the end of the open follow-up period using simple questions about satisfaction with the clothing, whether the child was happy to wear the clothing and how many sets of clothing the participant has used with the reasons collected if sets can no longer be worn.

g) Cost-effectiveness and cost utility

This analysis is being conducted by Dr Tracey Sach at the University of East Anglia and will be described elsewhere.

The number of children with mutations of the *FLG* genotype will also be reported and used to inform a planned sub-group analysis, to test whether there is any evidence of a difference in the effect of the therapeutic clothing according to presence/absence of these mutations.

2.10.3. Safety outcomes

a) Number of skin infections – defined as parental-reported skin infections that require antibiotic or antiviral treatment.

The weekly online/postal questionnaire will ask if the child has had any prescriptions for eczema over the past week and will be instructed to record any details on the diary card. This will be given to the research nurse at each clinic visit to record any skin infections on the eCRF.

b) Serious adverse events

The silk clothing is unlikely to result in any adverse device effects other than potentially the number of skin infections so only serious adverse events will be recorded. This will capture any hospitalisations due to eczema.

2.11. Interim analysis

No interim analyses of outcome data are planned.

An internal pilot RCT will be conducted over the first 6 months of the trial to assess recruitment, adherence with the trial clothing and retention.

3. GENERAL ANALYSIS CONSIDERATIONS

3.1. Analysis samples

The main approach for the analysis will be to analyse participants as randomised regardless of the adherence with their allocated group without imputation for missing data for all primary and secondary outcomes (intention to treat principle). Sensitivity analyses will explore the effect of missing data and adherence with the allocated group. See section 6.2 for further details.

3.2. Procedures for missing data

Missing items in questionnaires

Missing items on the DFI questionnaire will be imputed by the participant specific mean of the completed responses if 8 or more of the 10 items are completed. The score will not be calculated if 3 or more items are missed.

For missing items on the POEM questionnaire, the total score will be calculated according to guidance on the Centre for Evidence Based Dermatology website:

- If one question is left unanswered this is scored as 0 and the scores are summed and expressed as usual out of a maximum of 28
- If two or more questions are left unanswered the questionnaire is not scored.

See http://www.nottingham.ac.uk/research/groups/cebd/resources/poem.aspx.

No utility score will be calculated for participants where items are missed on the EQ-5D, ADQoL and CHU-9D.

Missing baseline data

Missing baseline scores are expected to be rare as data are collected at the first clinic visit. However any missing baseline scores in analyses using the baseline as a covariate will be imputed using the mean score at each centre in order to be able to include these participants in the analysis. These simple imputation methods are superior to more complicated imputation methods when baseline variables are included in an adjusted analysis to improve the precision of the treatment effect [8].

Missing data on topical treatment usage on questionnaires

The weekly questionnaires ask about the number of days in the past week that emollients, topical steroids, topical calcinuerin inhibitors and wet/dry wraps were used. Some participants may not respond about all types of treatment every week. In the case where there is a response for some types of treatments but not all, the number of days that the treatment with no response was used will be assumed to be 0 for the calculation of the proportion of time that the topical treatment was used.

Missing outcome data

All missing data items will be tabulated by treatment group with reasons given where possible. Patterns of missing data will be explored. The characteristics of participants with missing data will be investigated in each group to examine the plausibility that data are missing at random. Mixed models (for repeated measures) will be used to handle missing values for EASI, TIS, global assessment of eczema and POEM collected in clinic. These models assume that missing data are missing at random. Sensitivity analysis will evaluate the robustness of the conclusions for the primary outcome if outcomes are assumed to be missing not at random. There will be no imputation for any of the other secondary outcomes.

Follow-up for the study includes weekly online or postal questionnaires. The number of questionnaire returned to the NCTU each week will be summarised and the total number of questionnaires returned over the 6 month RCT will also be summarised.

3.3. Visit and questionnaire windows

Participant weekly questionnaire can either be completed online or on paper and sent back to the NCTU. Participants can switch between completion methods at any time. The link to the weekly questionnaires will remain active for 3 days for questionnaires sent out in weeks 1 to 23, if the questionnaire is not completed in this period it will no longer be able to be completed. Data from paper based questionnaires will be entered as is, even where the completion date is outside of this 3 day window. The week 24 and week 32 questionnaires have longer time windows for completion as information is collected relating to the 6 month RCT period/2 month open follow-up period on satisfaction, the condition of the trial clothing and purchases of silk clothing. For the analysis of secondary outcomes from the questionnaires (POEM and topical treatment usage), only questionnaires completed prior to the 6 month clinic visit date will be included. This will ensure that there is no contamination due to children in the control group receiving silk clothing after the 6 month clinic visit.

The 2, 4 and 6 months clinic visits should be completed 8 weeks, 16 weeks and 24 weeks after the baseline visit respectively (± 14 days). Data from all visits will be included in the main analysis regardless of whether it was conducted within the visit window.

5. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1. Disposition

A flow of patients through the trial will be summarised in a CONSORT diagram that will include the numbers assessed for eligibility, reasons for exclusion, numbers randomised to the two treatment groups, numbers receiving the allocated intervention, losses to follow up and the numbers analysed.

4.2. Baseline characteristics

The baseline characteristics of the two groups with respect to demographic characteristics (age, gender, ethnicity), eczema characteristics (type of eczema, location, *FLG* genotype) and eczema severity (NESS, EASI, TIS, POEM, IGA and PGA), topical and other treatment usage for eczema in the month prior to randomisation and quality of life (DFI, EQ-5D, CHU-9D and ADQoL) will be summarised.

Continuous data will be summarised in terms of the mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations. Categorical data will be summarised in terms of frequency counts and percentages. The proportion of participants with missing values will also be given for each variable.

5. ASSESSMENT OF STUDY QUALITY

5.1. Data validation

The data management plan and validation plan details all programmed validation checks including missing values, out of range values, illogical values, invalid responses and cross form checks. Additional data checks will be conducted by the statistician when preparing the data for analysis in Stata.

5.2. Adherence

Adherence with wearing the trial clothing will be assessed on the participant weekly questionnaires by asking separately about the number of days and nights in the previous week that the clothing was worn. For each

participant, the proportion of days and nights that the study clothing was worn will be calculated and summarised. Adherence according to diary completion will be explored.

Participants will be classified as adherent if they wear the trial clothing for at least 50% of the days or nights where the diary had been completed, provided that at least 50% of the diary had been completed. Sensitivity analyses will also show adherence for all participants by making different assumptions about clothing wear during periods where the questionnaire was not completed (e.g. clothing worn for the same proportion of time as when questionnaires are returned, clothing not worn at all when the questionnaire is not completed).

Children allocated to the control group may also wear silk garments during the intervention period, either due to an error in the distribution of the trial clothing or due to parents purchasing silk clothing. At 6 months, the use of different types of clothing (pure cotton, silver impregnanted, silk clothing and stretchy garments), in addition to the trial clothing, will be tabulated by group.

5.3. Clinic visit attendance and questionnaire return

Follow-up visits in clinic are at 2 months, 4 months and 6 months. The number and percentage of participants attending these visits will be summarised in each group as well as the number of days between randomisation and these follow-up visits. The number of these visits taking place outside of the 14 day time window will be tabulated. Reasons will also be tabulated for participants who did not complete the study up to the 6 month clinic visit.

For the weekly questionnaires, the number and percentage of participants completing each questionnaire from baseline to week 24 and at week 32 will be summarised. The total number of questionnaires returned by each participant will also be summarised in the two groups. This will show whether completion changes according to time in the study and also the overall level of questionnaire completion in the two groups. The pattern of questionnaire completion will also be explored e.g. missing a few questionnaires out during the study, numbers completing the questionnaire up to a certain point and then no longer completing, etc.

The number of participants completing the 24 month questionnaire before the 6 month assessment visit will also be summarised.

The initial method of questionnaire completion will be summarised as well as whether participants switched methods (due to change in preference or holidays etc).

5.4. Protocol deviations

A protocol deviation is an unanticipated or unintentional divergence or departure from the expected conduct of a study inconsistent with the protocol, consent documents or other study procedures. Of particular importance are major deviations (violations) which may expose participants to increased risk; compromise the integrity of the entire study or affect participant eligibility.

Protocol deviations, as reported on the eCRF page, will be listed with information on treatment group and the type of deviation. Full details of the protocol deviations will also be listed.

5.5. Blinding of research nurses during the clinic visits

The primary outcome measure is assessed by a research nurse who should be unaware of the allocated intervention. At the end of each visit, the research nurse is asked if they have been accidentally unblinded since the last visit (yes/no, details are not collected on which group the research nurse believe the participants to be in). This will be summarised at each visit and overall to show the total number of participants where a research nurse became unblinded at any point during the study. Any unblinding during the study will be

explored descriptively by summarising outcomes according to group and blinding status (no unblinding/unblinded at some point during the study). The baseline characteristics of participants according to unblinding occurrences may be explored if appropriate.

5.6. Questionnaire completion

The completion of each of the questionnaires handed out at clinic visits (POEM, DFI, EQ5D, CHU-9D, ADQoL) will be summarised (fully completed, partially completed – scoreable, partially completed and not scoreable, visit attended but not completed).

The completion of the POEM on the weekly questionnaires will be summarised for each week and also the total number of weeks that the POEM was completed for each participant.

6. ANALYSIS OF EFFECTIVENESS

Analyses will be performed using Stata version 13 or above or MLwiN as appropriate. All tests will be two-tailed with point estimates, 95% confidence intervals and exact p-values for the treatment effect presented. Analyses using regression models will adjust for the stratification factors used in the randomisation: site and age. No formal adjustment for multiple significance testing will be applied. The primary approach for analysis will be as randomised without imputation of missing data.

All outcomes collected at the 2 monthly clinic visits will be summarised by time point and treatment group. All outcomes collected from the weekly questionnaires will be summarised by week and treatment group. For repeated measures, the mean score in each treatment group at each timepoint will also be presented on a graph.

6.1. Primary analysis

The primary analysis for the total EASI score will be performed using a multilevel model (MLM) framework, with observations at 2, 4 and 6 months (level 1) nested within participants (level 2) and including baseline EASI and the stratification factors (site and age) as covariates. The most appropriate covariance structure will be selected after a review of the data.

This model will use all the observed data and makes the assumption that missing EASI scores are missing at random given the observed data. The effect of trial clothing on eczema severity changing over the study period will be tested by including an interaction term between treatment group and timepoint in the model. If there is no evidence of a differential effect over time, a single treatment effect will be reported showing the difference in mean EASI score between the two groups. If there is evidence of an interaction effect then the treatment effect at each different time point will be reported.

The assumptions of the normality of the residuals from the fixed part of the model and the normality of the random effects at the cluster level will be checked.

Appropriate transformations will be considered if there is some suggestion that the assumptions for the multi-level linear model may not be met. Based on the distribution of the EASI scores at baseline, a log transformation is the most likely transformation that will be used. In this case, the treatment effect will be presented as the ratio of the geometric means of the EASI scores in the two groups.

6.2. Sensitivity and subgroup analyses for the primary outcome

6.2.1 Sensitivity analysis for missing data

Sensitivity analyses for missing data to explore departures from the missing at random assumption used in the primary analysis will be performed. Multiple imputation will be used to impute missing EASI values at 2, 4 and 6 months under a missing at random assumption with an imputation model including baseline values and questionnaire information. Imputations will be done separately for each allocated group if possible. It will be assumed that participants with missing EASI values who do not complete the follow-up to 6 months have systematically different outcomes. Best and worse case scenarios will be explored by subtracting or adding 3 points (the clinically meaningful difference used in the sample size calculation) for these participants to the EASI value imputed under the missing at random assumption. The analysis specified above will repeated to explore if the findings from this sensitivity analysis are similar to the main analysis.

6.2.2 Sensitivity analysis for adherence with allocation

To explore the effect of wearing the trial clothing, the complier average causal effect (CACE) will be estimated for the primary outcome using instrumental variable methods [9]. This will give an estimate of the treatment effect for children who actually wear the clothing compared to the estimate of the treatment effect from the as randomised analysis which is more useful for estimating the effect of prescribing the clothing.

Two estimates will be presented:

- Using the definition of adherence in section 5.2 to give the complier average causal effect for participants who wear the trial clothing for at least 50% of the time.
- Using the proportion of time that the trial clothing was worn to give an estimate of the trial clothing for each additional 10% of time worn. The proportion of time that the trial clothing is worn will be calculated based on days and nights and calculated as:

  total number of days and nights clothing worn/(total number of questionnaires completed*14)

6.2.3 Subgroup analysis for *FLG* genotype

A subgroup analysis based on presence or absence of mutation(s) in the *FLG* gene will be conducted for the primary outcome. Mutations in the *FLG* gene are found in up to 50% of eczema patients and are associated with disruption to the skin barrier function. Children with at least one *FLG* mutation may be more likely to benefit from clothing as this potentially acts to improve the barrier function of the skin. Conversely children with *FLG* mutations may have more severe eczema and therefore be resistant to silk as a treatment, or indeed *FLG* genotype may have no effect on treatment response.

For the sub-group analysis, study participants will be tested for up to six prevalent *FLG* loss of-function mutations (depending on quality/quantity of DNA): R501X, 2282del4, R2447X , S3247X, 3702delG and 3673delC. For the purposes of this subgroup analysis each of the 6 mutations will be assumed to have an equivalent effect on eczema risk, as predicted from what is known about filaggrin.

Participants will be categorised into three groups according to their *FLG* genotype for the 4 common mutations (R501X, 2282del4, R2447X , S3247X):

Group 1: *FLG* +/+ (none of the four mutations above) – control cohort
Group 2: *FLG* +/- (carrying one *FLG* null mutation) – heterozygous for one of the mutations above
Group 3: *FLG* -/- (carrying two *FLG* null mutations) – homozygous for one of the mutations above or compound heterozygous for two of the mutations above

Note that some participants will not be able to be grouped as above if consent was not given for the genetic component or the saliva sample provided was not adequate. The rare mutations 3702delG and 3673delC will not be used for the purposes of the subgroup analysis as successful testing for these mutations depends on the quality and quantity of DNA in each sample.

The primary outcome, EASI eczema severity, will be presented descriptively by timepoint, allocated group and *FLG* gene mutation.

If there is no evidence of a different effect of the clothing over time in the primary analysis, an interaction effect between the allocated treatment and *FLG* mutation will be added to the analysis model used for the primary outcome. This will estimate the difference in the treatment effect over the whole study period according to *FLG* mutation and will be presented with a 95% confidence interval.

If there is evidence of a different effect of the clothing over time in the primary analysis, the interaction effect between the allocated treatment and *FLG* mutation will be estimated for the 6 month timepoint only for ease of interpretation. This timepoint has been chosen as it is most relevant to patients as it provides information on longer term eczema control. The interaction effect at the 6 month timepoint will be presented with a 95% confidence interval.

6.3. Secondary outcomes

For all secondary outcomes assessed at multiple time points, analyses will begin by testing whether there is any evidence that the effect of trial clothing changes over the study period. Treatment effects will then be reported according to whether there is an interaction between the trial clothing and time, as for the primary outcome outlined above.

6.3.1. Global assessment of eczema

The research nurse and participant assessment scores will be dichotomised for the analysis to indicate good/bad eczema at each timepoint. Assessments of clear, almost clear, mild eczema will be grouped to indicate good eczema and assessment of moderate, severe or very severe eczema will be grouped to indicate bad eczema.

The dichotomised global assessment of eczema variable will be analysed using generalised estimating equations with an exchangeable correlation and binomial family and appropriate link function using the baseline assessment score, site and age as covariates. The risk difference and relative risk of `bad' eczema in the intervention group compared to the control group will be presented with a 95% confidence interval

6.3.2. TIS

The analysis of the total score from the three item severity scale will be analysed using the multilevel model framework as outlined above for the primary outcome. Suitable transformations will be explored if there is evidence that the assumptions for this analysis are not met.

6.3.3. POEM

POEM data is collected at each clinic visit and on the weekly questionnaires. These will be summarised and analysed separately.

POEM data collected at clinic visits

The analysis of the total POEM score derived from data collected at the clinic visits will be analysed using the multilevel model framework as outlined above for the primary outcome.

POEM data collected on weekly questionnaires

Only questionnaires completed prior to the 6 month clinic visit date will be included in this analysis. This will ensure that there is no effect on the treatment estimate due to children in the control group receiving silk clothing after the 6 month clinic visit.

The total POEM score each week will be summarised by group and the data presented in a graph.

For each participant, the mean and standard deviation of their weekly POEM scores will be calculated and summarised by group [10]. The between-group difference using the mean post-randomisation weekly POEM scores for each participant will be estimated using a linear model using site, age and baseline POEM score (taken in clinic) as covariates. The regression analysis will be weighted according to the number of weekly questionnaires included in the calculation of the mean POEM score.

These data will also be used in the future to explore different ways of analysing long term control of eczema.

6.3.4. Frequency of use of topical treatments

Topical treatment usage (emollients, topical steroids, topical calcinuerin inhibitors and wet/dry wraps) will be summarised as the proportion of days that topical treatments were used during the 6 month RCT. This will be done separately for the following topical treatments:

- emollients
- topical steroids,
- topical calcinuerin inhibitors and
- wet/dry wraps

This will be summarised for the participants where at least half of the weekly questionnaires were completed and as a sensitivity analysis for all participants, assuming that the use of topical treatments was the same at times when questionnaires were not completed as at the times when questionnaires were completed. In addition, the number of days that topical treatments were used will be presented graphically according to week to explore if their use changes over time.

The proportion of days that topical treatments were used will be analysed using a linear model including site, age and use of the topical treatment (yes/no) as baseline as covariates. The difference in the mean proportion of days with topical treatment usage between the two groups will be presented with a 95% confidence interval.

Some of the above topical treatments may be used by only a small number of participants during the trial in which case the proportion of days that the topical treatments may be an inappropriate summary measure. If a large number of participants do not use a topical treatment during the trial, the topical treatment usage will be summarised as a binary variable indicating any use/no use. Risk differences and risk ratios will be used to compare the two groups using generalised linear models with binomial distribution and appropriate link function (identity or log) including site, age and use of the topical treatment (yes/no) as baseline as covariates.

6.3.5. Potency of topical treatments

For each group, the potency of topical treatments (steroids and calcinuerin inhibitors) used at 6 months will be tabulated against the potency used at baseline.

Data collected at each clinic visit on whether there has been a change in eczema treatment since the last visit will be presented descriptively. For each participant, a binary variable will be derived showing if the participant had any treatment escalation over the 6 month RCT period. The risk difference and risk ratio for any treatment escalation during the 6 month RCT with 95% confidence intervals adjusted for site and age will be presented. These will be estimated using generalised linear models with binomial distribution and appropriate link function (identity or log).

6.3.6. Quality of life

Quality of life at 6 months is measured for families using the DFI, the parent/guardian using the EQ-5D and the child using the CHU-9D and ADQoL. The QoL outcomes for the total score for the DFI and the VAS score for the EQ-5D will be analysed using a linear model (ANCOVA) with baseline score and stratification variables (site and age) as covariates. The difference in mean quality of life scores between the two groups for each QoL outcome measure will be presented with a 95% confidence interval.

These QoL outcomes for the utility scores for EQ-5D, CHU-9D and ADQoL will be analysed as part of the health economic analysis (see Section 10).

6.3.7. Adherence with trial clothing (intervention group only)

This will be summarised using the proportion of days and nights that the study clothing was worn for participants where at least half of the questionnaires were completed and for all participants as outlined in section 5.2. Adherence with the trial clothing will be explored descriptively according to age group, week of the study and eczema severity.

The proportion of participants wearing the trial clothing for at least 50% of the days or nights during the study will be presented with a 95% confidence interval.

6.3.8 Durability and acceptability of trial clothing (intervention group only)

Information reported on the 6 month online/paper questions on the total number of pieces of trial clothing that can no longer be worn will be summarised and the number and percentage of participants with at least one piece of trial clothing that can no longer be worn at 6 months will be tabulated. The reasons that the trial clothing can no longer be worn will be tabulated.

Information from logs kept within the NCTU on clothing distribution will also be summarised to present information on timing of clothing returns.

The frequency of the responses to the questions about satisfaction with the trial clothing and whether the child was happy to wear the trial clothing will be tabulated. The proportion of participants (or their parents) satisfied or very satisfied with the garments and happy or very happy to wear the garments will be summarised with 95% confidence intervals.

Satisfaction and acceptability (happiness) with the clothing at 6 months will be explored by age group and eczema severity at 6 months compared to baseline.

7. ANALYSIS OF SAFETY

7.1. Number of skin infections

The number of skin infections during the 6 month RCT will be analysed using negative binomial regression with site and age (stratification factors) as covariates. The relative risk of skin infections in the intervention group compared to the control group will be presented with a 95% confidence interval.

7.2. Inpatient hospital stay due to eczema

This will be analysed using a generalised linear model with binomial family and appropriate link function with the stratification factors as covariates. The relative risk/risk difference for an inpatient stay due to eczema in the intervention group compared to the control group will be presented.

7.2. Serious adverse events

All serious adverse events will be tabulated by allocated group according to MedDRA preferred term. Serious adverse events will also be listed.

8. ANALYSIS OF OPEN FOLLOW-UP PERIOD

The baseline characteristics and characteristics at 6 months will be compared for each group for participants completing the 8 month questionnaire and not completing the 8 month follow-up questionnaire.

For each group, eczema severity using the POEM and topical treatment usage in the past week at 8 months will be summarised with the results at 6 months and the change between 6 and 8 months. The difference in mean POEM scores and days of topical treatment usage between 6 and 8 months will be presented with a 95% confidence interval. Use of the clothing during the follow-up period, durability, acceptability and opinion of and satisfaction with the trial clothing will be summarised/presented by allocated group and overall. No formal comparisons between groups will be conducted.

Based on all data collected, 95% confidence intervals will be calculated for the proportion of participants at 8 months who were satisfied/very satisfied with the clothing, happy/very happy to wear the clothing, felt that eczema improved due to the clothing and would ask their GP to prescribe the clothing.

9. EXPLORATORY ANALYSES

9.1 Eczema severity according to coverage of clothing

The EASI score is calculated based on the severity of eczema on the head and neck, upper limbs, trunk and lower limbs. The trial clothing however does not cover the head and neck. Therefore an exploratory analysis will be conducted on eczema severity scores in areas covered by the clothing compared to areas uncovered by the clothing, in order to test the theory that gaining eczema control in one site may reduce a patient's overall immunological response, and therefore disease activity at distant sites.

EASI scores will be summarised separately for the head and neck and other body areas combined (trunk, upper and lower limbs). The analysis outlined in section 6.1 for the overall EASI score will be repeated for the head and neck scores and the other body areas combined to inform the interpretation of the main result.

9.2 Brand of clothing

At randomisation, participants are further randomised to have one of two different brands of clothing which were available on prescription at the time of trial set up, Dermasilk™ or Dreamskin™. The participants in the control group are sent these after the 6 month follow-up visit has been completed. It is assumed that the effect of the different brands of clothing will be similar. A tertiary analysis described below will explore this.

Analysis sample

During the study there was a supply problem with DreamSkin leading to NCTU being unable to supply the brand of clothing as specified by the randomisation. DermaSilk was sent to these participants during this time. Any participants randomised during the time period that DreamSkin was out of stock for their required size will not be included in this tertiary analysis by brand of clothing. Out of stock periods by size will be prepared by the trial manager from the clothing inventory appendix.

Baseline characteristics

The baseline characteristics of the groups randomised to each clothing brand will be summarised by allocated group during the RCT. In addition the characteristics at 6 months of participants randomised to the control group will be summarised by brand of clothing.

Adherence, durability and acceptability by brand

For participants randomised to receive trial clothing during the RCT period, adherence with wearing the clothing will be summarised by brand as described in section 5.2. Information on the durability and acceptability of the trial clothing as outlined in section 6.3.8 will also be summarised by brand.

At 8 months information on how often the trial clothing was worn during the previous 2 months, satisfaction with the trial clothing and whether the child was happy to wear the clothing will be split by clothing brand and randomised group. Information on the number of garments given out, the number of garments that can no longer be worn and the reason that garments can no longer be worn will also be tabulated/summarised by brand of clothing and allocated group.

EASI

For participants randomised to receive trial clothing during the RCT period, the total EASI eczema severity score will be summarised by clothing brand and timepoint. The difference in mean eczema severity scores between the brands will be estimated with a 95% confidence interval using the model described in section 6.1.

POEM

Total POEM scores from the online questionnaires will be summarised by brand of clothing for:

- baseline and 2 months for the group randomised to receive the trial clothing during the RCT and
- 6 and 8 months for the control group.

The total POEM score after 2 months of clothing wear will be analysed using a linear regression model including terms for the randomisation stratification variables, POEM score prior to receiving the clothing (baseline for the intervention group and at 6 months for the control group) and allocated group for the RCT as covariates. The difference in mean total POEM score will be presented with a 95% confidence interval.

10. OTHER ANALYSES

The cost-effectiveness evaluation of the intervention as specified in the protocol will be conducted by Dr Tracey Sach at the University of East Anglia, and will be specified in a separate Health Economics analysis plan.

11. FINAL REPORT TABLES AND FIGURES

See dummy table document

12. APPENDICES

12.1. DreamSkin out of stock periods by size

This information will be filed with the SAP when available.

13. REFERENCES

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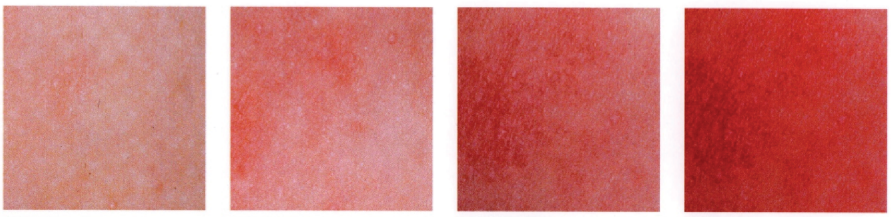
Appendix 7 Eczema Area and Severity Index resources for research nurses

EASI crib sheet

Erythema



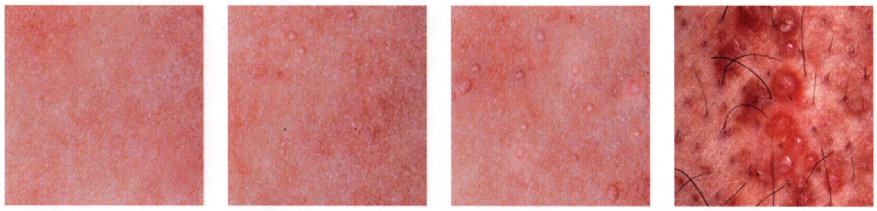
NONE

MILD
Faintly detectable erythema: very light pink

MODERATE
Dull red, clearly distinguishable

SEVERE
Deep/dark red

Infiltration/Papulation



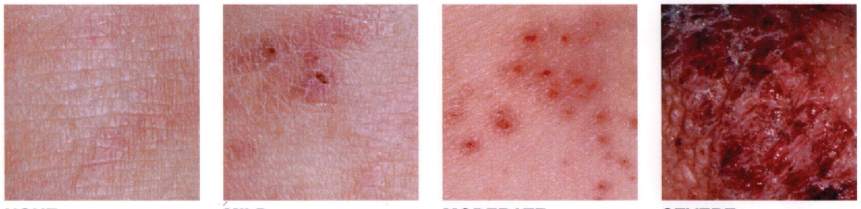
NONE

MILD
Barely perceptible elevation

MODERATE
Clearly perceptible elevation but not extensive

SEVERE
Marked and extensive

Excoriations



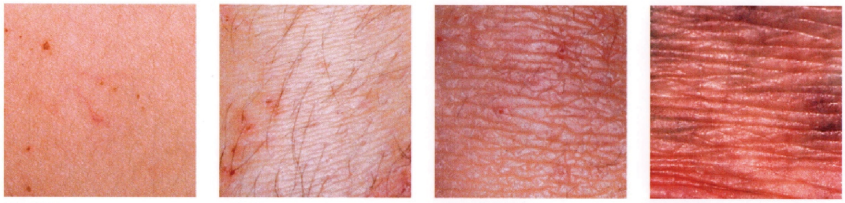
NONE

MILD
Scant evidence of excoriations with no signs of deeper skin damage (erosion, crust)

MODERATE
Several linear marks of skin with some showing evidence of deeper skin injury (erosion, crust)

SEVERE
Many erosive or crusty lesions

Lichenification



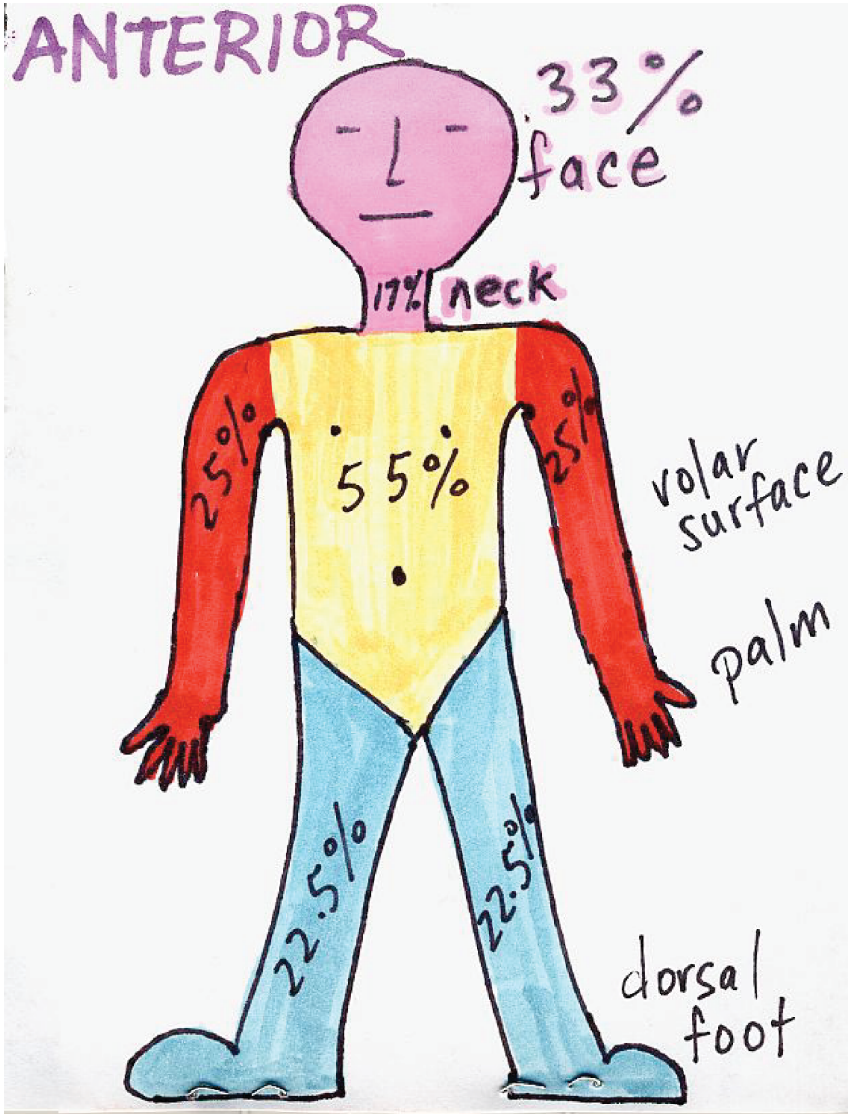
NONE

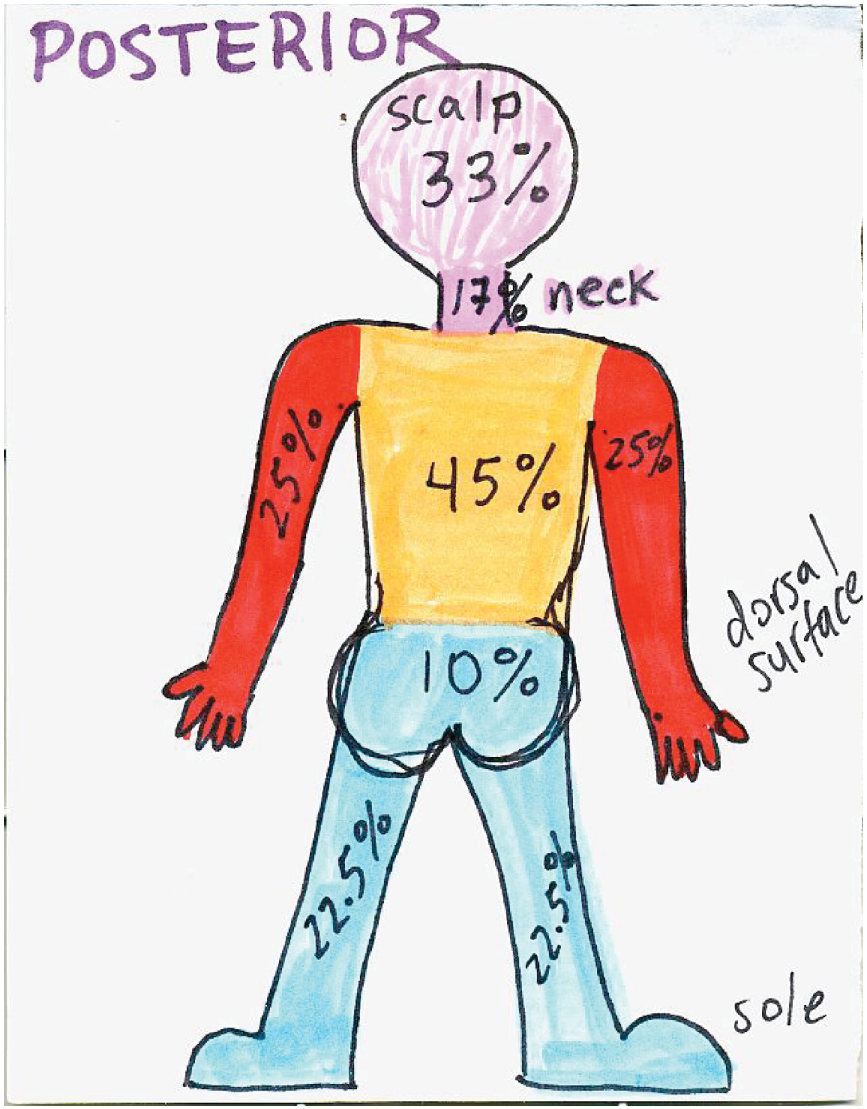
MILD
Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated

MODERATE
Definite thickening of the skin with skin markings exaggerated so that they form a visible criss-cross pattern

SEVERE
Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern

CLOTHES Trial - EASI crib sheet_v1.1_05 Nov 2013





Hand = 6% Hand and wrist = 10% Typical pattern of eczema in skin crease = 4%

Appendix 8 Participant sticker charts (intervention and control)

Please use this chart to record how long you have been in the study

Clothing for the relief of Eczema Symptoms

Place a sticker on the sun for each day you have been in the study.

Place a sticker on the moon for each night you have been in the study.

If you don't want to put the stickers on, you could cross the suns or moons out.

Month: ………………………			Month: ………………………			Month: ………………………		
01			01			01		
02			02			02		
03			03			03		
04			04			04		
05			05			05		
06			06			06		
07			07			07		
08			08			08		
09			09			09		
10			10			10		
11			11			11		
12			12			12		
13			13			13		
14			14			14		
15			15			15		
16			16			16		
17			17			17		
18			18			18		
19			19			19		
20			20			20		
21			21			21		
22			22			22		
23			23			23		
24			24			24		
25			25			25		
26			26			26		
27			27			27		
28			28			28		
29			29			29		
30			30			30		
31			31			31		

CLOTHES control sticker chart Final 1.0 – 5 Sept 2013

Appendix 9 Case report form worksheet

CLOTHES

Randomised controlled trial of silk therapeutic clothing for the long-term management of eczema in children

WORKSHEET

Participant Initials: ☐☐☐

Participant ID: ☐☐☐☐☐

Sponsor: University of Nottingham

General Instructions

Determining Eligibility

Visit 1 should be performed to determine the eligibility of the participant for inclusion into the trial. If at any point it is determined that the participant is not eligible for inclusion it is not necessary to continue with any further assessments.

Randomising

If all assessments have been performed and the patient is eligible:

- Proceed to enrol and randomise the patient by following this link: https://ctsu2.nottingham.ac.uk/1132/login.asp

Enrol the participant by entering the:

- Gender
- Date of Birth
- Initials
- Height in cm
  Then on the contacts page add:
- Contacts details and preference for either **online** or postal weekly questionnaires.

Once enrolled the participant will be assigned a unique participant ID. Please record this on the worksheet. It is only necessary to enrol participants who will be randomised.

Once the enrolment details and contact details have been added the participant can be randomised.

Completing the eCRF

Once the participant has been randomised please follow this this link and enter the visit 1 data within 7 days of the visit:
https://mcwapctu01.nottingham.ac.uk/macro/

The worksheets should be filed locally in a locked filing cabinet (there is no need to copy and send to the co-ordinating centre)

Serious Adverse Events

If the participant experiences any adverse events after being randomised these should be reported on the paper SAE form and faxed into the NCTU. Please see Trial Manual for Fax details.

Completing this worksheet

This is a worksheet to help collect the information in the clinic.
Worksheets will need to be retained if information is not being recorded into the patient's notes, as they constitute source data.

Participant initials | | | |

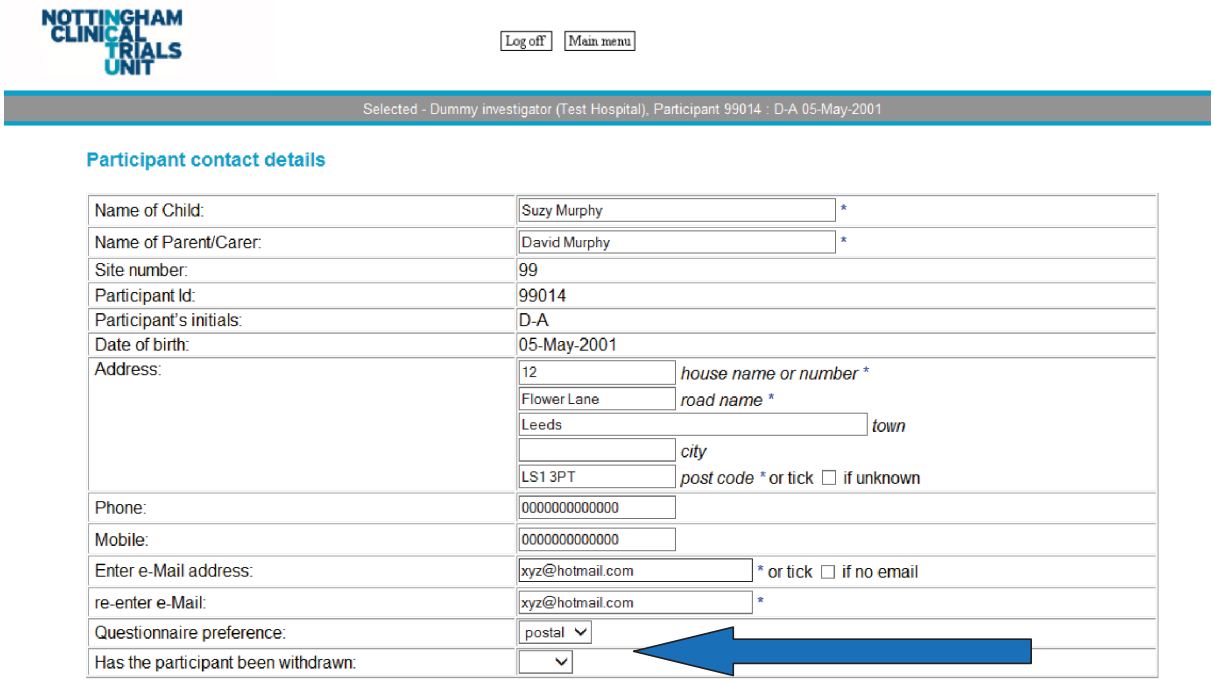
These should be recorded as 3 digits eg HKP, however if the participant does not have a middle initial it should be recorded as eg: H-P

Participant ID: | | | | | |

The 5 digit participant ID will be assigned once randomised, it is made up of 2 digit site ID followed by a sequential 3 digit number.

Online / Postal weekly questionnaires

- If at any point during the study the participant/parent/guardian wishes to change their preference for online questionnaires to postal or vice versa this can be updated on the contacts details page.
- If the participant is withdrawn from the study and therefore no longer wishes to receive the links/reminders for the questionnaires, the site or the trial manager are able to mark the participant as withdrawn.



CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐	VISIT 1 - BASELINE
Participant ID: ☐☐☐☐☐	

VISIT INFORMATION	
Date of Visit:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY

INFORMED CONSENT			
Consent Type	**Was written Informed Consent obtained?**		**Date of Informed Consent** DD/MMM/YYYY
	Yes	**No**	
Study Informed Consent *(Mandatory)*	☐	☐	☐☐/☐☐☐/20☐☐
Informed Consent for Genetic Study *(Optional)*	☐	☐	☐☐/☐☐☐/20☐☐
Informed Consent for Storage of Genetic Samples *(Optional- if 'Yes' above question must also be Yes)*	☐	☐	☐☐/☐☐☐/20☐☐
Parent/Guardian agreed to be added to the Centre of Evidence Based Dermatology's mailing list *(Optional)*	☐	☐	☐☐/☐☐☐/20☐☐
Guardian/Parent would like to receive a copy of the study results *(Optional)*	☐	☐	☐☐/☐☐☐/20☐☐

DEMOGRAPHY		
Date of birth:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY	
Initials:	☐☐☐	
Gender:	Male ☐	Female ☐
Ethnicity (tick one only)	White ☐	Black (Other) ☐
	Indian ☐	Chinese ☐
	Pakistani ☐	Other Asian (non–Chinese) ☐
	Bangladeshi ☐	Mixed Race ☐
	Black Caribbean ☐	Other ☐
	Black African ☐	Not Given ☐

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐	VISIT 1 - BASELINE
Participant ID: ☐☐☐☐☐	

BASELINE CHARACTERISTICS			
		No	**Yes**
Does the child have a history of any of the following conditions?	Asthma	☐	☐
	Allergic rhinitis (hayfever, perennial rhinitis)	☐	☐
	Food allergy (eliminates a food from diet)	☐	☐
	Anaphylaxis (have an Epipen/Jext/Anapen)	☐	☐
What are the types/patterns of Eczema? (currently present)	Flexural	☐	☐
	Discoid	☐	☐
	Reverse Pattern	☐	☐
Where on the body is the Eczema? (at the moment)	Head and Neck	☐	☐
	Hands and Wrists	☐	☐
	Feet and Ankles	☐	☐
	Limbs	☐	☐
	Trunk	☐	☐
Has your child's eczema been previously treated by the following:	GP	☐	☐
	Secondary Care (dermatologist or other specialist)	☐	☐

- **To be eligible at least one patch of eczema should be present on the trunk or the limbs.**

UK DIAGNOSTIC CRITERIA			
In order to qualify as a case of atopic eczema with the UK diagnostic criteria, the child must have:	**No**	**Yes**	
1. Has child had an itchy skin condition in the last 12 months	☐	☐	
Plus three or more of:	**No**	**Yes**	**N/A**
2. Has child had onset below age 2 (not used in children under 4 years)	☐	☐	☐
3. Has child had a history of flexural involvement	☐	☐	
4. Has child had a history of a generally dry skin	☐	☐	
5. Has child had a personal history of asthma or hayfever (in children aged under 4 years, history of atopic disease in a first degree relative may be included)	☐	☐	
6. Visible flexural dermatitis as per photographic protocol	☐	☐	

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐	VISIT 1 - BASELINE
Participant ID: ☐☐☐☐☐	

- **See Trial Manual for guidance**

ECZEMA TREATMENT

- **Please only record medications used on the areas covered by the clothing, not those used on hands/feet**
- **If more than 2 medications for each category have been used in the last month please enter the most frequently used medication**
- **Main emollient/steroid/calcineurin inhibitors = most frequently used**
- **Please see emollient ladder/steroid ladders for classification of consistency/potency**

EMOLLIENTS

Has the child used Emollients on the body within the last month? No ☐ Yes ☐

Name of Emollient Used on Body	Consistency (tick one only)	Main Emollient?
1. _____	Light ☐ Creamy ☐ Greasy ☐ Very Greasy ☐	Yes ☐ No ☐
2. _____	Light ☐ Creamy ☐ Greasy ☐ Very Greasy ☐	Yes ☐ No ☐

Please see Emollient ladder for classification of medications into Light, Creamy, Greasy and Very Greasy

TOPICAL STEROIDS

Has the child used topical steroids on the body within the last month? No ☐ Yes ☐

Name of Steroid Used on Body	Potency (tick one only)	Main Steroid?
1. _____	Mild ☐ Moderate ☐ Potent ☐ Very Potent ☐	Yes ☐ No ☐
2. _____	Mild ☐ Moderate ☐ Potent ☐ Very Potent ☐	Yes ☐ No ☐

Please see Steroid ladder for classification of medications into Mild, Moderate, Potent or Very Potent.

Participant initials: ☐☐☐	VISIT 1 - BASELINE
Participant ID: ☐☐☐☐☐	

CALCINEURIN INHIBITORS		
Has the child used Calcineurin Inhibitors on the body within the last month? eg Protopic (Tacrolimus), Elidel (Pimecrolimus) **No ☐ Yes ☐**		
Name of Calcineurin Inhibitor Used on Body	**Strength** (tick one only)	**Main Calcineurin Inhibitor?**
1. _____ _____	Mild ☐ Moderate ☐	Yes ☐ No ☐
2. _____ _____	Mild ☐ Moderate ☐	Yes ☐ No ☐

Protopic (Tacrolimus) = 0.03% = Mild

Elidel (Pimecrolimus) = 1% = Moderate

MEDICATIONS	
How many times have wet/dry wraps been used in the last month for their eczema? (tick one only) (this includes tubifast, itchopaste bandage)	None ☐ 1-4 times ☐ 5-10 times ☐ >10 times ☐ (Participant should be excluded if ≥ 5)
Do you/your child use any other treatment in addition to Emollients, Steroids and Calcineurin Inhibitors for their eczema eg tablets, or antihistamines?	No ☐ Yes ☐
If yes, please specify	_____ _____
Any new prescribable treatments used in the last month?	No ☐ Yes ☐
If yes, please specify e.g. methotrexate, cyclosporin, aziathioprine, light therapy, prednisolone, mycophenolate mofetil are prohibited medications	_____

Participant initials: ☐☐☐	VISIT 1 - BASELINE
Participant ID: ☐☐☐☐☐	

NOT FOR DATABASE

CHECKLIST		
Do you/your child currently use silk clothing for eczema?	No ☐	Yes ☐
If yes, prepared to stop using them?	No ☐ If No, then participant is not eligible	Yes ☐
Currently enrolled in any other trial?	No ☐ If Yes, then participant is not eligible	Yes ☐
Does the skin show signs of Infection?	No ☐ If yes, recommend that the patient contacts their normal medical team (GP, Nurse, dermatologist) as appropriate	Yes ☐

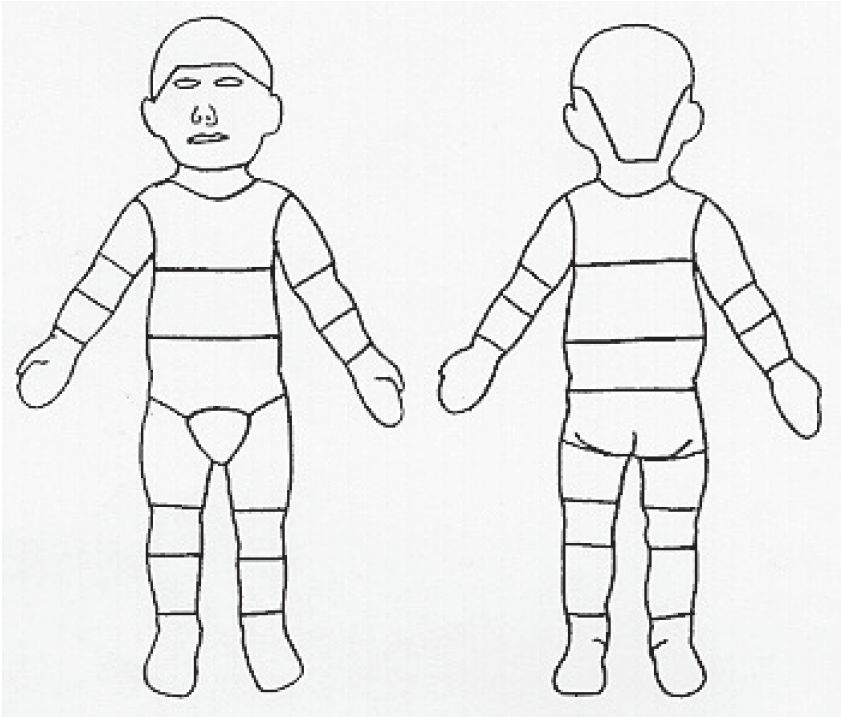
Participant initials: ☐☐☐ VISIT 1 - BASELINE

Participant ID: ☐☐☐☐☐

☐ **Mark if not done**

NOTTINGHAM ECZEMA SEVERITY SCORE (NESS)

Surface area measurement using tick boxes
Record a tick in each box if more than 2cm² (size of a 10 pence coin) is involved with AE. Calculate the total ticks by adding together the number of recorded ticks for both the front and back of the surface diagram. The final score is calculated using the table below.



Number of ticks	Score	Final score (tick one)
0-2	1	
3-5	2	
6-10	3	
11-20	4	
>20	5	

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐	VISIT 1 - BASELINE
Participant ID: ☐☐☐☐☐	

1. Clinical Course (ask the Parent)

In the Last 12 months has your child's skin condition been:	Score (please circle one answer)
a). Present for less than 6 weeks in total?	1
b). Present for between 6 weeks and less than 3 months in total?	2
c). Present for between 3 months and less than 6 months in total?	3
d). Present for between 6 months and less than 9 months in total?	4
e). Present for more than 9 months in total?	5

2. Clinical Intensity (ask the Parent)

In the last 12 months, how often has your child's sleep usually been disturbed by itching or scratching due to their skin problem?	Score (please circle one answer)
a). Sleep is not usually disturbed	1
b). 1 night per week on average	2
c). 2 or 3 nights per week on average	3
d). 4 or 5 nights per week on average	4
e). 6 or more nights per week on average	5

3. Extent of Atopic Eczema by examination (see diagram opposite for details)

Score (please circle one answer)
1
2
3
4
5

4. Final Assessment severity

Mild: total score 3-8	
Moderate: total score 9-11	
Severe: total score 12-15	

- **If total score is 8 or less then they are not eligible to be included in the study.**

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐	VISIT 1 - BASELINE
Participant ID: ☐☐☐☐☐	

☐ **Mark if not done**

THREE ITEM SEVERITY SCALE (TIS)

Criteria	**Score** (tick one only)
Erythema	Absent (0) ☐ Mild (1) ☐ Moderate (2) ☐ Severe (3) ☐
Oedema / papulation	Absent (0) ☐ Mild (1) ☐ Moderate (2) ☐ Severe (3) ☐
Excoriation	Absent (0) ☐ Mild (1) ☐ Moderate (2) ☐ Severe (3) ☐

Representative Body Site: Choose one representative body site to assess all three signs. The representative site should be in an area covered by the clothing, and be the area that, in the view of the parent/participant, is most bothersome. The representative body site may change from visit to visit.

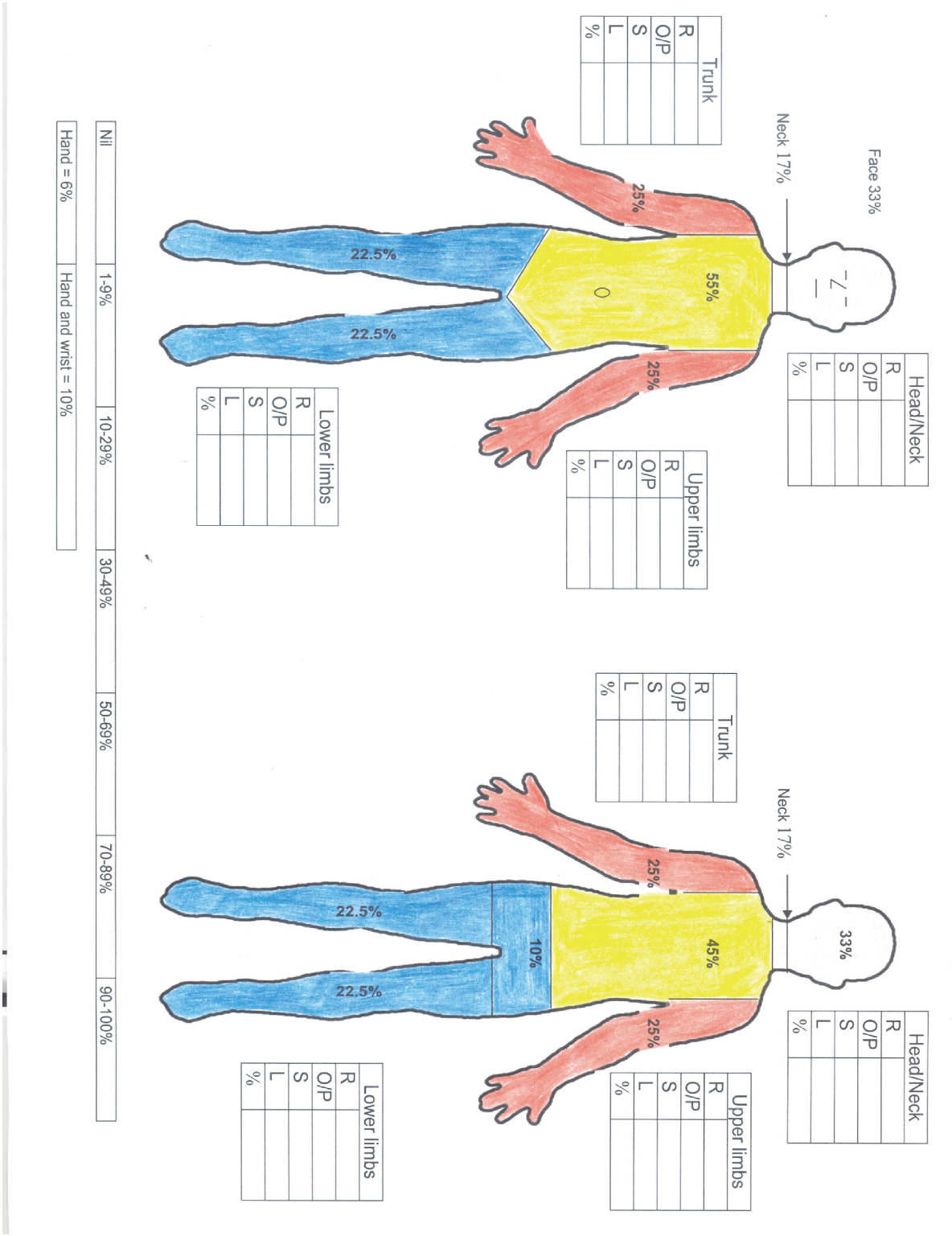
Total Score: ☐☐

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: | | | |

Participant ID: | | | | | |

VISIT 1 - BASELINE



CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐ VISIT 1 - BASELINE

Participant ID: ☐☐☐☐☐

☐ **Mark if not done**

- Assess each body area for **redness (erythema), papulation & oedema, scratching (excoriation) and lichenification (lined skin)**
- Using the photographic comparison table, assign a score for each of the signs in each of the four body areas. Assess each sign for the entire body region – so for example a patient may have grade 1 erythema in some areas, but grade 3 erythema in others. If that is the case, then the "average of the two" is taken and so the score become 2. Likewise, if they have some areas that are grade 2 and others that are grade 3, then the score becomes 2.5.
- Score the percentage area of each region affected by eczema

ECZEMA AREA AND SEVERITY INDEX (EASI)

Body Area	% Area affected by Eczema (tick one only)				Criteria	Score (tick one only)						
						Absent (0)	(0.5)	Mild (1)	(1.5)	Moderate (2)	(2.5)	Severe (3)
Head and Neck	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Upper Limbs	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Trunk	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Lower Limbs	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐

Participant initials: ☐☐☐	VISIT 1 - BASELINE
Participant ID: ☐☐☐☐☐	

HYPERLINEAR PALMS			
Hyperlinear palms?	No ☐	Yes ☐	Unsure ☐

Please see Trial Manual for details

☐ **Mark if not done**

INVESTIGATOR'S GLOBAL ASSESSMENT (IGA)

How is the child's eczema <u>today</u>?

☐	☐	☐	☐	☐	☐
Clear	Almost clear	Mild	Moderate	Severe	Very severe

	Tick when completed	Completed by: (tick one only)	
• **PATIENT'S GLOBAL ASSESSMENT (PGA) (included in 'Clinic Questions')** To be completed by parent/guardian or child Please request that where possible if the child performs the baseline assessment, the child completes the follow up questionnaires or if the parent/guardian performs the baseline assessment, the parent/guardian completes the follow up questionnaires.	☐	Parent/Guardian	☐
		Child	☐

Participant initials: ☐☐☐	VISIT 1 - BASELINE
Participant ID: ☐☐☐☐☐	

INCLUSION CRITERIA		
To be eligible for this trial all the inclusion criteria must be answered Yes	**No**	**Yes**
1. Child aged 1 to 15 years at baseline.	☐	☐
2. Diagnosis of moderate or severe eczema (atopic dermatitis). Presence of eczema will be confirmed using the UK Diagnostic Criteria for Atopic Eczema and eczema severity judged using the Nottingham Eczema Severity Scale (NESS) (Score of 9 or above)	☐	☐
3. Resident within travelling distance of a recruiting centre.	☐	☐
4. Child should have at least one patch of eczema on the trunk or the limbs.	☐	☐
5. Parents/legal guardian able to give informed consent	☐	☐

EXCLUSION CRITERIA		
To be eligible for this trial all the exclusion criteria must be answered No	**No**	**Yes**
1. Child who has taken systemic medication (including light therapy) or oral steroids for eczema within the previous three months.	☐	☐
2. Child who has started a new treatment regimen within the last month.	☐	☐
3. Child who has used wet/dry wraps ≥5 times in the last month.	☐	☐
4. Child who is currently using silk clothing for their eczema and are unwilling to stop using the clothing during the trial.	☐	☐
5. Child who is currently taking part in another clinical trial.	☐	☐
6. Child who has expressed a wish not to take part in the trial.	☐	☐

Participant initials: ☐☐☐ VISIT 1 - BASELINE

Participant ID: ☐☐☐☐☐

NOT FOR DATABASE

SURVEY OF SKIN PROBLEMS – For Parents of children aged 3 and under

1. In the **last year**, has your child had an **ITCHY** skin condition – by *itchy* we mean scratching or rubbing the skin? ☐ Yes ☐ No

If you have answered "NO" please skip to Question 4
If you have answered "YES" please answer all the questions

2. At what age did your child's ITCHY skin condition start?

_____years _____ months

3. Has this skin condition **ever** affected the skin creases in the past – by *skin creases* we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes?
☐ Yes ☐ No

4. In the **last year**, has your child suffered from a **dry skin** in general?
☐ Yes ☐ No

5. Does anyone in your child's immediate family (i.e. mother, father, brother or sisters) suffer from:
eczema? ☐ Yes ☐ No
hay fever? ☐ Yes ☐ No
asthma? ☐ Yes ☐ No

SURVEY OF SKIN PROBLEMS – For Parents of children aged 4 to 15 years

1. In the **last year**, has your child had an **ITCHY** skin condition – by *itchy* we mean scratching or rubbing the skin? ☐ Yes ☐ No

If you have answered "NO" please skip to Question 5
If you have answered "YES" please answer all the questions

2. Has your child had this ITCHY skin condition in the **LAST WEEK?**
☐ Yes ☐ No

3. How old was your child when this skin condition began?
Under 2 [ ] **2 to 5 [ ]** **6 to 10 [ ]** **Over 10 [ ]**

4. Has this skin condition **ever** affected the skin creases in the past – by *skin creases* we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes?
☐ Yes ☐ No

5. In the **last year**, has your child suffered from a **dry skin** in general?
☐ Yes ☐ No

6. Does anyone in your child's immediate family (i.e. mother, father, brother or sisters) suffer from:
eczema? ☐ Yes ☐ No
hay fever? ☐ Yes ☐ No
asthma? ☐ Yes ☐ No

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐	VISIT 1 - BASELINE
Participant ID: ☐☐☐☐☐	

Please ensure Visit 1 Parent/Guardian/Child Questionnaires are completed during the visit:

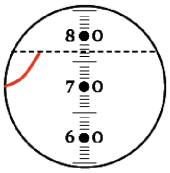
	Tick when completed	Completed by	
• **PATIENT ORIENTED ECZEMA MEASURE (POEM)** To be completed by parent/guardian or child	☐	Patient /Guardian	☐
		Child	☐
• **CLINIC QUESTIONS** To be completed by parent/guardian or child	☐		
• **DERMATITIS FAMILY IMPACT QUESTIONNAIRE (DFI)** To be completed by parent/guardian	☐		
• **EQ-5D-3L** To be completed by parent/guardian	☐	Which Parent/Guardian:	
• **THE CHILD HEALTH UTILITY 9 DIMENSIONS (CHU-9D)** To be completed by parent/guardian or child for children of aged 5 or over only	☐		
• **ADQoL** To be completed by parent/guardian or child	☐		
Comments on ADQoL:			

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐	VISIT 1 - BASELINE
Participant ID: ☐☐☐☐☐	

EQ5D: 'Your Own Health State Today'

- If the line does not cross the scale, draw a horizontal line:



Even though the line does not cross the VAS this response can still be scored by drawing a horizontal line from the end point of the response to the VAS. In this example the response should be coded as 77

- If a circle is drawn, select middle of circle as the measurement.
- If the response is not clear, please record as 'missing

RANDOMISATION	
Participant randomised into the trial?	No ☐ Yes ☐ If yes please fill in participant ID on the front and at the top of each page.
The below information will need to recorded to enable randomisation of the participant, please also record all contact details on the contact sheet.	
Please record patient's height (cm)	☐☐☐
Please give details of child's build/clothing size (i.e. any info that will help trial team select the appropriate size clothing)	
Record preference for type of weekly questionnaires	Paper ☐
	Online ☐

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐ VISIT 1 - BASELINE

Participant ID: ☐☐☐☐☐

NOT FOR DATABASE

REMINDERS

- **Discuss with the participant/guardian/carer:**
  1. **If any visits occurred to a healthcare professional within the last 4 weeks**
  2. **If any prescriptions were made for eczema within the last 4 weeks**

  If the response is yes to any of the above please record on pages 33-38.

- **Discuss what will happen next**
- **Book an appointment for the next clinic visit**
- **If consent has been obtained to collect a saliva sample, has a sample been collected today and recorded on the sample collection page?**
- **File a copy of consent form in the hospital notes (if recruited by secondary care)**
- **Send a copy of consent form to GP (if primary care or direct advert)**
- **Send a letter to GP with a copy of Patient Information Leaflet**
- **Put recruitment sticker on patient's notes along with a copy of the Patient Information Leaflet**

Please ensure the participant is given the following:

- **Diary**
- **Spare weekly questionnaires and envelopes**
- **Travel expenses**
- **Small gift**

Investigator's/designee's Signature: _____ Date ☐☐/☐☐☐/2 0☐☐
DD/MMM/YYYY

Participant initials: ☐☐☐	VISIT 2 – 2 Month Follow Up
Participant ID: ☐☐☐☐☐	

☐ **Mark if visit not done**	
VISIT INFORMATION	
Date of Visit:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY

MEDICATIONS		
In the last 2 months roughly how often have emollients been used? (tick one only)	Never ☐ Sometimes ☐ Always ☐	Rarely ☐ Often ☐
In the last 2 months roughly how often have steroids or calcineuron inhibitors been used? (tick one only)	Never ☐ Sometimes ☐ Always ☐	Rarely ☐ Often ☐
In the last 2 months roughly how often have wet/dry wraps been used for their eczema? (tick one only) (this includes tubifast, itchopaste bandage)	None ☐ 5-10 times ☐	1-4 times ☐ >10 times ☐
Has the eczema treatment changed since the last clinic visit?	Yes ☐	No ☐
If yes, type of change	Escalation ☐ Reduction ☐	Neutral Change ☐ Unsure ☐

If Unsure, please specify	_____

Participant initials: ☐☐☐	VISIT 2 – 2 Month Follow Up
Participant ID: ☐☐☐☐☐	

☐ **Mark if not done**

THREE ITEM SEVERITY SCALE (TIS)

Criteria	**Score** (tick one only)
Erythema	Absent (0) ☐ Mild (1) ☐ Moderate (2) ☐ Severe (3) ☐
Oedema / papulation	Absent (0) ☐ Mild (1) ☐ Moderate (2) ☐ Severe (3) ☐
Excoriation	Absent (0) ☐ Mild (1) ☐ Moderate (2) ☐ Severe (3) ☐

Representative Body Site: Choose one representative body site to assess all three signs. The representative site should be in an area covered by the clothing, and be the area that, in the view of the parent/participant, is most bothersome. The representative body site may change from visit to visit.

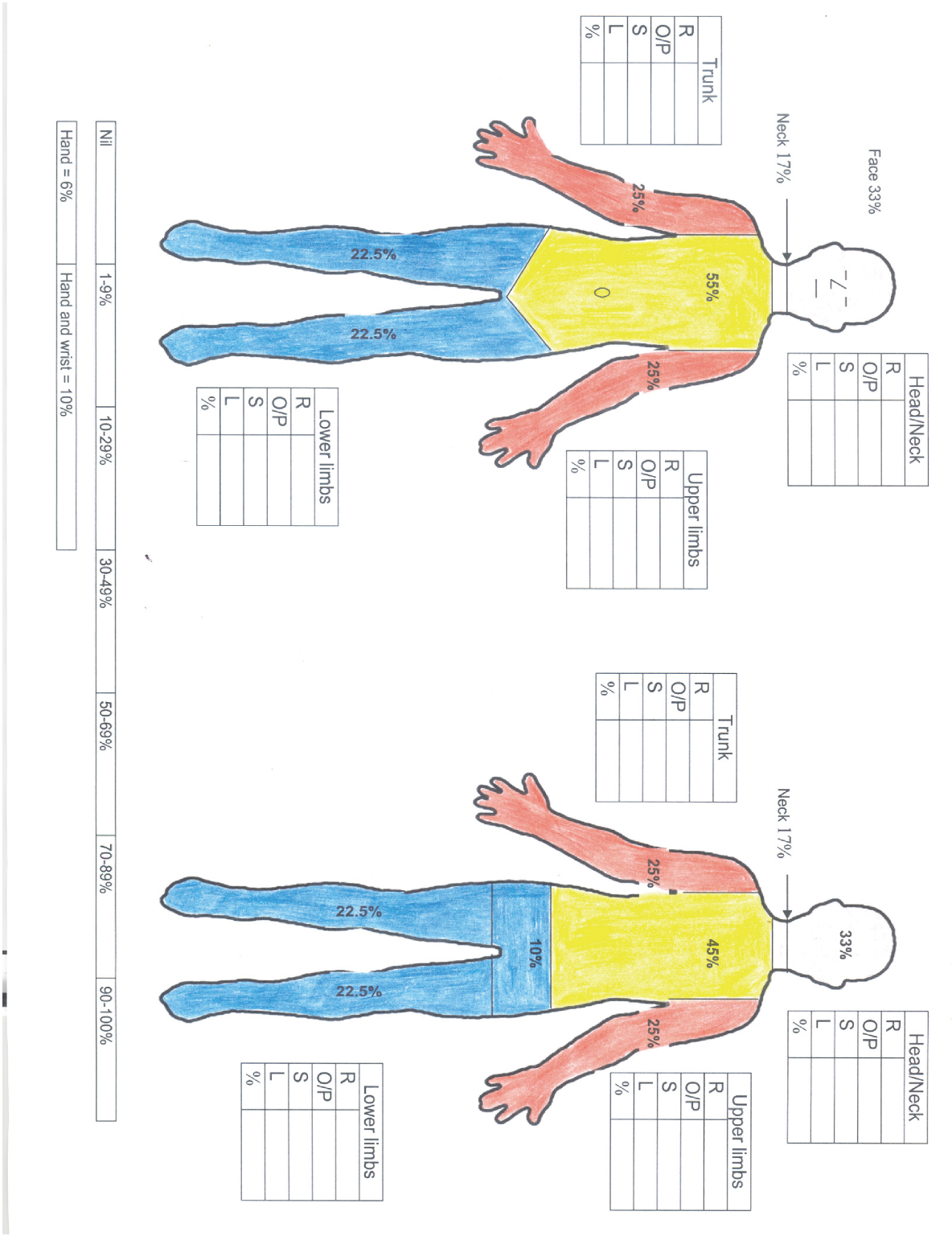
Total Score: ☐☐

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: | | | |

Participant ID: | | | | | |

VISIT 2 – 2 Month Follow Up



CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐ VISIT 2 – 2 Month Follow Up

Participant ID: ☐☐☐☐☐

☐ **Mark if not done**

- Assess each body area for **redness (erythema), papulation & oedema, scratching (excoriation) and lichenification (lined skin)**
- Using the photographic comparison table, assign a score for each of the signs in each of the four body areas. Assess each sign for the entire body region – so for example a patient may have grade 1 erythema in some areas, but grade 3 erythema in others. If that is the case, then the "average of the two" is taken and so the score become 2. Likewise, if they have some areas that are grade 2 and others that are grade 3, then the score becomes 2.5.
- Score the percentage area of each region affected by eczema

ECZEMA AREA AND SEVERITY INDEX (EASI)

Body Area	% Area affected by Eczema (tick one only)				Criteria	Score (tick one only)						
						Absent (0)	(0.5)	Mild (1)	(1.5)	Moderate (2)	(2.5)	Severe (3)
Head and Neck	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Upper Limbs	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Trunk	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Lower Limbs	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐

Participant initials: ☐☐☐	VISIT 2 – 2 Month Follow Up
Participant ID: ☐☐☐☐☐	

☐ **Mark if not done**

INVESTIGATOR'S GLOBAL ASSESSMENT (IGA)

How is the child's eczema <u>today</u>?

☐	☐	☐	☐	☐	☐
Clear	Almost clear	Mild	Moderate	Severe	Very severe

Please ensure Visit 2 Parent/Guardian/Child Questionnaires are completed during the visit:

	Tick when completed	Completed by: (tick one only)	
• **PATIENT'S GLOBAL ASSESSMENT (PGA) (included in 'Clinic Questions')** To be completed by parent/guardian or child Please request that where possible if the child performs the baseline assessment, the child completes the follow up questionnaires or if the parent/guardian performs the baseline assessment, the parent/guardian completes the follow up questionnaires.	☐	Parent/Guardian	☐
		Child	☐
• **PATIENT ORIENTED ECZEMA MEASURE (POEM)** To be completed by parent/guardian or child	☐	Parent/Guardian	☐
		Child	☐
• **CLINIC QUESTIONS** To be completed by parent/guardian or child	☐		

Participant initials: ☐☐☐	VISIT 2 – 2 Month Follow Up
Participant ID: ☐☐☐☐☐	

UNBLINDING	
Have you (nurse) become accidentally unblinded since last visit?	No ☐ Yes ☐
If yes, please briefly describe circumstances of unblinding.	_____ _____

NOT FOR DATABASE:

REMINDERS	
Please collect the diary from the parent/guardian/child and ensure it is fully completed prior to the parent/guardian/child leaving the clinic.	
• **Has the participant had any healthcare visits for eczema?** • **Has the participant been prescribed any topical treatment for eczema?** • **Has the participant had any skin infections?** • **Has the participant or parent/carer made any purchases for eczema?** • **Has the participant or parent/carer had any time off work and school due to eczema?**	Please use the data recorded in the diaries to complete the eCRF, any extra information that is gained through the clinic visit can be recorded on the pages at the end of the worksheet.
• **Please ensure the diary has been issued** • **Book an appointment for the next clinic visit** • **If consent has been obtained to collect a saliva sample and this has not been previously collected, has a sample been collected today and recorded in the CRF?** • **If any protocol deviations have taken place ensure this is recorded on the protocol deviation worksheet.**	

Investigator's/designee's Signature: _____ Date ☐☐/☐☐☐/2 0☐☐
DD/MMM/YYYY

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐	VISIT 3 - 4 Month Follow Up
Participant ID: ☐☐☐☐☐	

☐ **Mark if visit not done**	
VISIT INFORMATION	
Date of Visit:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY

MEDICATIONS		
Has the eczema treatment changed since the last clinic visit?	Yes ☐	No ☐
If yes, type of change	Escalation ☐	Neutral Change ☐
	Reduction ☐	Unsure ☐
If Unsure, please specify	_____	

☐ **Mark if not done**				
THREE ITEM SEVERITY SCALE (TIS)				
Criteria	**Score** (tick one only)			
Erythema	Absent (0) ☐	Mild (1) ☐	Moderate (2) ☐	Severe (3) ☐
Oedema / papulation	Absent (0) ☐	Mild (1) ☐	Moderate (2) ☐	Severe (3) ☐
Excoriation	Absent (0) ☐	Mild (1) ☐	Moderate (2) ☐	Severe (3) ☐

Representative Body Site: Choose one representative body site to assess all three signs. The representative site should be in an area covered by the clothing, and be the area that, in the view of the parent/participant, is most bothersome. The representative body site may change from visit to visit.

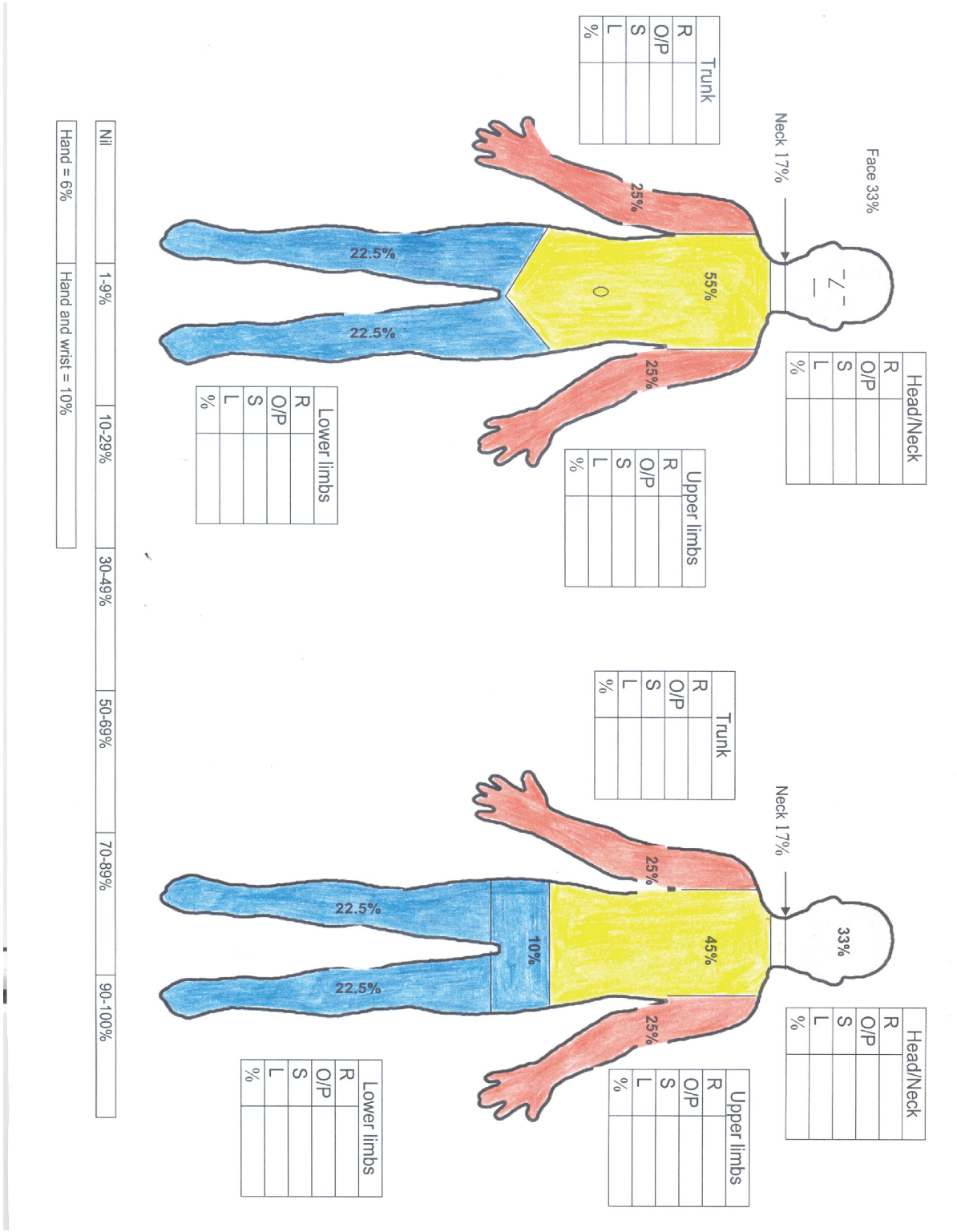
Total Score: ☐☐

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: | | | |

Participant ID: | | | | | |

VISIT 3 - 4 Month Follow Up



CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐ VISIT 3 - 4 Month Follow Up

Participant ID: ☐☐☐☐☐

☐ **Mark if not done**

- Assess each body area for **redness (erythema), papulation & oedema, scratching (excoriation) and lichenification (lined skin)**
- Using the photographic comparison table, assign a score for each of the signs in each of the four body areas. Assess each sign for the entire body region – so for example a patient may have grade 1 erythema in some areas, but grade 3 erythema in others. If that is the case, then the "average of the two" is taken and so the score become 2. Likewise, if they have some areas that are grade 2 and others that are grade 3, then the score becomes 2.5.
- Score the percentage area of each region affected by eczema

ECZEMA AREA AND SEVERITY INDEX (EASI)

Body Area	% Area affected by Eczema (tick one only)				Criteria	Score (tick one only)						
						Absent (0)	(0.5)	Mild (1)	(1.5)	Moderate (2)	(2.5)	Severe (3)
Head and Neck	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Upper Limbs	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Trunk	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Lower Limbs	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐

Participant initials: ☐☐☐ VISIT 3 - 4 Month Follow Up

Participant ID: ☐☐☐☐☐

☐ **Mark if not done**

INVESTIGATOR'S GLOBAL ASSESSMENT (IGA)

How is the child's eczema <u>today</u>?

☐	☐	☐	☐	☐	☐
Clear	Almost clear	Mild	Moderate	Severe	Very severe

Please ensure Visit 3 Parent/Guardian/Child Questionnaires are completed during the visit:

	Tick when completed	Completed by: (tick one only)	
• **PATIENT'S GLOBAL ASSESSMENT (PGA) (included in 'Clinic Questions')** To be completed by parent/guardian or child Please request that where possible if the child performs the baseline assessment, the child completes the follow up questionnaires or if the parent/guardian performs the baseline assessment, the parent/guardian completes the follow up questionnaires.	☐	Parent/Guardian	☐
		Child	☐
• **PATIENT ORIENTED ECZEMA MEASURE (POEM)** To be completed by parent/guardian or child	☐	Parent/Guardian	☐
		Child	☐
• **CLINIC QUESTIONS** To be completed by parent/guardian or child	☐		

Participant initials: ☐☐☐	VISIT 3 - 4 Month Follow Up
Participant ID: ☐☐☐☐☐	

UNBLINDING	
Have you (nurse) become accidentally unblinded since last visit?	No ☐ Yes ☐
If yes, please briefly describe circumstances of unblinding.	_____ _____

NOT FOR DATABASE:

REMINDERS

Please collect the diary from the parent/guardian/child and ensure it is fully completed prior to the parent/guardian/child leaving the clinic.

- **Has the participant had any healthcare visits for eczema?**
- **Has the participant been prescribed any topical treatment for eczema?**
- **Has the participant had any skin infections?**
- **Has the participant or parent/care made any purchases for eczema?**
- **Has the participant or parent/carer had any time off work and school due to eczema?**

Please use the data recorded in the diaries to complete the eCRF, any extra information that is gained through the clinic visit can be recorded on the pages at the end of the worksheet.

- **Please ensure the diary has been issued**
- **Book an appointment for the next clinic visit**
- **The parent who filled in the EQ-5D-3L at visit 1 was _____ (see page 17). Please request this same parent brings the child to the next visit, if possible, for questionnaire consistency.**
- **If consent has been obtained to collect a saliva sample and this has not been previously collected, has a sample been collected today and recorded in the CRF?**
- **If any protocol deviations have taken place ensure this is recorded on the protocol deviation worksheet.**

Investigator's/designee's Signature: _____ Date ☐☐/☐☐☐/2 0☐☐
DD/MMM/YYYY

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐	VISIT 4 - 6 Month Follow Up
Participant ID: ☐☐☐☐☐	

☐ **Mark if visit not done**

VISIT INFORMATION

Date of Visit:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY

HEIGHT

This should be entered onto the eCRF as soon as possible, even if the rest of the visit data is not entered until a later date

Height at this visit	☐☐☐ **cm**

ECZEMA TREATMENT

- **Please only record medications used on the areas covered by the clothing, not those used on hands/feet**
- **If more than 2 medications for each category have been used in the last month please enter the most frequently used medication**
- **Main emollient/steroid/calcineurin inhibitors = most frequently used**
- **Please see emollient ladder/steroid ladders for classification of consistency/potency**

EMOLLIENTS

Has the child used Emollients on the body within the last month? No ☐ Yes ☐

Name of Emollient used on body	Consistency (tick one only)	Main Emollient?
1. _____	Light ☐ Creamy ☐ Greasy ☐ Very Greasy ☐	Yes ☐ No ☐
2. _____	Light ☐ Creamy ☐ Greasy ☐ Very Greasy ☐	Yes ☐ No ☐

Please see Emollient ladder for classification of medications into Light, Creamy, Greasy and Very Greasy

TOPICAL STEROIDS

Has the child used topical steroids on the body within the last month? No ☐ Yes ☐

Name of Steroid used on body	Potency (tick one only)	Main Steroid?
1. _____	Mild ☐ Moderate ☐ Potent ☐ Very Potent ☐	Yes ☐ No ☐

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐	VISIT 4 - 6 Month Follow Up
Participant ID: ☐☐☐☐☐	

2. _____	Mild ☐ Moderate ☐ Potent ☐ Very Potent ☐	Yes ☐ No ☐

Please see Steroid Ladder for classification of medications into Mild, Moderate, Potent or Very Potent.

CALCINEURIN INHIBITORS		
Has the child used Calcineurin Inhibitors on the body within the last month? (eg Protopic, Elidel) **No ☐ Yes ☐**		
Name of Calcinuerin Inhibitor used on body	**Strength** (tick one only)	**Main Calcineurin Inhibitor?**
1. _____	Mild ☐ Moderate ☐	Yes ☐ No ☐
2. _____	Mild ☐ Moderate ☐	Yes ☐ No ☐

Protopic (Tacrolimus) = 0.03% = Mild

Elidel (Pimecrolimus) = 1% = Moderate

MEDICATIONS		
Has the eczema treatment changed since the last clinic visit?	Yes ☐	No ☐
If yes, type of change	Escalation ☐	Neutral Change ☐
	Reduction ☐	Unsure ☐
If Unsure, please specify	_____	

SKIN INFECTIONS	
If infection is suspected this should be followed up after the visit and added to the infections log if necessary.	
Does the skin appear infected at this visit?	No ☐ Yes ☐

Participant initials: ☐☐☐ VISIT 4 - 6 Month Follow Up

Participant ID: ☐☐☐☐☐

☐ **Mark if not done**

THREE ITEM SEVERITY SCALE (TIS)

Criteria	**Score** (tick one only)
Erythema	Absent (0) ☐ Mild (1) ☐ Moderate (2) ☐ Severe (3) ☐
Oedema / papulation	Absent (0) ☐ Mild (1) ☐ Moderate (2) ☐ Severe (3) ☐
Excoriation	Absent (0) ☐ Mild (1) ☐ Moderate (2) ☐ Severe (3) ☐

Representative Body Site: Choose one representative body site to assess all three signs. The representative site should be in an area covered by the clothing, and be the area that, in the view of the parent/participant, is most bothersome. The representative body site may change from visit to visit.

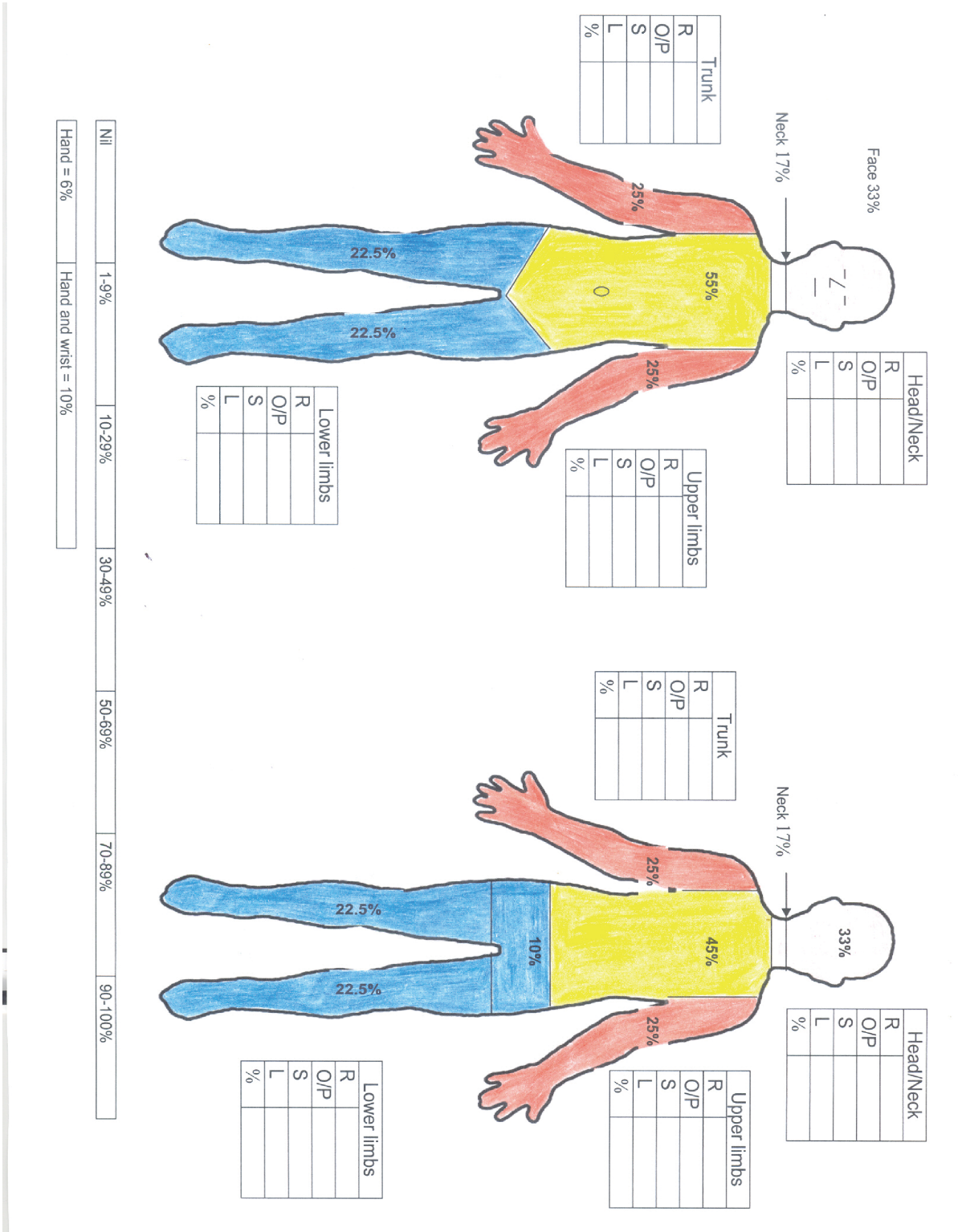
Total Score: ☐☐

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: | | | |

Participant ID: | | | | | |

VISIT 4 - 6 Month Follow Up



CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

VISIT 4 - 6 Month Follow Up

☐ **Mark if not done**

- Assess each body area for redness (erythema), papulation & oedema, scratching (excoriation) and lichenification (lined skin)
- Using the photographic comparison table, assign a score for each of the signs in each of the four body areas. Assess each sign for the entire body region – so for example a patient may have grade 1 erythema in some areas, but grade 3 erythema in others. If that is the case, then the "average of the two" is taken and so the score become 2. Likewise, if they have some areas that are grade 2 and others that are grade 3, then the score becomes 2.5.
- Score the percentage area of each region affected by eczema

ECZEMA AREA AND SEVERITY INDEX (EASI)

Body Area	% Area affected by Eczema (tick one only)				Criteria	Score (tick one only)						
						Absent (0)	(0.5)	Mild (1)	(1.5)	Moderate (2)	(2.5)	Severe (3)
Head and Neck	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Upper Limbs	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Trunk	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐
Lower Limbs	Nil ☐	50-69% ☐			Redness	☐	☐	☐	☐	☐	☐	☐
	1-9% ☐	70-89% ☐			Oedema/Papulation	☐	☐	☐	☐	☐	☐	☐
	10-29% ☐	90-100% ☐			Scratching	☐	☐	☐	☐	☐	☐	☐
	30-49% ☐				Lichenification	☐	☐	☐	☐	☐	☐	☐

Participant initials: ☐☐☐	VISIT 4 - 6 Month Follow Up
Participant ID: ☐☐☐☐☐	

HYPERLINEAR PALMS			
Hyperlinear palms?	No ☐	Yes ☐	Unsure ☐

Please see Trial Manual for details

☐ **Mark if not done**

INVESTIGATOR'S GLOBAL ASSESSMENT (IGA)

How is the child's eczema <u>today</u>?

☐	☐	☐	☐	☐	☐
Clear	Almost clear	Mild	Moderate	Severe	Very severe

Please ensure Visit 4 Parent/Guardian/Child Questionnaires are completed during the visit:

	Tick when completed	Completed by: (tick one only)	
• **PATIENT'S GLOBAL ASSESSMENT (PGA) (included in 'Clinic Questions')** To be completed by parent/guardian or child	☐	Parent/Guardian Child	☐ ☐
• **PATIENT ORIENTED ECZEMA MEASURE (POEM)** To be completed by parent/guardian or child	☐	Parent/Guardian Child	☐ ☐
• **CLINIC QUESTIONS** To be completed by parent/guardian or child	☐		
• **DERMATITIS FAMILY IMPACT QUESTIONNAIRE (DFI)** To be completed by parent/guardian	☐		
• **EQ-5D-3L** To be completed by parent/guardian	☐		
• **THE CHILD HEALTH UTILITY 9 DIMENSIONS (CHU-9D)** To be completed by parent/guardian or child <u>for children of aged 5 or over only</u>	☐		
• **ADQoL** To be completed by parent/guardian or child	☐		
Comments on ADQoL:			

Participant initials: ☐☐☐	Visit 4 - 6 Month Follow Up
Participant ID: ☐☐☐☐☐	

UNBLINDING	
Have you (nurse) become accidentally unblinded since last visit?	No ☐ Yes ☐
If yes, please briefly describe circumstances of unblinding.	_____ _____

NOT FOR DATABASE:

REMINDERS

Please collect the diary from the parent/guardian/child and ensure it is fully completed prior to the parent/guardian/child leaving the clinic.

- **Has the participant had any healthcare visits for eczema?**
- **Has the participant been prescribed any topical treatment for eczema?**
- **Has the participant had any skin infections?**
- **Has the participant or parent/carer made any purchases for eczema?**
- **Has the participant or parent/carer had any time off work and school due to eczema?**

Please use the data recorded in the diaries to complete the eCRF, any extra information that is gained through the clinic visit can be recorded on the pages at the end of the worksheet.

- **If consent has been obtained to collect a saliva sample and this has not been previously collected, has a sample been collected today and recorded in the CRF?**
- **If any protocol deviations have taken place ensure this is recorded on the protocol deviation worksheet.**

Investigator's/designee's Signature: _____ Date ☐☐/☐☐☐/2☐☐☐
DD/MMM/YYYY

Participant initials: ☐☐☐ **Participant ID:** ☐☐☐☐☐	END OF TRIAL For database: 777

To be completed when the participant reaches their 6 month visit or if they choose to withdraw from the trial completely.

END OF TRIAL	
Has the participant completed the 6 month clinic visit?	No ☐ Yes ☐
If No, date of withdrawal:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY
Participant Status: If No, check the primary reason for Discontinuation *(tick one box):*	Death ☐ Withdrawal of Consent ☐ Withdrawal of Consent due to Adverse Event ☐ Lost to Follow Up ☐ Trial terminated by sponsor ☐ Other ☐ If Withdrawal of Consent or other, please specify _____

Investigator's/designee's Signature: _____ Date ☐☐/☐☐☐/2 0☐☐
DD/MMM/YYYY

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

SUMMARY INFORMATION: SAMPLE COLLECTION

A sample should only be collected if consent was obtained for the genetic substudy.

SAMPLE COLLECTION				
	Was sample collected?		**Date of assessment** DD/MMM/YYYY	**If No, please give reason**
	No	**Yes**		
Saliva sample	☐	☐	D D M M M Y Y Y Y	

CLOTHES WORKSHEET, Final Version 26 MAR 2014

Participant initials: ☐☐☐ **Participant ID:** ☐☐☐☐☐	SUMMARY INFORMATION: HEALTHCARE VISITS FOR ECZEMA

Pages 40-44 can be used to record any information collected during the clinic visit, it is not necessary to transcribe all information from the diary to these pages. The diary data can be entered directly into the eCRF.

HEALTHCARE VISITS FOR ECZEMA

Has the participant had any healthcare visits for eczema? No ☐ Yes ☐

No.	Date of Visit	Tick if estimated	Type of visit 1= GP, 2 = Practice Nurse, 3 = Outpatients, 4= Inpatient, 5 = Other (If Other, specify)	Number of nights in hospital
1	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
2	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
3	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
4	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
5	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
6	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
7	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
8	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
9	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
10	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
11	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
12	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
13	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
14	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
15	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
16	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
17	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
18	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
19	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐
20	D D M M M 2 0 Y Y	☐	☐ ----------	☐☐

Participant initials: ☐☐☐	SUMMARY INFORMATION: ECZEMA PRESCRIPTIONS
Participant ID: ☐☐☐☐☐	

Pages 40-44 can be used to record any information collected during the clinic visit, it is not necessary to transcribe all information from the diary to these pages. The diary data can be entered directly into the eCRF.

Please have the parent detail all prescriptions, even if repeat prescriptions

ECZEMA PRESCRIPTIONS

Has the participant been prescribed any treatment for their eczema? No ☐ Yes ☐

No.	Date of Prescription	Tick if estimated	What was Prescribed?	Details (size/amount)
1	D D M M M 2 0 Y Y	☐		
2	D D M M M 2 0 Y Y	☐		
3	D D M M M 2 0 Y Y	☐		
4	D D M M M 2 0 Y Y	☐		
5	D D M M M 2 0 Y Y	☐		
6	D D M M M 2 0 Y Y	☐		
7	D D M M M 2 0 Y Y	☐		
8	D D M M M 2 0 Y Y	☐		
9	D D M M M 2 0 Y Y	☐		
10	D D M M M 2 0 Y Y	☐		
11	D D M M M 2 0 Y Y	☐		
12	D D M M M 2 0 Y Y	☐		
13	D D M M M 2 0 Y Y	☐		
14	D D M M M 2 0 Y Y	☐		
15	D D M M M 2 0 Y Y	☐		
16	D D M M M 2 0 Y Y	☐		
17	D D M M M 2 0 Y Y	☐		
18	D D M M M 2 0 Y Y	☐		
19	D D M M M 2 0 Y Y	☐		
20	D D M M M 2 0 Y Y	☐		

Participant initials: ☐☐☐ **Participant ID:** ☐☐☐☐☐	SUMMARY INFORMATION: SKIN INFECTIONS

Pages 40-44 can be used to record any information collected during the clinic visit, it is not necessary to transcribe all information from the diary to these pages. The diary data can be entered directly into the eCRF.

SKIN INFECTIONS

Has the participant had any skin infections which required treatment with antibiotics or antivirals? No ☐ Yes ☐

No.	Start date of Skin Infection									Tick if estimated
1	D	D	M	M	M	2	0	Y	Y	☐
2	D	D	M	M	M	2	0	Y	Y	☐
3	D	D	M	M	M	2	0	Y	Y	☐
4	D	D	M	M	M	2	0	Y	Y	☐
5	D	D	M	M	M	2	0	Y	Y	☐
6	D	D	M	M	M	2	0	Y	Y	☐
7	D	D	M	M	M	2	0	Y	Y	☐
8	D	D	M	M	M	2	0	Y	Y	☐
9	D	D	M	M	M	2	0	Y	Y	☐
10	D	D	M	M	M	2	0	Y	Y	☐
11	D	D	M	M	M	2	0	Y	Y	☐
12	D	D	M	M	M	2	0	Y	Y	☐
13	D	D	M	M	M	2	0	Y	Y	☐
14	D	D	M	M	M	2	0	Y	Y	☐
15	D	D	M	M	M	2	0	Y	Y	☐
16	D	D	M	M	M	2	0	Y	Y	☐

The start date of the infection should be considered as the date of the prescription.

Participant initials: ☐☐☐	SUMMARY INFORMATION: PURCHASES FOR ECZEMA
Participant ID: ☐☐☐☐☐	

Pages 40-44 can be used to record any information collected during the clinic visit, it is not necessary to transcribe all information from the diary to these pages. The diary data can be entered directly into the eCRF.

PURCHASES FOR ECZEMA

Has the participant or parent/carer made any purchases or incurred any out of pocket expenses as a result of eczema? No ☐ Yes ☐

No.	Date of Purchase	Tick if estimated	Item Bought	Cost ££:pp	Estimated cost if you didn't need to buy a specialist item
1	D D M M M 2 0 Y Y	☐			
2	D D M M M 2 0 Y Y	☐			
3	D D M M M 2 0 Y Y	☐			
4	D D M M M 2 0 Y Y	☐			
5	D D M M M 2 0 Y Y	☐			
6	D D M M M 2 0 Y Y	☐			
7	D D M M M 2 0 Y Y	☐			
8	D D M M M 2 0 Y Y	☐			
9	D D M M M 2 0 Y Y	☐			
10	D D M M M 2 0 Y Y	☐			
11	D D M M M 2 0 Y Y	☐			
12	D D M M M 2 0 Y Y	☐			
13	D D M M M 2 0 Y Y	☐			
14	D D M M M 2 0 Y Y	☐			
15	D D M M M 2 0 Y Y	☐			
16	D D M M M 2 0 Y Y	☐			
17	D D M M M 2 0 Y Y	☐			
18	D D M M M 2 0 Y Y	☐			
19	D D M M M 2 0 Y Y	☐			
20	D D M M M 2 0 Y Y	☐			

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

SUMMARY INFORMATION: TIME OFF WORK AND SCHOOL DUE TO ECZEMA

Pages 40-44 can be used to record any information collected during the clinic visit, it is not necessary to transcribe all information from the diary to these pages. The diary data can be entered directly into the eCRF.

TIME OFF WORK AND SCHOOL DUE TO ECZEMA

Has the participant or parent/carer had any time off work and school due to eczema? No ☐ Yes ☐

No.	Date started	Tick if estimated	Time off school/nursery HH:MM	Parental/carer time off from paid employment HH:MM	Reason
1	D D M M M 2 0 Y Y	☐			
2	D D M M M 2 0 Y Y	☐			
3	D D M M M 2 0 Y Y	☐			
4	D D M M M 2 0 Y Y	☐			
5	D D M M M 2 0 Y Y	☐			
6	D D M M M 2 0 Y Y	☐			
7	D D M M M 2 0 Y Y	☐			
8	D D M M M 2 0 Y Y	☐			
9	D D M M M 2 0 Y Y	☐			
10	D D M M M 2 0 Y Y	☐			
11	D D M M M 2 0 Y Y	☐			
12	D D M M M 2 0 Y Y	☐			
13	D D M M M 2 0 Y Y	☐			
14	D D M M M 2 0 Y Y	☐			
15	D D M M M 2 0 Y Y	☐			
16	D D M M M 2 0 Y Y	☐			
17	D D M M M 2 0 Y Y	☐			
18	D D M M M 2 0 Y Y	☐			
19	D D M M M 2 0 Y Y	☐			
20	D D M M M 2 0 Y Y	☐			

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

PROTOCOL DEVIATIONS

PROTOCOL DEVIATIONS

Any Protocol Deviations to report? **No** ☐ **Yes** ☐

No.	Deviation (enter code as below)	Date of deviation	Tick if estimated	Comments
1	☐	D D M M M 2 0 Y Y	☐	
2	☐	D D M M M 2 0 Y Y	☐	
3	☐	D D M M M 2 0 Y Y	☐	
4	☐	D D M M M 2 0 Y Y	☐	
5	☐	D D M M M 2 0 Y Y	☐	
6	☐	D D M M M 2 0 Y Y	☐	
7	☐	D D M M M 2 0 Y Y	☐	
8	☐	D D M M M 2 0 Y Y	☐	
9	☐	D D M M M 2 0 Y Y	☐	
10	☐	D D M M M 2 0 Y Y	☐	

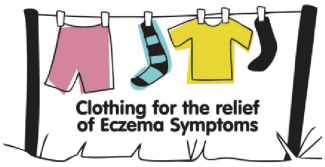
(Record multiple reasons on separate lines) **CODES**

1= Inclusion / Exclusion Criteria Deviation, 2= Trial procedure not performed per protocol 3= Informed Consent Deviation
4= Subject Non-Compliance with Protocol 5= Treatment Randomisation Error 6= Other (specify in comments)

Appendix 10 Participant diary

Participant ID: | | | | | | Participant initials: | | |

Date of birth: | | / | | | | / | | | |



CLOTHES Diary

Date of first visit	d	d/	m	m	m/	y	y	y	y
Date you received letter/clothing	d	d/	m	m	m/	y	y	y	y
Date of next clinic visit	d	d/	m	m	m/	y	y	y	y

Diary number [ ] *(to be completed by the research nurse)*

Useful Contact Details	
General study questions and appointments Local Research Nurse:	**You/your child's eczema treatment** You/your child's GP or consultant:
Clothing and re-ordering of clothing **Study manager** Nottingham Clinical Trials Unit Nottingham Health Science Partners C Floor, South Block Queens Medical Centre Nottingham NG7 2UH Tel: 0115 8844938 E-mail: clothes@nottingham.ac.uk	**General clinical trial queries and complaints** Patient Advice and Liaison Service (PALS):

REMEMBER NOT TO TELL THE NURSE IF YOUR CHILD HAS BEEN WEARING THE CLOTHING OR NOT!

Participant ID: | | | | | | Participant initials: | | | |

Date of birth: | | / | | | | / | | | | |

What to put in this diary

This diary is for you to write down information about details of eczema-related appointments, prescriptions or things that you have bought because of your child's eczema, plus time which has been missed at school and work. There is also space for you to jot down anything you would like to discuss with the nurse at your next clinic visit.

We would ask you to complete this diary when necessary and to bring it with you each time you visit the hospital where the research nurse will discuss it with you. You will be given a new diary at the end of each appointment.

Can we remind you that the nurse does not know whether or not you/your child has been wearing the clothing, so **please do not wear the clothing to your visit or discuss any aspects of your clothing with the research nurse.** Also – please do not write anything in this diary about the clothing, as the research nurse may see this.

If you have any questions about the use of the clothing, then please contact the study manager as detailed on the front cover and **NOT** the research nurse.

Washing instructions for trial clothing

How do I use the garments?
Please wear the garments as often as possible, both during the day and at night (either as underwear or as pyjamas).

Moisturising creams should be applied thinly to the skin (just enough for the skin to glisten) and should be applied a few minutes before putting on the clothing to allow the creams to be absorbed into the skin.

How do I care for the garments?
You will be given 3 sets of garments during the trial. This will allow one set to be in use, one in the wash and one spare. We recommend that you use all three sets within one week, rotating frequently.

To machine wash: Wash at up to 40°C using your usual mild non-biological detergent. The fibres of the garment are quite delicate and washing the garment inside a pillowcase on a delicate cycle will protect it during the wash. If possible, lay the garment flat to dry.

To hand wash: place in hand-hot water containing your usual mild non-biological detergent and agitate by hand for a few minutes. Rinse well with plenty of warm, clean water and squeeze dry. Do not wring. If possible, lay the garment flat to dry.

Other important points:

- Please don't use bleach. Make sure there are no bleaching agents in your detergent (such as Vanish)
- Please don't use fabric softeners
- Please do not tumble dry
- Any reduction in garment length is likely to be due to a tightening of the knit. A cool steam iron can be used to restore the shape of a garment that appears to have shrunk.

Participant ID: Participant initials:

Date of birth:

CLOTHES: Examples of out of pocket expenditure related to eczema

During the study we are asking you to make a note of anything you pay for out of pocket as a result of your child having eczema that you would not otherwise have had to purchase.

Based on experience some parents/carers find it difficult to know what type of items we are interested in them recording. Here are some examples of the type of things we would like you to record purchasing and the price you paid. This list is not exhaustive, there may be other items you think are relevant that are not on the list. Equally there may be things on this list which you haven't had to purchase any differently as a result of your child having eczema and thus you should not record these.

We are interested in the **difference in cost** of looking after a child with eczema to a child without eczema thus you should only put the whole price down if the item is something you would not have bought if your child did not have eczema (e.g. an emollient). Some items you may have bought even if they had not had eczema (e.g. sun cream, washing powder) but you have to buy a more expensive make/brand in order to get one that does not irritate your child's eczema, in this case please record how much this cost, and if you know, how much you would have paid for the same thing if your child did not have eczema.

Please only record those items actually purchased during the time you are involved in the study.

Clothing	**Special food**
Night wear, underwear, school uniform, and day wear made from natural fibres such as cotton	Nut-free foods Special milk e.g. goats, oat or lacto free milk
Over the counter products	**Laundry and bedding**
Emollients, moisturiser, bio oil, sun cream Special shampoos, shower or bath gels Vitamins & mineral supplements, anti-histamines, herbal remedies Bandages, tubi-grips	Purchased bedding (sheets, pillow cases, duvet cases) made of natural fibres Anti-allergic pillows and duvets Bath towels made from natural fibres Special laundry powder/liquid undertake more laundry increasing electricity bills & amount of liquid used
Equipment	**Appointments**
Air cooler Water softener	Travel and parking costs to NHS or private visits Appointments with alternative medicine practitioners e.g. allergy testing, homeopath etc

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐/☐☐☐☐

Health care visits for eczema

Please complete the date and tick the box for the type of visit you/your child has had. Please complete one line for each visit

Date	GP	Practice nurse	Outpatients	In hospital	Number of nights in hospital
Eg 15/03/2013	☑	☐	☐	☐	☐
	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐

Participant ID: | | | | | | Participant initials: | | | | Date of birth: | | / | | | / | | | |

Eczema prescriptions

Please record details of any prescriptions you/your child has had for eczema. Please complete one line for each item

Date	What was prescribed?	Details (size/amount)
Eg 15/03/2013	*Betamethasone ointment*	*100g tube*

Participant ID: | | | | | | Participant initials: | | | | Date of birth: | | / | | | / | | | | |

Purchases for eczema

Please record details of anything you have had to buy specifically because of you/your child's eczema. If you have had to buy something more expensive then please also record what you think you would have spent on the same item if you did not have to take eczema into account (eg natural fibre bath towel vs normal bath towel). Don't worry if you don't know this. Please complete one line for each item.

Date	Item bought	Cost	Estimated cost if you didn't need to buy a specialist item
16/03/2013	*Natural fibre bath towel*	*£25.00*	*£15.00*

Participant ID: | | | | | | Participant initials: | | | | Date of birth: | | / | | | / | | | |

Time off work and school due to eczema

Please record any time you have had off paid employment and time your child has had off nursery/school due to their eczema. Please complete one line for each episode.

Date started	Time off school/nursery	Parental/carer time off from paid employment related	Reason
Eg 13/03/2013	*2 hours 12 minutes*	*2 hours 45 minutes*	*Visit to GP with Skin infection*
25/03/2013	*No time off - out of school hours*	*3 hours 50 minutes*	*Visit to hospital to see dermatologist*

Participant ID: | | | | | | Participant initials: | | | | Date of birth: | | / | | | / | | | | |

Anything page

This page can be used for anything. You can record additional notes for the nurse, you/your child's drawings etc.

Please remember to bring this diary to your clinic visit.

Appendix 11 Weekly participant questionnaire

Participant ID: Participant initials: Date of birth:

Date of completion:

The University of Nottingham

Clothing for the relief of Eczema Symptoms

Weekly questionnaire **Week number**

We hope that you/your child has had a good week. Please select one response for each of the seven questions below about your child's eczema. If your child is old enough to understand the questions then please fill in the questionnaire together. Please leave blank any questions you feel unable to answer.

Over the last week

1 On how many days has your/your child's skin been itchy because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

2 On how many nights has your/your child's sleep been disturbed because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

3 On how many days has your/your child's skin been bleeding because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

4 On how many days has your/your child's skin been weeping or oozing clear fluid because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

5 On how many days has your/your child's skin been cracked because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

6 On how many days has you/your child's skin been flaking off because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

7 On how many days has you/your child's skin felt dry or rough because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

CLOTHES on-line questionnaire – weekly –Final 2.0 1 August 2013

Participant ID: ☐ Participant initials: ☐ Date of birth: ☐/☐/☐

Please select one response for each of the questions below.

Over the last week:

Has your child had any visits to a health care professional?

Yes ◯ No ◯ If yes please record details in the diary card

Has your child had any prescriptions for eczema?

Yes ◯ No ◯ If yes please record details in the diary card

Have you bought anything specifically because of your child's eczema?

Yes ◯ No ◯ If yes please record details in the diary card

Have you had any time off work and/or has your child had any time off school or nursery because of their eczema?

Yes ◯ No ◯ If yes please record details in the diary card

Please select one response for each of the questions below.

Over the last week, on how many days have you/your child used the following:

Topical Steroids

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Emollients

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Topical Calcineurin Inhibitors

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Wet/Dry Wraps

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Participant ID: ☐ Participant initials: ☐ Date of birth: ☐/☐/☐

Only for patients randomised to clothing

Over the last week

On how many nights has the clothing been worn for at least some of the night?

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ Not Known ◯

On how many days has the clothing been worn for at least some of the day?

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ Not known ◯

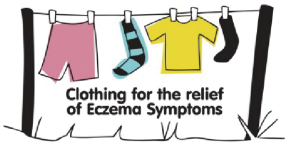
CLOTHES on-line questionnaire – weekly –Final 2.0 1 August 2013

Appendix 12 Participant week 24 (6-month) questionnaire

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐/☐☐☐☐

Date of completion: ☐☐/☐☐/☐☐☐☐

The University of Nottingham



Six-month questionnaire **Week 24 (6 months)**

We hope that you/your child has had a good week. Please select one response for each of the seven questions below about your child's eczema. If your child is old enough to understand the questions then please fill in the questionnaire together. Please leave blank any questions you feel unable to answer.

Over the last week

1 On how many days has your/your child's skin been itchy because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

2 On how many nights has your/your child's sleep been disturbed because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

3 On how many days has your/your child's skin been bleeding because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

4 On how many days has your/your child's skin been weeping or oozing clear fluid because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

5 On how many days has your/your child's skin been cracked because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

6 On how many days has you/your child's skin been flaking off because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

7 On how many days has you/your child's skin felt dry or rough because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐☐/☐☐☐☐

Please select one response for each of the questions below.

Over the last week:

Has your child had any visits to a health care professional?

Yes ◯ No ◯ If yes please record details in the diary card

Has your child had any prescriptions for eczema?

Yes ◯ No ◯ If yes please record details in the diary card

Have you bought anything specifically because of your child's eczema?

Yes ◯ No ◯ If yes please record details in the diary card

Have you had any time off work and/or has your child had any time off school or nursery because of their eczema?

Yes ◯ No ◯ If yes please record details in the diary card

Please select one response for each of the questions below.

Over the last week, on how many days have you/your child used the following:

Topical Steroids

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Emollients

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Topical Calcineurin Inhibitors

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Wet/Dry Wraps

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐☐/☐☐☐☐

Over the past week

On how many nights has the clothing been worn for at least some of the night?

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ Not Known ◯

On how many days has the clothing been worn for at least some of the day?

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ Not known ◯

How satisfied were you with the clothing overall?

Very satisfied	Satisfied	Neither satisfied or dissatisfied	Dissatisfied	Very Dissatisfied
◯	◯	◯	◯	◯

Were you/your child happy to wear the clothing?

Very happy	Happy	Neither happy nor unhappy	Unhappy	Very unhappy
◯	◯	◯	◯	◯

Comments ☐

CLOTHES 6 month on-line questionnaire –Final 2.0_05 Sept 2013

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐☐/☐☐☐☐

Condition of trial clothing

	Body suits / vests	**Leggings**
How many vests/bodysuits and leggings have you had since the start of the study (please include those you have returned)?	☐	☐
How many can you still wear?	☐	☐
How many can you not wear?	☐	☐

Why can you not wear them? (please select all that apply)

Too small	○	○
Worn out/torn	○	○
Lost	○	○
Other	○	○
Reason:	☐	☐

CLOTHES 6 month on-line questionnaire –Final 2.0_05 Sept 2013

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐☐/☐☐☐☐

Apart from the clothing received for the trial, over the **last 6 months**, did you/your child wear any of the following?

Pure cotton clothing

Yes ◯ No ◯

Silver impregnated clothing

Yes ◯ No ◯

Silk clothing

Yes ◯ No ◯

Stretchy garments eg tubifast, comfifast, skinnies

Yes ◯ No ◯

Other

Yes ◯ No ◯

Please name _____

CLOTHES 6 month on-line questionnaire –Final 2.0_05 Sept 2013

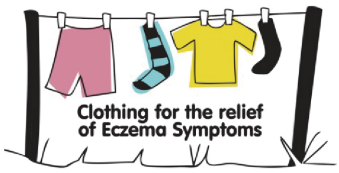
Appendix 13 Participant week 32 (8-month) questionnaire

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐/☐☐☐☐

Date of completion: ☐☐/☐☐/☐☐☐☐

Suggested date of completion:

The University of Nottingham



Eight-month on-line questionnaire **Week 32 (8 months)**

We hope that you/your child has had a good week. Please select one response for each of the seven questions below about your child's eczema. If your child is old enough to understand the questions then please fill in the questionnaire together. Please leave blank any questions you feel unable to answer.

Over the last week

1 On how many days has your/your child's skin been itchy because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

2 On how many nights has your/your child's sleep been disturbed because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

3 On how many days has your/your child's skin been bleeding because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

4 On how many days has your/your child's skin been weeping or oozing clear fluid because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

5 On how many days has your/your child's skin been cracked because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

6 On how many days has you/your child's skin been flaking off because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

7 On how many days has you/your child's skin felt dry or rough because of their eczema?

No days ◯ 1-2 days ◯ 3-4 days ◯ 5-6 days ◯ Every day ◯

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐☐/☐☐☐☐

Please select one response for each of the questions below.

Over the last week:

Has your child had any visits to a health care professional?

Yes ◯ No ◯

Has your child had any prescriptions for eczema?

Yes ◯ No ◯

Have you bought anything specifically because of your child's eczema?

Yes ◯ No ◯

Have you had any time off work and/or has your child had any time off school or nursery because of their eczema?

Yes ◯ No ◯

Please select one response for each of the questions below.

Over the last week, on how many days have you/your child used the following:

Topical Steroids

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Emollients

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Topical Calcineurin Inhibitors

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Wet/Dry Wraps

0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐☐/☐☐☐☐

Over the past 2 months, how often has the trial clothing been worn?

All/most of the time (days and nights)	All/most of the time (days only)	All/most of the time (nights only)	Some of the time	Rarely	Never
◯	◯	◯	◯	◯	◯

How satisfied were you with the clothing overall?

Very satisfied	Satisfied	Neither satisfied or dissatisfied	Dissatisfied	Very Dissatisfied
◯	◯	◯	◯	◯

Were you/your child happy to wear the clothing?

Very happy	Happy	Neither happy nor unhappy	Unhappy	Very unhappy
◯	◯	◯	◯	◯

Comments

CLOTHES 8 month on-line questionnaire_Final 3.0_21 Oct 2013

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐☐/☐☐☐☐

Condition of trial clothing

	Body suits / vests	**Leggings**
How many vests/bodysuits and leggings have you had since the start of the study (please include those you have returned)?	☐	☐
How many can you still wear?	☐	☐
How many can you not wear?	☐	☐

Why can you not wear them? (please select all that apply)

Too small	○	○
Worn out/torn	○	○
Lost	○	○
Other	○	○
Reason:	☐	☐

CLOTHES 8 month on-line questionnaire_Final 3.0_21 Oct 2013

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐☐/☐☐☐☐

Your opinion of the trial clothing

Do you feel that you/your child's eczema has improved wearing the trial clothing?

Yes ◯ No ◯ Not sure ◯

Would you ask your GP to prescribe the clothing?

Yes ◯ No ◯ Not sure ◯

Have you asked your GP to prescribe the clothing?

Yes ◯ No ◯

If you have, did they prescribe the clothing?

Yes ◯ No ◯

If your GP did prescribe the clothing, what did they prescribe?

If your GP did not prescribe the clothing, what reason did s/he give (please tick all that apply)

Too expensive ◯ No proof that they work ◯ No reason given ◯ Other ◯

Please specify

CLOTHES 8 month on-line questionnaire_Final 3.0_21 Oct 2013

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐ Date of birth: ☐☐/☐☐/☐☐☐☐

Have you purchased any silk clothing for eczema during the trial?

Yes ◯ No ◯

If yes, select all types purchased.

Vest	◯	Number purchased	☐	Total cost (£)	☐
Leggings	◯	Number purchased	☐	Total cost (£)	☐
Body suit	◯	Number purchased	☐	Total cost (£)	☐
Other	◯	Number purchased	☐	Total cost (£)	☐

Please specify

☐

THANK YOU FOR TAKING PART IN THE CLOTHES TRIAL

CLOTHES 8 month on-line questionnaire_Final 3.0_21 Oct 2013

Appendix 14 Additional data on outcomes collected at clinic visits to inform future sample size calculations

TABLE 52 Arithmetic mean of EASI scores on original scale and log-transformed EASI scores

Allocated group	Baseline	2 months	4 months	6 months
Standard care				
n	151	137	133	139
Mean (SD)	9.6 (7.8)	7.8 (7.2)	7.7 (8.7)	6.5 (6.4)
Log-transformed mean (SD)	2.13 (0.68)	1.89 (0.77)	1.79 (0.86)	1.70 (0.80)
Intervention				
n	149	139	135	133
Mean (SD)	11.4 (10.6)	8.8 (10.6)	7.7 (10.1)	7.3 (10)
Log-transformed mean (SD)	2.22 (0.76)	1.86 (0.88)	1.75 (0.86)	1.69 (0.87)

Note
One was added to the EASI scores before transformation because some EASI scores were 0 at follow-up.

TABLE 53 Correlation between outcomes assessed at clinic visits

Follow-up (months)	Baseline	2 months	4 months
EASI			
2	0.71 ($n = 276$)	–	
4	0.65 ($n = 268$)	0.79 ($n = 265$)	–
6	0.62 ($n = 272$)	0.70 ($n = 266$)	0.77 ($n = 261$)
TIS			
2	0.51 ($n = 276$)	–	
4	0.49 ($n = 269$)	0.51 ($n = 265$)	–
6	0.42 ($n = 273$)	0.45 ($n = 266$)	0.62 ($n = 262$)

Note
Spearman's correlation coefficients are presented for all outcomes.

Appendix 15 Additional data on weekly Patient Oriented Eczema Measure scores

TABLE 54 Weekly POEM scores

Week	Standard care (*N* = 151)	Intervention (*N* = 149)
Week 1		
Mean (SD)	15.8 (5.6)	15 (6.0)
n	134	131
Week 2		
Mean (SD)	15.7 (6.1)	13.2 (6.8)
n	127	125
Week 3		
Mean (SD)	15.8 (6.4)	13 (6.1)
n	128	125
Week 4		
Mean (SD)	16.1 (6.4)	11.8 (6.5)
n	129	122
Week 5		
Mean (SD)	15.4 (6.5)	11.7 (7.1)
n	124	123
Week 6		
Mean (SD)	15 (6.8)	11.7 (6.8)
n	122	120
Week 7		
Mean (SD)	14.6 (6.4)	12.2 (7.1)
n	115	125
Week 8		
Mean (SD)	15.1 (6.7)	12 (6.6)
n	117	121
Week 9		
Mean (SD)	14.2 (6.7)	11.4 (6.5)
n	114	123
Week 10		
Mean (SD)	14.6 (6.3)	10.9 (6.2)
n	123	116

continued

TABLE 54 Weekly POEM scores (*continued*)

Week	Standard care (*N* = 151)	Intervention (*N* = 149)
Week 11		
Mean (SD)	14.1 (6.9)	10.6 (6.7)
n	118	121
Week 12		
Mean (SD)	13.4 (6.7)	11.5 (7)
n	113	122
Week 13		
Mean (SD)	13.7 (6.7)	11.5 (7.1)
n	116	115
Week 14		
Mean (SD)	13.8 (7)	11.7 (7.1)
n	116	119
Week 15		
Mean (SD)	12.9 (6.8)	11.6 (6.8)
n	110	116
Week 16		
Mean (SD)	13.3 (7.2)	10.9 (6.6)
n	114	111
Week 17		
Mean (SD)	13.4 (7.2)	11.2 (6.6)
n	110	107
Week 18		
Mean (SD)	13.4 (6.7)	11.4 (7.6)
n	114	112
Week 19		
Mean (SD)	13.6 (6.6)	10.4 (6.8)
n	110	114
Week 20		
Mean (SD)	12.4 (6.6)	10.8 (7)
n	107	114
Week 21		
Mean (SD)	13.5 (6.5)	10.7 (6.5)
n	100	110
Week 22		
Mean (SD)	12.6 (7)	11 (7.2)
n	108	109

TABLE 54 Weekly POEM scores (*continued*)

Week	Standard care (*N* = 151)	Intervention (*N* = 149)
Week 23		
Mean (SD)	13.6 (6.7)	10.3 (7)
n	90	104
Week 24		
Mean (SD)	13.4 (6.5)	11.4 (7.4)
n	61[a]	71[a]

a A total of 242 (81%) participants completed the POEM scale at 24 weeks, but data from the online questionnaires were included in the analysis only if they were completed on or before the 6-month clinic visit date to ensure that no contamination occurred as a result of children in the standard care group receiving silk clothing after the 6-month clinic visit.

TABLE 55 Correlation between weekly POEM scores at baseline, 8, 16 and 24 weeks

Follow-up (weeks)	Baseline	8 weeks	16 weeks
8	0.47 (*n* = 238)	–	
16	0.39 (*n* = 225)	0.64 (*n* = 202)	–
24	0.35 (*n* = 241)	0.55 (*n* = 208)	0.64 (*n* = 211)

Note
Spearman's correlation coefficients are presented for all outcomes.
Baseline POEM was collected in clinic.

Appendix 16 Eczema severity according to coverage of garments

The EASI score is calculated based on the severity of AE on the head and neck, upper limbs, trunk and lower limbs. The trial garments, however, did not cover the head and neck. Therefore, an exploratory analysis was conducted for the EASI scores for the head and neck only and the EASI scores for the other body areas combined.

Figure 26 shows that EASI scores for the body areas covered by the garments were similar in the standard care and intervention group at each follow-up visit, and EASI scores for the head and neck were similar in each group at each follow-up visit.

Body areas covered by garments are upper limbs, trunk and lower limbs. All scores above range between 0 and 72. Scores for the body areas covered by the garments (upper limbs, trunk and lower limbs) are combined and weighted based on the child's age at randomisation (as for the calculation of the EASI total score and rescaled in order that the sum of the weights for the covered body areas was 1).

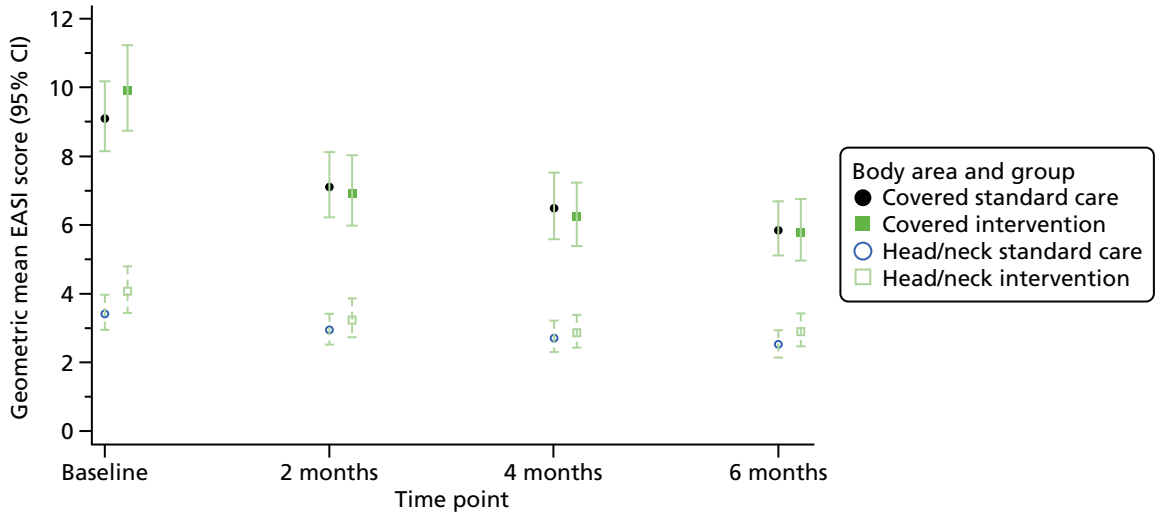


FIGURE 26 Eczema Area and Severity Index body region scores according to coverage of garments, by group.

Appendix 17 Causal effect of adherence with wearing trial garments

This section presents CACE estimates for all participants with EASI scores at 6 months, based on the sensitivity analysis for garment wear for periods when questionnaires were not completed (*Table 56*).

TABLE 56 Causal effect of adherence with wearing trial garments (all participants at 6 months)

Estimate	*n*	Adjusted ratio of geometric means (95% CI)
ITT at 6 months[a]	272	0.982 (0.844 to 1.144)
CACE: binary – garments worn for at least 50% of days or 50% of the nights[b]	272	
Assuming that garments worn for the same proportion of time when questionnaires not completed as when completed		0.978 (0.815 to 1.175)
Assuming that garments not worn when questionnaires not completed		0.973 (0.769 to 1.230)
CACE: each additional 10% of time garments worn[b,c]	272	
Assuming that garments worn for the same proportion of time when questionnaires not completed as when completed		0.997 (0.971 to 1.024)
Assuming that garments not worn when questionnaires not completed		0.996 (0.966 to 1.027)

ITT, intention to treat.
a Analysed using linear regression with log-transformed EASI score at 6 months as the outcome variable and adjusted for randomisation stratification variables and baseline EASI score.
b Analysed using instrumental variable regression.
c Percentage of time worn calculated as (total number of days and nights clothing worn × 100)/(total number of questionnaires completed × 14).

Appendix 18 Further exploratory analysis according to brand of garment

In addition to exploration of the primary outcome by brand (as summarised in the main report), we also explored the impact of brand of garments on self-reported symptoms (POEM). For this analysis, we used data from baseline and 2 months (for the intervention group), and 6 and 8 months (for the standard care group), in order to maximise the available data.

Results are shown in *Table 57*. There was no difference in mean POEM scores 2 months after receiving the clothing for DreamSkin compared with DermaSilk (difference in means –0.57, 95% CI –2.35 to 1.21; $n = 187$), using a linear regression model adjusting for POEM score prior to receiving the clothing, site, age and treatment group.

Adherence to and acceptability of the garments at 8 months by allocated group and allocated garment brand are shown in *Table 58*.

TABLE 57 Self-reported AE symptoms using POEM scores collected on online/paper questionnaires by brand of garment and allocated group

	Standard care		Intervention	
Self-reported symptoms	DermaSilk (*N* = 62)	DreamSkin (*N* = 51)	DermaSilk (*N* = 67)	DreamSkin (*N* = 63)
Prior to receiving garments[a]				
Mean (SD)	13.3 (7.2)	13.2 (6.2)	18.1 (6.1)	16.1 (5.6)
Median (25th, 75th centile)	12 (8, 19)	11.5 (9, 18)	18 (13, 23)	16 (12, 19)
n	53	42	67	63
2 months after receiving garments[b]				
Mean (SD)	11.8 (7.6)	12.3 (7.2)	12.6 (6.2)	11.2 (6.5)
Median (25th, 75th centile)	11 (5.5, 18.5)	12 (7, 17)	13 (8, 18)	10 (6, 16)
n	48	39	58	49

a POEM scores from online/postal questionnaire at 6 months for standard care group and baseline clinic visit for intervention group.
b POEM scores from online/postal questionnaire at 8 months for standard care group and week 8 for intervention group. The intervention group received the trial garments at baseline. The standard group received the trial garments after their 6-month clinic visit.

TABLE 58 Adherence to and acceptability of clothing during the open follow-up period (between 6 and 8 months) by brand of clothing and allocated group

Adherence and acceptability	Standard care, *n* (%)		Intervention, *n* (%)	
	DermaSilk (*N* = 48)	DreamSkin (*N* = 39)	DermaSilk (*N* = 52)	DreamSkin (*N* = 51)
Frequency clothing worn during the follow-up period				
Never	2 (4)	2 (5)	6 (12)	11 (22)
Rarely	4 (8)	11 (28)	6 (12)	11 (22)
Some of the time	12 (25)	10 (26)	14 (27)	8 (16)
All/most of the time (days only)	1 (2)	–	1 (2)	1 (2)
All/most of the time (nights only)	24 (50)	10 (26)	11 (21)	11 (22)
All/most of the time (days and nights)	2 (4)	5 (13)	12 (23)	8 (16)
Not answered	3 (6)	1 (3)	2 (4)	1 (2)
Satisfaction with the clothing overall				
Very dissatisfied	–	1 (3)	2 (4)	4 (8)
Dissatisfied	3 (6)	6 (15)	2 (4)	5 (10)
Neither	11 (23)	12 (31)	12 (23)	11 (22)
Satisfied	19 (40)	14 (36)	18 (35)	17 (33)
Very satisfied	12 (25)	4 (10)	16 (31)	13 (25)
Not answered	3 (6)	2 (5)	2 (4)	1 (2)
Child happy to wear clothing				
Very unhappy	–	2 (5)	2 (4)	6 (12)
Unhappy	7 (15)	6 (15)	2 (4)	2 (4)
Neither	10 (21)	9 (23)	10 (19)	9 (18)
Happy	16 (33)	12 (31)	18 (35)	14 (27)
Very happy	12 (25)	9 (23)	18 (35)	19 (37)
Not answered	3 (6)	1 (3)	2 (4)	1 (2)

Note
Table shows data for participants included in the exploratory analysis according to brand of clothing (see *Figure 12*) and completing the questionnaire at 8 months.

Appendix 19 Health economics analysis plan

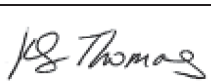
CLOTHES Trial

FINAL Health Economic Analysis Plan

Authors: Tracey Sach

CLOTHES trial team

Version 1.0 – 13.01.16

The following people have reviewed the Health Economic Analysis Plan and are in agreement with the contents			
Name	**Role**	**Signature**	**Date**
Tracey Sach	Author		**13.01.16**
Prof Alan Montgomery	Trial Statistician		**19 Jan 2016**
Prof Kim Thomas	Chief Investigator		**13.01.16**

The HEAP has also been reviewed by Lisa Irvine, Senior Research Associate in Health Economics at the University of East Anglia.

Objective

This economic analysis plan aims to provide a detailed description of the economic evaluation to be conducted alongside the CLOTHES trial. It describes how the data will be collected, analysed and reported.

Summary of clinical trial

Eczema is a chronic skin condition that can have a large impact on the quality of life of patients and their families. Non-pharmacological therapies are often appealing to people suffering eczema, and so silk therapeutic garments represent an attractive therapy for many. Silk therapeutic garments are included in the British National

Formulary meaning that doctors can prescribe these items to patients should they deem it necessary. However, the effectiveness and cost-effectiveness of these garments in the management of eczema is as yet unproven. The CLOTHES trial will test the hypothesis that 'silk therapeutic garments plus standard eczema care' is superior to 'standard care alone' for children with moderate to severe eczema.

It will be a parallel group, observer-blind, pragmatic, multi-centre randomised controlled trial of 6 months' in length. Three hundred children aged 1 to 15 years with moderate to severe eczema will be randomised (1:1) to receive silk therapeutic garments plus standard eczema care, or standard eczema care alone. The primary outcome is eczema severity at 2, 4 and 6 months, using the validated Eczema Area and Severity Index (EASI) recommended by the HOME initiative. Secondary outcomes include: patient-reported eczema symptoms (collected weekly for 6 months to capture long-term control); global assessment of severity; quality of life of the child, family and main carer; use of standard eczema treatments (emollients, topical corticosteroids, calcineurin inhibitors and wet wraps); frequency of infections; and cost-effectiveness. The acceptability and durability of the clothing will also be assessed, as will adherence in wearing the garments. A nested qualitative study will assess the views of children wearing the garments, and those of healthcare providers and commissioners.

Recruitment started in November 2013, and the trial is expected to be completed by June 2016. The trial was funded as part of the NIHR HTA programme and sponsored by the University of Nottingham. Full details of results will be published in the National Institute for Health Research Journal series.

Comparators to be included

100% silk garments made from antimicrobially protected knitted sericin-free silk used in addition to standard eczema care

The specific products being used are Dreamskin™ and Dermasilk™. Participants will be asked to wear the clothing as much as possible including at night, and when possible during the day. Participants will receive three sets of garments (long-sleeved vest and leggings, or body suits and leggings depending on the age of the child). Replacement clothing is also available as required should the child grow or garments get spoiled.

Participants allocated to the therapeutic clothing will continue to use their standard eczema care (including emollients, topical corticosteroids and topical calcineurin inhibitors), as described below.

Standard care

All participants (active and control groups) will continue with standard eczema care in line with NICE guidance (NICE, 2007). A child's standard eczema care will not change unless the research nurse thinks that the skin may be infected. If an infection

is suspected the research nurse will recommend that the patient contact their normal medical team (GP, Nurse, dermatologist) as appropriate.

Standard advice about what clothing to use for a child with eczema will be provided (avoid wool, and wear cool loose clothing – especially cotton and linen), but specific products will not be recommended.

If a child is currently using "specialist" cotton clothing (e.g. special sleep suits with built-in mittens), the use of these garments will be recorded, but will not be grounds for exclusion. However, participants in the control group will be asked to refrain from using prescription clothing (including silk clothing and synthetic garments used for wet wrapping) during the trial.

Study design – Economic evaluation

Guidelines for economic evaluations`

The economic evaluation will adhere to published and well accepted guidelines for the economic evaluation of health care interventions as appropriate. [1-3]

Study Question

To estimate the within trial cost-effectiveness of silk therapeutic clothing with standard care compared to standard care alone from an NHS perspective in the base case and from an NHS and family perspective in secondary analyses.

Blinding

The health economics analysis will be undertaken blinded to intervention group as much as is possible. Thus the majority of resource use items can be valued and utility values scored along with estimation of QALYs without knowledge of intervention group. It will be possible to conduct some preliminary analysis to examine costs and outcomes in the two (unidentified) groups at this point. However the costs of the intervention, i.e. the silk clothing costs are specific to group. Assigning these costs would require knowledge of intervention group and the health economist would need to become unblinded at this point. Final analysis, including the cost of intervention, will therefore not be carried out blinded to intervention group.

Form of economic analysis

Two types of economic evaluation will be conducted as part of this within trial economic evaluation: A cost-effectiveness analysis and Cost-utility analysis.

Perspective

The analysis will primarily take an NHS perspective, reflecting that Personal Social Services costs are unlikely to be relevant for childhood eczema. A secondary analysis will capture costs incurred by the family to assess whether the intervention makes a significant difference to these.

Resource use: identification, measurement and valuation

The range of resource use and costs captured will be in keeping with the chosen perspective.

Intervention resource use

The cost of the intervention will include the cost of silk clothing and replacement garments needed due to growth or wear and tear. The unit costs for this will be taken from the HSCIC Prescription Cost Analysis as the Net Ingredient Cost per Item (NIC) which does not include any discounts, costs/fees of dispensing nor adjust for income from prescription payments. An alternative method of costing the NHS cost of prescribed medications will be explored in sensitivity analyses.

Resource use associated with wider health care contacts related to eczema

The resource use is recorded on the diary card and entered by the research nurse at each of the study visits. To aid memory an online/paper questionnaire prompts participants to complete their diary if a health care professional is visited for eczema in the last week. Resource use will focus on those resources consumed as a result of the child's eczema and will include health care visits (number of appointments to GP, practice nurse, outpatients, other and nights in inpatient care), prescriptions (topical corticosteroids, topical calcineurin inhibitors, emollients (including bath emollients), wet/dry wraps, antibiotics/antivirals for skin infections, other eczema-related prescriptions). This resource use will be recorded at study visits at baseline, 2, 4, 6, and 8 months.

Resource use will be valued using published national sources of unit costs (UK£sterling for the most recent year available)(Curtis 2014, NHS reference costs 2013-14, HSCIC 2014).

Resource use incurred by the family related to their child's eczema

The resource items recorded in this component reflect a family or more societal perspective.

Figure 1 shows the types of resource use items families were asked about at study visits but families were not limited to these examples. Respondents were asked to place a monetary value on the additional cost incurred as a result of eczema, for instance if they bought a more expensive washing detergent because it is kinder on the persons with eczema skin they were asked to state the amount over and above that which they would have paid for a normal washing detergent.

In addition families were asked to record time off work and school as a result of eczema. The time of parents will be valued using the mean gross hourly wage rate for all employee jobs in the UK as reported in the Annual Survey of Hours and Earnings (ASHE) in 2014 since we will not know the respondents personal earnings. [Accessed online on 5th January 2016: http://www.ons.gov.uk/ons/rel/ashe/annual-survey-of-hours-and-earnings/index.html] This approach is known as the human capital approach and assumes a person's productivity is equal to their wage rate to place a maximum cost on the time off work. Time off school will be reported in hours and minutes and not valued due to a lack of evidence about the cost of lost schooling.

Presentation of cost results

To ensure transparency and reproducibility the unit costs used to attach monetary costs to resource use will be clearly displayed in tabular format with source of unit cost displayed in addition to the actual unit cost used. (see appendix 1 for an example)

Resource use and costs will be presented clearly in tabular format to ensure transparency in the final figures reported. Mean and SD resource use and costs will be presented by intervention group and health sector (Primary care, secondary care, Family costs). (see appendix 2 for an example)

Outcomes: effectiveness and utility

The primary measure of effectiveness for the cost effectiveness analysis will be the difference in the number achieving treatment success at 6 months – defined as those with at least a 50% improvement compared to baseline on the primary outcome measure Eczema Area and Severity Index (EASI) (Barbier et al 2004). Secondary analyses will be conducted using continuous data from the Dermatitis Family Impact Scale.

A cost utility analysis, where effectiveness is measured in terms of the Quality Adjusted Life Years (QALYs) for child and main carer, will be undertaken. Utility will be measured in all children using the disease specific Atopic Dermatitis Quality of Life scale (ADQoL), and in those aged 5 or over by the generic health-related quality of life instrument the Child Health Utility index (CHU-9D). The CHU-9D is being used

with children aged 7 and over self-completing and parental proxy completion for 5 and 6 year olds. In addition, the main carer will record their own utility using the EQ-5D-3L. All three utility instruments will be measured at baseline and 6 months and used to estimate QALYs for the trial period by using linear interpolation and area under the curve with and without baseline adjustment (Manca et al, 2007). The primary cost-utility analysis will report the incremental cost per QALY based on the ADQoL since we will have this completed for all children in the study. Secondary analyses will report the cost per QALY based on the CHU-9D for those aged 5 and over. Statistical modelling will explore the potential to impute values for those children too young to complete the instrument but some strong assumptions are made in such an analysis, including that the utility values of those aged under 5 in a similar disease state as the 5 and overs will be the same irrespective of the age difference. In addition, a cost per QALY for the main carers using their EQ-5D-3L values will be estimated separately. Previous work has not explored the ability of the EQ-5D to detect impacts on carers quality of life for this condition. (see appendix 3 for example tables).

Length of follow-up

Since this is a within-trial analysis the trial period will be used (6 months) for both costs and outcomes in the base case. Therefore costs and benefits will not be discounted, reflecting the short time horizon.

Statistical analysis and analysis of uncertainty

In line with statistical analyses an intention to treat population will be used in primary analyses. The economic evaluation will be a 'within trial analysis'. This means that costs and benefits will only be evaluated for the trial follow-up period (6 months). Costs in both arms of the study will be estimated using the methods described above. We will calculate outcomes and QALYs again as described above. This information on costs and benefits will be used to conduct incremental economic analysis comparing the silk therapeutic clothing in addition to usual care to usual care alone. This will be done for both the cost-effectiveness and cost-utility analyses. Conclusions will be based on results achieved. If one arm is clearly dominant (less costly and more effective) a recommendation can be made on this basis. If non-dominance occurs (that is if costs are greater and the intervention is more effective or if the intervention is cheaper and less effective), an incremental cost-effectiveness ratio (ICER) will be produced and a value judgement about value for money will need to be made. ICERs will be calculated using accepted methodology (Ramsey et al 2015, Drummond et al 2005).

Since costs and benefit data may be skewed we will use non-parametric bootstrapping to estimate mean costs, mean QALY estimates, and net benefit. Estimates of cost and benefits will be placed upon cost-effectiveness planes. Bootstrapping will also be used to estimate cost-effectiveness acceptability curves (CEACs)(Glick et al, 2007), these will show the probability that each of the

intervention groups is the most cost-effective option at different monetary valuations of the outcome variable. A range of ceiling ratio (or willingness to pay per QALY) values will be tested but this will include £20,000 and £30,000 per QALY given thresholds used by NICE in cost-utility calculations (NICE, 2013).

The analysis will be undertaken unadjusted and adjusted to control for differences in baseline characteristics (e.g. costs, age, baseline EASI score) using regression methods to estimate differences in costs and QALYs between intervention groups.

Assumptions will need to be made in the estimation of costs and QALYs in this analysis. There may also be cases where there is uncertainty over the best values to use in the analysis. These assumptions and sources of uncertainty will be recorded. Where these are likely to affect results we will carry out sensitivity analysis. Sensitivity analysis tests the robustness of results in the face of any uncertainties. It also improves the generalisability of results by indicating what could happen with different values of a parameter. The sensitivity analysis will include the following:

- Imputing missing values – the base case will be a complete case analysis but if there is significant (>10%) missing data it may bias results. If there is missing data, the extent and nature of the missingness will be explored in order to choose an appropriate approach to deal with the missing data. If missing data is a significant issue multiple imputation will be used to impute missing values and presented as secondary analyses.
- Run a per protocol economic analysis to estimate the cost-effectiveness of the intervention for those participants who complied with the protocol to wear the silk clothes as much as possible day and night. Participants will be classified as adherent if they wear the trial clothing for at least 50% of the days or nights where the diary had been completed, provided that at least 50% of the diary had been completed.
- If the statistical analysis finds a significant difference in effectiveness on the primary outcome measure for those with mutations in the gene encoding for filaggrin FLG as defined on page 17 of the Statistical Analysis Plan, the economic evaluation will be re-run as part of a subgroup analysis for presence of the FLG genotype.
- The cost of the silk therapeutic garments may be a major cost driver affecting the likely cost-effectiveness or not of the garments. To test this the unit cost of the garments will be varied to find the unit cost at which it would change the decision about cost-effectiveness.
- We are also collecting utility information from the main carer. Since the evidence about how to analyse this in addition to the child's utility is limited (Al-Janabi et al 2011) we will present cost per QALY for the child as the base case and cost per QALY per carer (since only one carer completed the EQ-5D an assumption that any change in utility might be double for two parents families could be tested) separately in sensitivity analyses.
- Method of estimating prescription costs will be tested. The main analysis will rely on the HSCIC Prescription Cost Analysis as the Net Ingredient Cost per

Item (NIC). In sensitivity analysis an alternative based on the NHS Business Services Authority formula to estimate the actual cost to the NHS:

Actual Cost = (Net Ingredient Cost less the discount) + Payment for Consumables + Payment for Containers (10p for splitting packs) + Out of Pocket Expenses

Source:www.nhsbsa.nhs.uk/documents/prescriptionservices/gp_faqsver4.doc. Accessed 5th January 2016.

Will be used employing the methods outlined in a personal communication from Kirsty Garfield at the University of Bristol to cost eczema prescriptions in the NIHR RfPB funded "Choice Of Moisturiser in Eczema Treatment (COMET): A feasibility study of pragmatic, single blind, randomised clinical trial to compare the clinical and cost effectiveness of leave-on emollients in treat" study.

- If feasible, a sensitivity analysis will consider the resource use data collected in the observational period (8 months) in order to assess the likely costs of the intervention over an 8-month period of time to reflect more fully the wear and tear of the garments and growth of children. However, health outcomes will not be measured at 8 months so it will not be possible to repeat the economic evaluation for an 8 months period.

All statistical analysis will be undertaken in STATA 14 64-bit SE.

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FIGURE 1: CLOTHES Examples of out of pocket expenditure related to eczema

During the study we are asking you to make a note of anything you pay for out of pocket as a result of your child having eczema that you would not otherwise have had to purchase.

Based on experience some parents/carers find it difficult to know what type of items we are interested in them recording. This leaflet gives some examples of the type of things we would like you to record purchasing and the price you paid. This list is not exhaustive, there may be other items you think are relevant that are not on the list. Equally there may be things on this list which you haven't had to purchase any differently as a result of your child having eczema and thus you should not record these.

We are interested in the difference in cost of looking after a child with eczema to a child without eczema thus you should only put the whole price down if the item is something you would not have bought if your child did not have eczema (e.g. an emollient). Some items you may have bought even if they had not had eczema (e.g. sun cream, washing powder) but have to buy a more expensive make/brand in order to get one that does not irritate your child's eczema, in this case please record an estimate of how much more you think you have had to pay for the item.

Please only record those items actually purchased during the time you are involved in the study.

Clothing	**Special food**
Night wear, underwear, school uniform, and day wear made from natural fibres such as cotton	Nut-free foods Special milk e.g. goats, oat or lacto free milk
Over the counter products	**Laundry and bedding**
Emollients, moisturiser, bio oil, sun cream Special shampoos, shower or bath gels Vitamins & mineral supplements, anti-histamines, herbal remedies Bandages, tubi-grips	Purchased bedding (sheets, pillow cases, duvet cases) made of natural fibres Anti-allergic pillows and duvets Bath towels made from natural fibres Special laundry powder/liquid undertake more laundry increasing electricity bills & amount of liquid used
Equipment	**Appointments**
Air cooler Water softener	Travel and parking costs to NHS or private visits Appointments with alternative medicine practitioners e.g. allergy testing, homeopath etc

Appendix 1: Example of the "Unit costs in 2014/15 UK pounds sterling" table

Table 1: Example of the "Unit costs in 2014/15 UK pounds sterling" table

Resource Item	Unit cost	Source
Intervention		
Silk therapeutic garments (Various)	£	PCA
Primary health care	£	PSSRU
GP (Per surgery consultation lasting 11.7 minutes)	£	PSSRU
Practice nurse (per consultation)	£	PSSRU
Pharmacist (per home visit)	£	DH
Secondary health care		
A&E (per visit)	£	PSSRU
Outpatients first visit (dermatology, non consultant led)	£	DH
Outpatients follow up visit (dermatology, non consultant led)	£	DH
Cost per bed day on a general medical ward	£	DH
Medications		
Various	£	PCA

Appendix 2: Examples of tables for mean resource use and costs

Table 2: Example of the "Mean (Standard Deviation) Resource Use and Mean Difference in Resource Use per Patient (95% Confidence Interval)" table

Resource use item	**Silk therapeutic clothing (n=)** Number (SD)	**Usual care (n=)** Number (SD)	**Mean difference (95% CI)**
Intervention			
Silk therapeutic garments (number)			
Primary health care			
GP (number of visits)			
Practice nurse (number of visits)			
Pharmacist (number of visits)			
NHS walk-in centre (number of visits)			
Secondary health care			
Inpatients (number of bed days)			
A&E (number of visits)			
Outpatients first and follow-up visit (number)			
Medications			
Prescription items (number)			

Table 3: Example of the "Mean (Standard Deviation) Cost and Cost Difference (95% Confidence Interval) Per Patient over the 6 months Intervention arm compared to usual care arm (in 2014/15 UK pounds sterling)" table

Resource use item	**Silk therapeutic clothing (n=):** **mean (SD) £'s**	**Usual Care (n=):** **mean (SD) £'s**	**Mean difference** **(95% CI) £'s**
Intervention resource use			
Silk therapeutic garments		**0.00** **(0.00)**	
Primary health care			
GP			
Practice nurse			
District nurse			
NHS walk in centre			
Total Primary health care costs			
Secondary health care			
Cost of inpatients			
A&E			
Outpatients first and follow-up visit			
Day hospital visits			
Total prescription costs			
Total health care costs			

This table will include considerably more resource items than those illustrated here and will be presented for children and for adults with and without asthma as a co-morbidity.

Appendix 3: Examples of tables reporting outcomes

Table 4: Mean (SD) utility values for intervention and control group at baseline and follow-up for the ADQoL, CHU-9D (both for childrens HRQL) and EQ-5D-3L for parental HRQL

	Intervention Group		Control Group	
	Baseline	**6 Months**	**Baseline**	**6 Months**
ADQoL all				
ADQoL under 5's				
ADQoL 5 and overs				
CHU-9D 5 and overs				
EQ-5D-3L for parents HRQL				

Table 5: Quality-adjusted Life Years (SD) for intervention and control group at baseline and follow-up for the ADQoL, CHU-9D (both for children's HRQL) and EQ-5D-3L for parental HRQL

	Intervention Group	Control Group
ADQoL all		
ADQoL under 5's		
ADQoL 5 and overs		
CHU-9D 5 and overs		
EQ-5D-3L for parent's HRQL		

Appendix 20 Nested qualitative study: further information

Children data analysis

TABLE 59 Demographic information of child participants

Child characteristics	Site
Focus group	
Girl, age (years)	
5–6	Nottingham
5–6	Nottingham
5–6	Nottingham
7–8	London
7–8	Cambridge
Boy, age (years)	
5–6	Nottingham
7–8	London
7–8	Cambridge
Face-to-face interview	
Girl, age (years)	
9	Isle of Wight
9	Isle of Wight
15	Isle of Wight
12	Cambridge
9	Isle of Wight
Boy, age (years)	
11	Isle of Wight
9	Isle of Wight
10	Cambridge
Telephone interview	
Girl, age (years)	
9	Cambridge
10	Cambridge
Boy, age (years)	
13	Cambridge

Child interview and focus group topic guide

- Grand tour question:
  - Tell me a bit about your eczema, what it's like living with it?
- Mini tour questions:
  - How have you got on with the special clothing?
  - How much did you wear the clothing (day/night/away from home)?
  - What was it like wearing the clothing (skin condition, comments from others)?
- Example questions:
  - Can you tell me about any differences you have noticed (skin condition/well-being)?
- Experience questions:
  - Were there particular things you liked or did not like about using the special garments?

Parent data analysis

TABLE 60 Demographic information of parent participants with reported usage

Sex of child (age, years)	Parent	Site	Reported usage
Standard care[a]			
Girl (14)[b]	Father	Nottingham	Occasional nights
Girl (9)	Mother	Portsmouth	Every day and night
Girl (6)	Mother	Isle of Wight	Most nights
Girl (14)	Mother	Isle of Wight	One night
Girl (12)	Mother	Isle of Wight	Very occasional nights
Girl (2)	Mother	London	Twice
Girl (4)	Mother	London	Every night
Girl (8)	Mother	London	Most nights and 1 or 2 days
Boy (11)	Father	London	Most nights and occasional days
Boy (5)	Mother	London	1 or 2 nights
Boy (8)	Father	London	Every night and weekend days
Girl (9)	Mother	Cambridge	Top virtually every day and night, leggings some nights
Boy (2)	Father	Cambridge	Every night
Boy (4)	Mother	Nottingham	Every night
Boy (5)	Mother	Isle of Wight	Every day and night except PE day
Girl (10)	Mother	Nottingham	Every night
Girl (5)	Mother	Cambridge	Every night

TABLE 60 Demographic information of parent participants with reported usage (*continued*)

Sex of child (age, years)	Parent	Site	Reported usage
Intervention			
Boy (2)	Mother	Portsmouth	Every night
Boy (2)	Mother	Isle of Wight	Every day and night
Boy (2)	Mother	Isle of Wight	Day and night, less over time
Boy (4)	Mother[c]	Isle of Wight	Virtually every day and night
Boy (4)	Father[c]	Isle of Wight	Virtually every day and night
Boy (11)	Mother	Isle of Wight	Day and night, approximately 50%
Boy (2)	Mother	Isle of Wight	Virtually every day and night
Girl (6)	Mother	London	Every night
Boy (3)	Mother	London	Every night and leggings only everyday
Boy (2)	Mother	Cambridge	Every night
Boy (5)	Mother	Cambridge	Every night and occasional daytime at the weekend
Girl (3)	Mother	Nottingham	Every day and night
Boy (13)	Mother	Nottingham	Every day and night except PE days
Boy (10)	Mother	Isle of Wight	Every day and night, less in the day when hot
Boy (4)	Mother	London	Every day and night
Boy (7)	Mother	London	Every night

PE, physical education.
a Participants in the standard care group received the garments after their 6-month visit so all had some experience of using them.
b Daughter attended focus group with father.
c Both parents of one boy took part in one focus group.

Parent interview and focus group topic guide

- Grand tour question:
  - Tell me a bit about the eczema, what it's like living with it?
- Mini tour questions:
  - How have you got on with the special clothing?
  - How much did you/your child wear the clothing (day/night/away from home)?
  - What was it like wearing the clothing (skin condition, comments from others)?
  - How did you get on with looking after the garments (washing, size)?
- Example questions:
  - Can you tell me about any differences you have noticed (skin condition/behaviour/well-being)?
- Experience questions:
  - Were there particular things you or your child liked or did not like about using the silk garments?
  - How would you feel about continuing to use the special clothing (what things might make you continue or make you stop, barriers to use)?
  - What makes you think that the garments have worked or not worked?

Stages 1–3 of parent data analysis

Stage 1

All transcripts were read in full to ensure immersion in the detail of the data as a whole. Transcripts were annotated with key emergent themes.

Stage 2

The recurring key themes and subthemes from the initial readings of the transcripts are presented in *Table 61*.

Stage 3

The draft framework presented in stage 2 was applied to the transcripts and data were coded and annotated, similarities and differences in data were identified and recurring themes and subthemes were refined, combined and developed. A refined framework was developed in which repetition across themes was removed and data clearly fitted with one theme only (*Table 62*).

TABLE 61 Initial themes and subthemes (stage 2)

Key themes	Subthemes
Desperation	Tried everything
	Impact on quality of life
	Allergies
	Fear of some treatments
	Hope for improvement
Trial garments	Fit and look
	Wear and tear
	Washing
Effect of the garments	Amount of wear
	Difference to skin condition
	Difference to well-being
Being in the trial	Motivation
	Inconvenience

TABLE 62 Refined themes and subthemes (stage 3)

Key themes	Subthemes
Despair and hope	Treatments
	Adjustments
	Quality of life
	Hopes for the trial
Fit, durability and care	Look, feel and fit
	Durability
	Laundry care
Perceived impact of the garments	Patterns of use
	Effect of garments
	Continued use post trial
Engaging in the trial	Experience of participation
	Commitment
	Important outcome measures

Clinician and commissioner data analysis

TABLE 63 Demographic information of clinician and commissioner participants

Job role	Region
Community dermatology specialist nurse	Northwest
Consultant dermatologist	Midlands
Consultant dermatologist	Southeast
Commissioning pharmacist	Midlands
GP with special interest	Midlands
GP	Central south
Dermatology clinical nurse specialist	Northeast
Dermatology support nurse – primary care	Northwest
Lead dermatology clinical nurse specialist – community	Northwest
Paediatric dermatology specialist nurse – primary care	Midlands
Paediatric dermatology clinical nurse specialist – secondary care	Central south
Pharmacist	Northwest
GP (specialist)	Midlands
Clinical commissioning group prescribing lead (GP)	Northeast
Consultant dermatologist	Northeast
Community pharmacist	Midlands
Clinical commissioning group prescribing lead (GP)	Northeast
Paediatric dermatology clinical nurse specialist	Central south
Dermatology clinical nurse specialist	Midlands
Dermatology specialty doctor	Northeast
Dermatology specialist nurse	Central south

Clinician and commissioner interview guide

- What is your experience of prescribing silk garments for children with eczema?
- What makes you select this line of treatment?
- Are there any barriers to you enabling children to use these garments?
    - Perceived cost.
    - Lack of evidence.
    - Durability of the garments.
- Do you think it is a reasonable expectation that GPs should prescribe silk garments?
- If no, who do you think is the most appropriate person to prescribe these garments?
- Do you think they should be prescribed at all? Can you explain the reason for this?

Stages 1–3 of clinician and commissioner data analysis

Stage 1

All transcripts were read in full to ensure immersion in the detail of the data as a whole. Transcripts were annotated with key emergent themes.

Stage 2

The recurring key themes and subthemes from the initial reading of transcripts are presented in *Table 64*.

Stage 3

The draft framework presented in stage 2 was applied to the transcripts and data were coded and annotated, similarities and differences in data were identified and recurring themes and subthemes were refined, combined and developed. A refined framework was developed in which repetition across themes was removed and data clearly fitted with one theme only (*Table 65*).

TABLE 64 Initial themes and subthemes

Key themes	Subthemes
Knowledge and evidence base	Lack of knowledge
	Lack of evidence base
Using silk garments	Unclear indications for use
	Top of ladder of treatment options
	Quality of product
Prescription and expected outcomes	Rarely prescribed
	Who should prescribe
	Subjective and objective outcome measures

TABLE 65 Refined themes and subthemes

Key themes	Subthemes
Knowledge base	Lack of evidence base
	Information from manufacturers
	Treatments protocols
Reasons to use silk garments	Failure of other treatment regimens
	Greater concordance
	Avoiding referral to secondary care
	Cost-effectiveness
Reasons for not using silk garments	Lack of familiarity/experience
	Cost
	Contentious prescription
	Quality of product
Outcome measures	Existing measures
	Clinical improvement
	Patient reports

Appendix 21 Summary of amendments to report after the funding body review stage

TABLE 66 Editorial amendments following NIHR HTA review

Summary of change	Revised wording
Plain English summary amended	Details of adherence in wearing the clothing added
Implication for practice amended	Removed 'Clinical commissioners can now be encouraged to make informed decisions on the basis of these robust trial findings'
Strengths and limitations amended	Added further mention of the independent nature of the trial and its pragmatic nature in reflecting normal patterns of adherence

TABLE 67 Editorial amendments following review by clothing suppliers

Summary of change	Revised wording
Health economic analysis updated to correct an error in how the garments were costed	All figures updated throughout the report with revised cost-effectiveness analysis. Clarification added that unit costs refer to sets of garments, rather than individual items
Conclusion amended to remove reference to this being the first independent trial	Revised wording in abstract: 'This trial adds to the evidence base to guide clinical decision-making'
Clarified that prescription data showing an increase in silk prescribing by the NHS over the last 5 years is for all indications, not just for eczema	'All indications' added where relevant
Potential confusion around our definition of adherence was clarified. Clarification was added relating to the CACE analysis demonstrating the likely impact of adherence in wearing the garments on the trial results	*Methods* and *Results* amended to clarify our definition of non-adherence, and CACE analysis expanded to aid understanding of how to interpret these findings
Details of the amount of topical corticosteroid used have been added (based on prescription data)	Added to *Table 30*
Removed potentially inflammatory statements	Removed from *Discussion*: 'Were the UK NHS to stop prescribing such items, millions of pounds could be saved each year, which could then be better invested into more effective treatments'
Clarified that the nested qualitative study was conducted by colleagues at the University of Hull and results were not disclosed to the trial team until after data analysis was complete	Details added to *Chapter 5*
Reference to previous small studies being sponsored by the silk manufacturers removed	*Chapter 7, Involvement of clothing suppliers after completion of the trial* section amended
Discussion updated to address concerns about interpretation of study results with regard to inclusion of participants with mild disease at baseline and the impact of adherence in wearing the garments	Discussion updated to reiterate the relevant sensitivity and subgroup analyses, and recognition that children with all severities of AE (as assessed by EASI at baseline) were included

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