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			
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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.

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- 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:

$$(E + I + Ex + L) \times \text{area category}$$

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 impregnated, 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

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

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

3.   Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: Development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Archives of Dermatology. 2004;140(12):1513-9.

4.   Lawson, Lewis J, Finlay, Reid, Owens. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact questionnaire. British Journal of Dermatology. 1998;138(1):107-13.

5.   Dolan P. Modeling valuations for EuroQol health states. Medical care. 1997 Nov;35(11):1095-108. PubMed PMID: 9366889. Epub 1997/11/21. eng.

6.   Stevens KJ, Brazier JE, McKenna SP, Doward LC, Cork MJ. The development of a preference-based measure of health in children with atopic dermatitis. British Journal of Dermatology. 2005;153(2):372-7.

7.   Stevens K. Valuation of the Child Health Utility 9D Index. PharmacoEconomics. 2012 Aug 1;30(8):729-47. PubMed PMID: 22788262. Epub 2012/07/14. eng.

8.   White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. Statistics in medicine. 2005 Apr 15;24(7):993-1007. PubMed PMID: 15570623. Epub 2004/12/01. eng.

9.   Dunn G, Maracy M, Dowrick C, Ayuso-Mateos JL, Dalgard OS, Page H, et al. Estimating psychological treatment effects from a randomised controlled trial with both non-compliance and loss to follow-up. The British journal of psychiatry : the journal of mental science. 2003 Oct;183:323-31. PubMed PMID: 14519610. Epub 2003/10/02. eng.

10.   Senn S, Stevens L, Chaturvedi N. Repeated measures in clinical trials: simple strategies for analysis using summary measures. Statistics in medicine. 2000;19(6):861-77.