

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

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**Short title:** CLOTHES Trial – Clothing for the relief of Eczema Symptoms

**Acronym:** CLOTHES

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## SYNOPSIS

Title	Randomised controlled trial of silk therapeutic clothing for the long-term management of eczema in children
Acronym	CLOTHES
Short title	Clothing for the Relief of Eczema Symptoms
Chief Investigator	Dr Kim Thomas
Objectives	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.
Trial Configuration	Observer-blind, parallel group randomised controlled trial
Setting	Recruitment into this trial will be based in secondary care hospitals. GP practices and other local hospitals within travelling distance of the recruiting hospital will be approached to act as Patient Identification Centres (PICS).
Sample size estimate	Three hundred participants provides 90% power, at the 5% significance (two-tailed) to detect a 3-point difference between the groups in mean EASI scores over the first 6 months of the study; assuming a SD of 13, a correlation between EASI scores at different time points of 0.6 and loss to follow up of 10%.
Number of participants	300 children aged 1 to 15 years
Eligibility criteria	Participants aged 1 to 15 years with moderate to severe eczema will be eligible to participate.
Description of interventions	The medical device under investigation is a knitted, sericin-free silk therapeutic garment with a CE mark for use in eczema. Patients will be randomised to standard care alone or standard care plus therapeutic clothing.
Duration of study	Overall duration of the study is anticipated to be approximately 36 months and is planned to start in Q2 2013. Each participant will participate in the trial for 8 months.
Randomisation and blinding	The randomisation schedule is based on a computer generated pseudo-random code using random permuted blocks of randomly varying size and is stratified by site and age. Research nurses will assess eczema severity (primary outcome) and will remain blinded throughout the trial.
Outcome measures	Primary outcome will be eczema severity measured by the objective Eczema Area and Severity Index (EASI) at baseline 2,

	4 and 6 months.
Statistical methods	All analyses will be carried out using Stata 11.2 or MLwiN. This trial will be analysed as intention-to-treat (ITT) at 6 months. The primary analysis of EASI will be performed using a multilevel model framework with observations at 2, 4 and 6 months, nested with participants and including baseline EASI and the stratification factors (site and age group) as covariates.

SUPERSEDED

## ABBREVIATIONS

ADQoL	Atopic Dermatitis Quality of life preference based index
AE	Adverse Event
ANCOVA	Analysis of Covariance
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DFI	Dermatitis Family Impact Questionnaire
EASI	Eczema Area and Severity Index
EQ-5D-3L	EuroQol 5 Dimension 3 level questionnaire
FLG	Gene Encoding Filaggrin
GCP	Good Clinical Practice
HTA	Health Technology Assessment
ICF	Informed Consent Form
IGA	Investigator Global Assessment
ITT	Intention To Treat
MLM	Multilevel model
NESS	Nottingham Eczema Severity Scale
NHS	National Health Service
NIHR	National Institute of Health Research
PGA	Patient Global Assessment
P/GIS	Parent / Guardian Information Sheet
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
POEM	Patient Oriented Eczema Measure
RCT	Randomised Control Trial
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TIS	Three Item Severity Scale
TMG	Trial Management Group
TSC	Trial Steering Committee

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## TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

### Study Background

Eczema is a chronic, inflammatory skin condition that is common in childhood ([Williams, Stewart et al. 2008](#)). Whilst most cases of eczema can be successfully treated with topical medications, many parents express concern at using these preparations and are keen to explore non-pharmacological treatment options.

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 rough fibres next to the skin ([http://www.nhs.uk/Conditions/Eczema-\(atopic\)/Pages/Treatment.aspx](http://www.nhs.uk/Conditions/Eczema-(atopic)/Pages/Treatment.aspx)). In response to this need, new clothing products have become available in recent years, and these are now marketed as having beneficial effects in the treatment of eczema. The therapeutic silk garments included in this study are available on prescription through the NHS, but the trial evidence supporting their use is currently limited ([Vlachou, Thomas et al. 2009](#)).

The effectiveness of these therapeutic silk garments is lodged as a treatment uncertainty in the UK Database of Uncertainties about the Effectiveness of Treatments (DUETs).

Loss of function mutations in the gene encoding filaggrin (*FLG*) affect skin barrier function and are a strong and significant risk factor in eczema. These mutations are present in approximately 9% of the UK population and because of their role in skin barrier formation they may affect an individual's response to silk clothing as a treatment for eczema.

### Existing research

The 2000 HTA systematic review of eczema treatments ([Hoare, Li Wan Po et al. 2000](#)) found no RCTs looking at therapeutic clothing for the treatment of eczema, although there was some evidence to suggest that smoother fibres were less aggravating to eczematous skin ([Diepgen, Salzer et al. 1995](#)). This review has recently been updated and has revealed six small RCTs looking at therapeutic clothing for the treatment of eczema; two using silver coated textiles ([Gauger, Fischer et al. 2006](#)), ([Juenger, Ladwig et al. 2006](#)) one using MEDIELE ([Ozawa 2008](#)), one using Ethylene Vinyl Alcohol (EVOH) fibre ([Yokoyama, Kimata et al. 2009](#)) and two RCTs using DermaSilk™ ([Koller, Halmerbauer et al. 2007](#); [Stinco, Piccirillo et al. 2008](#)). These silk clothing trials were too small (22 and 30 participants respectively) and of limited duration (12 and 4 weeks respectively) to inform clinical practice.

On the basis of the limited trial data to-date, it is not possible to establish whether or not silk clothing provides measurable benefits for patients with atopic eczema. Despite the limited trial evidence, these garments are currently available on prescription in the UK and their popularity amongst patients is growing.

## TRIAL / STUDY OBJECTIVES AND PURPOSE

### PURPOSE

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

## 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.

## SECONDARY OBJECTIVE

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.

## TRIAL / STUDY DESIGN

### TRIAL / STUDY CONFIGURATION

Three hundred children with eczema (atopic dermatitis) will be randomised into a study comprising an independent, observer-blind, parallel group randomised controlled trial (RCT) to evaluate the addition of silk therapeutic clothing (a CE marked medical device), compared to standard eczema care (Figure 1), followed by an open follow-up period.

Figure 1: Trial Design

Length of study		0 to 6 months		7 to 8 months
Intervention Group	Randomisation	Standard care + silk clothing	End of RCT	Standard care + silk clothing
Control Group		Standard care only		Standard care + silk clothing

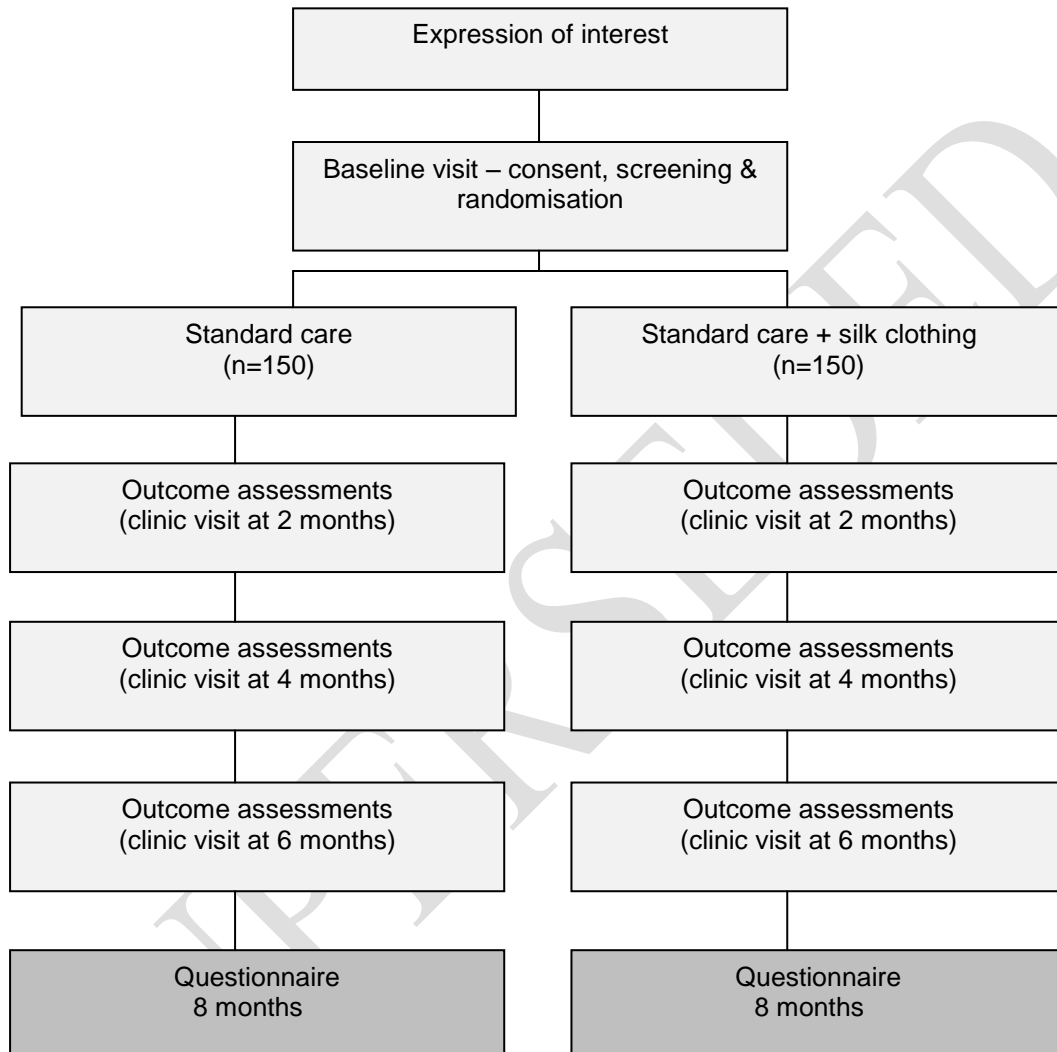
Children will be randomised to receive standard care plus silk therapeutic clothing (three sets of long sleeved tops and leggings, or bodysuits for infants), or standard care alone. Patients randomised to therapeutic clothing will be further randomised to have one of two different types (brands) available on prescription - Derasilk™ and Dreamskin™. Patients will be unaware of the brand of clothing they will receive. The primary outcome for the RCT (eczema severity measured by EASI), will be assessed at baseline, two, four and six months by research nurses blinded to allocation status.

In order to provide additional information about the clothing and potentially encourage continued participation in the standard care group, participants will receive the clothing (randomly assigned to one of two different types (brands) available on prescription - Derasilk™ and Dreamskin™), on completion of the randomised controlled part of the study at six months. Patients will be unaware of the brand of clothing they will receive. At eight months from randomisation both groups will be asked to complete a questionnaire recording eczema symptoms, and satisfaction with the clothing (including adherence, acceptability and durability).

To determine whether there is an effect of mutations of the gene encoding for filaggrin (an abnormality associated with impaired skin barrier function) saliva samples will be taken from participants where separate informed consent has been obtained at their first visit.

An internal pilot RCT will be conducted over the first six months of trial recruitment in order to assess ability to recruit, adherence with the clothing and retention in the trial.

**Figure 2 - Flowchart**



**Primary endpoint**

The primary end point is eczema severity measured by the objective Eczema Area and Severity Index (EASI) ([Barbier, Paul et al. 2004](#)) 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.

## Secondary endpoints

- 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.
- b) Three Item Severity scale (TIS) at baseline, 2, 4 and 6 months, assessed by the research nurses and used to assess eczema severity.
- 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.
- d) Self reported eczema symptoms using the Patient Oriented Eczema measure (POEM)([Charman, Venn et al. 2004](#))
- e) Health Related Quality of Life at baseline and 6 months: Dermatitis Family Impact (DFI)([Lawson, Lewis-Jones et al. 1998](#)); will assess the impact of the child's health on the whole family, EQ-5D-3L will provide a utility measure for the main carer; and age-appropriate utility measures (Atopic Dermatitis Quality of life preference based index ADQoL) will be used to provide an eczema-specific utility score([Stevens, Brazier et al. 2005](#)), and a general health utility score for the child (CHU-9D)([Stevens 2012](#))
- f) Durability of the garments, adherence and acceptability of use (as assessed by children and parents/carers).
- g) Cost-effectiveness and cost utility.

The number of children with mutations on the gene encoding for filaggrin will also be reported and used to inform a planned sub-group analysis, to test the hypothesis that children with at least one mutation on the gene encoding for filaggrin are more likely to respond favourably to the therapeutic clothing if it compensates for loss of barrier function. Specific consent for this testing will be obtained.

## Safety endpoints

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

Given that it is unlikely that silk clothing will result in any adverse device effects other than potential changes in the number of skin infections, only serious adverse events will be collected.

## Tertiary endpoints:

Additional exploratory analysis will be conducted based on eczema severity scores in areas covered by the clothing (body and limbs) compared to areas uncovered by the clothing (head and neck), 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.

Whilst it is assumed that the different brands of clothing be similar, the effects in each group may be investigated, if appropriate.

The examination of all tertiary end points will be considered exploratory.

Further details about the statistical analyses will be provided in the Statistical Analysis Plan which will be finalised prior to database lock and unblinding of the study.

### Stopping rules and discontinuation

An internal pilot RCT will be conducted over the first six months of trial recruitment. Progress with recruitment and retention will be monitored monthly by the Trial Management Group (TMG). If progress is below target, strategies will be implemented to improve progress.

Table 1 pre-specifies the stop/go criteria to be assessed by the Trial Steering Committee at 6 months (target recruitment = 75 participants within six months of the first participant being randomised).

**Table 1 - Pilot stop/go criteria**

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

Adherence in wearing the clothing will be assessed regularly by the TMG in the intervention group only, and will act as a trigger for concern if participants report using the clothing less than 50% of the time.

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee as appropriate in making this decision.

### RANDOMISATION AND BLINDING

The randomisation schedule is based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (CTU) in accordance with their standard operating procedure (SOP) and held on a secure University of Nottingham server. The randomisation is stratified by recruiting hospital and by child's age - <2years; 2 to 5 years; and >5 years.

Access to the sequence will be confined to the data management team and administrators at the Nottingham CTU who will be responsible for distribution of the clothing. Investigators and Research Nurses will access the randomisation website by means of a remote, internet-based randomisation system developed and maintained by the Nottingham CTU. 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.

Participants will be informed of their treatment allocation by letter from the co-ordinating centre. Those allocated to receive the therapeutic clothing will receive their first supplies at this time. Participants will be randomly allocated to one of the therapeutic clothing brands available on prescription in the UK as they enter the trial. They will not be aware of which brand of clothing they have received. Packaging, labelling and distribution of clothing will be performed by staff at the co-ordinating centre and sent to participants by post. Sizes will be determined by collection of the participant's height at randomisation

Whilst it will not be possible to blind participants to their treatment allocation, efforts will be made to minimise expectation bias by emphasising in the trial literature that the evidence supporting the use of therapeutic clothing for eczema is currently limited, and that we do not yet know if this clothing offers any benefit over standard care. The study literature will also avoid the use of terms such as “specialist” or “therapeutic” clothing for the same reason.

Where possible research nurses will remain blinded throughout the trial: participants will be reminded in the study literature and 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. All questions relating to the acceptability and use of the clothing will be completed by either postal or on-line questionnaire (according to patient preference), and telephone contact with participants will be made by trial staff from the co-ordinating centre whenever possible. If the research nurses become unblinded, this will be recorded and used to inform a sensitivity analysis.

	<b>Blinding status</b>	<b>Comments</b>
<b>Participants</b>	Not Blinded	Not possible to blind participants, efforts will be made to minimise expectation bias.
<b>Research nurses and PI</b>	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.
<b>Trial staff at Nottingham CTU</b>	Not blinded	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.
<b>Statistician</b>	Blinded	Statistician will finalise the analysis plan prior to revealing the treatment codes.

#### **Maintenance of randomisation codes and procedures for breaking code**

Only the trial team and the data manager at the Nottingham CTU will be aware of the allocation to intervention or control group. Since the intervention is clothing, no special arrangements are necessary for breaking of the randomisation code.

#### **TRIAL MANAGEMENT**

The trial is funded by the NHS Health Technology Assessment Programme. It is sponsored by the University of Nottingham, and will be managed and co-ordinated from the Centre of Evidence Based Dermatology in Nottingham and the Nottingham Clinical Trials Unit.

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

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

Due to the low risk of the clothing, no data monitoring committee will be required.

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

## **DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT**

The overall duration of the study is anticipated to be approximately 36 months. It is planned that recruitment will take up to 18 months. Target recruitment for the pilot phase of the trial is 75 participants enrolled over the first 6 months of recruitment.

Each participant will participate in the trial for 8 months (treatment period) and her/his participation will commence upon signing the consent form. Participants will be randomised to intervention or control groups for the first 6 months. Participation in the RCT will end after 6 months, at which point participants in the control group (standard care) will be given the therapeutic clothing and will be followed up until 8 months post randomisation. Participants allocated to the intervention group will continue with their randomised intervention until the garments are no longer usable. Further supplies of clothing will not be given to these patients during the follow-up period from 6 to 8 months post-randomisation.

### **End of the Trial**

The end of the study will be receipt of the last questionnaire of the last participant.

## **SELECTION AND WITHDRAWAL OF PARTICIPANTS**

### **Recruitment**

Recruitment into this trial will be based in six secondary care hospitals (with further contingency centres as required). GP practices and other local hospitals in the surrounding area will be approached to act as Patient Identification Centres (PICS).

Potential participants will also be identified through direct local advertising (including but not limited to e-mail distribution lists, radio and TV interviews, websites and articles). If other potential sources for recruitment become apparent during the trial, these will also be included. A dedicated website will be available for the purpose of this trial.

If identified through secondary or primary care the initial approach will be from a member of the patient's usual care team (which may include the investigator), and information about the trial will be on display in the relevant clinical areas. The initial approach may be made by invitation letter or in person at a clinic.

The investigator or their nominee, e.g. from the research team, will inform the participant and their parent/legal guardian of all aspects pertaining to participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not be available printed in other languages.

It will be explained to the potential participant and their parent/legal guardian that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time.



## Eligibility criteria

### 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 ([Williams, Burney et al. 1994](#)) and eczema severity judged using the Nottingham Eczema Severity Scale (NESS) ([Emerson 2000](#))
- Resident within travelling distance of a recruiting centre.

### Exclusion criteria

- Parents / legal guardian unable to give informed consent (of if the child expressed a wish not to take part in the trial).
- 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  $\geq 5$  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.

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.

### Expected duration of participation

Study participants will be enrolled in the study for 8 months.

### Removal of participants from therapy or assessments

Participants (child or parent/ legal guardian) may be withdrawn from the trial at any time. They will be made aware (through the participant information sheets) that withdrawing from the trial will not affect their future care, but that the data already collected cannot be erased and will still be used in the final analysis. The primary reasons for discontinuation/withdrawal will be recorded.

Participants who withdraw after randomisation will not be replaced.

### Informed consent

All parents/legal guardians will provide written informed consent for their child to take part in the trial. The Informed Consent Form will be signed and dated by the parent/legal guardian before they enter the trial. For children wishing to do so, assent will be given on the same form, but this will not be mandatory. In the event of any conflict between the parent's and child's wishes, the child WILL NOT enter the study. The Investigator will explain the details of the trial and provide age appropriate Participant Information Sheets, ensuring that the participant and/or parent/legal guardian has sufficient time to consider participating or not. The Investigator will answer any questions that the child and/or parent/legal guardian has concerning study participation.

Separate informed consent will be obtained for the provision of a saliva sample (for genetic testing), and parents / legal guardians will be offered the possibility of opting out of this part of the study if they wish. No samples will be taken until informed consent has been gained. In line with current guidance patients will not receive their filaggrin test results ([Fabsitz, McGuire et al. 2010](#))

Informed consent will be collected from each parent/legal guardian before they undergo any interventions (including physical examination) related to the study. One copy of this will be kept by the parent/legal guardian, one will be kept by the Investigator, and a third will be retained in the child's notes.

Should there be any subsequent amendment to the final protocol that might substantially affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form, which will be signed by the parent/legal guardian.

## **TRIAL INTERVENTION AND REGIMEN**

### **Interventions:**

#### **Silk clothing:**

The medical device under investigation is a knitted, sericin-free silk therapeutic garment with a CE mark for use in eczema. Sericin is a protein that coats the outside of silk fibres and has the potential to cause allergic reactions. Medical grade silk (such as silk used for stitches during operations), has the sericin removed for this reason.

The specific products being used are Dreamskin™ and Dermalilk™. 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). This will give sufficient garments to allow for washing between uses. Washing instructions will be provided in line with manufacturers recommendations. Adherence in wearing the garments will be collected using sticker/tick charts as an aide memoir and weekly questionnaires.

The clothing will have product labels removed and be supplied using trial-specific packaging prior to distribution from the co-ordinating centre. Clothing will be replaced as required during the six-month RCT (e.g. because they are worn out or because the child has grown). Once the randomised part of the trial is complete at six months, garments will NOT be replaced.

Participants will be asked about their use of clothing and willingness of GPs to prescribe them at 8 months. It will be explained to participants at this stage that it is not possible for the trial team to recommend use of the garments, or to insist that their GPs prescribe them.

Participants allocated to the therapeutic clothing will continue to use their standard eczema care (including emollients, topical corticosteroids and topical calcineurin inhibitors).

#### **Standard care:**

All participants (active and control groups) will continue with their standard eczema care in line with NICE guidance ([NICE December 2007](#)). No efforts will be made to intervene or change a child's standard eczema care unless the research nurse thinks that the skin may be infected. If research nurses suspect infection they will recommend that the patients 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.

**Table 2 - Study Assessments**

= RCT
= observational period

Outcomes collected	0 months	2 months	4 months	6 months	8 months
Informed consent for main study	√				
Informed consent for genetic study (optional)	√				
Eligibility checks	√				
Eczema severity (NESS)	√				
Supply garments	√ intervention			√ control	
Demographics	√				
Collect saliva sample (Optional)	√				
Issue diary and wall chart	√	√	√	√	
EASI & TIS	√	√	√	√	
Investigator and Patient Global Assessment (IGA and PGA)	√	√	√	√	
Topical treatment usage	√	√	√	√	
Medication for skin infection	√	√	√	√	
Use of wet and dry wraps	√	√	√	√	
On-line questionnaire (weekly) including POEM	√	√	√	√	
Final on-line questionnaire					√
DFI	√			√	
EQ-5D-3L of parent or proxy	√			√	
Child utility scales (Stevens 2005, CHU-9D)	√			√	
Number of infections	√	√	√	√	
Serious adverse events		√	√	√	
NHS and family resource use	√ & Diary	√ & Diary	√ & Diary	√ & Diary	√
Adherence	Diary	Diary	Diary	Diary	√
Durability of clothing				√	√
Acceptability (parent & child)				√	√
Replace garments if required		√	√		

NESS = Nottingham Eczema Severity Scale; TIS = Three Item Severity scale; EASI – Eczema Area and Severity Index; POEM = Patient Oriented Eczema Measure; DFI = Dermatitis Family Impact questionnaire; EQ-5D-3L – EuroQol Five Dimension, Three Levels questionnaire; CHU-9D – The Child Health Utility 9 dimensions

### Data Collection Methods

#### Face-face visits with the research nurse

These interviews will take place at baseline (recruitment visit), 2 months, 4 months and 6 months.

The visits will include the following:

- i. check of eligibility criteria (recruitment visit only)
- ii. baseline characteristics / demographics (recruitment visit only)
- iii. collection of single saliva sample –optional (planned to be collected at the recruitment visit but can be collected at any visit according to patient preference)
- iv. examining the child's skin for disease severity and signs of infection (using the Eczema Area and Severity Index,EASI); Three Item Severity score – TIS; and Investigator Global Assessment, IGA).
- v. Patient-reported eczema severity (Patient Global Assessment. PGA) and number of skin infections treated with antibiotics or anti-viral treatments
- vi. Review of topical medication usage (prescriptions issued and changes in treatment regimen)
- vii. Quality of life questionnaires (at baseline and 6 months only) – dermatitis family impact questionnaire, EQ-5D, eczema utility scale and CHU-9D.

### **Treatment diaries /memory aides**

All participants will be given an eczema diary as an aide memoir to record health resource use and a sticker chart to record progress in the trial – participants randomised to wear the clothing for the first six months will have a chart where they can record when they have worn the clothing and participants randomised to the control group will have a chart to record each week they have been in the trial.

Each week the parent / legal guardian, if they have expressed a wish to complete the questions on-line will be sent a link (via e-mail) to an on-line questionnaire. This short questionnaire will be completed by referring to the diary / wall chart, and will record how their eczema has been that week, health service resource use (including, prescriptions and health professional contacts related to eczema), and adherence with / the clothing (intervention group only).

Participants who do not wish to complete the questions on-line will be asked to complete a form and post it back to the Clinical Trials Unit.

### **End of Trial Follow-up Questionnaire**

Parents / legal guardians of participants will be sent an end of trial follow-up questionnaire (on-line or postal) at eight months post-randomisation. This will seek information about current eczema status, adherence, acceptability and their opinion of the therapeutic clothing.

### **Concomitant Treatment**

Participants will be asked not to start new eczema treatments (other than antibiotics for infection) unless medically indicated, and will be discouraged from routinely using wet or dry wrap dressings. Any changes to a child's treatment regimen, or use of wet / dry wrapping will be recorded, but the child will remain in the trial.

### **Compliance**

Compliance with the protocol will be monitored. This will include following up patients who have not completed questionnaires and/or attended for clinic visits. Any instances of the research nurse being unblinded will be recorded. Adherence in wearing the garments will be collected weekly until 6 months and then at the end of the study (8 months). Participants randomised to wear the clothing for the first six months will have the option of using a sticker or tick chart to record the days and nights when they wear the clothing, which will act as an aid when they complete the questionnaires.

### **Criteria for terminating trial**

This trial involves CE marked clothing that are being used within their normal licensing authorisation. As such, it is very low risk. However, if severe adverse effects associated with the clothing occur frequently, the study may be terminated on the advice of the Trial Steering Committee.

The Investigator may stop the trial or terminate one centre if new information becomes available causing major safety concerns, or if there are issues with trial conduct.

Should the trial be terminated the research data will not be destroyed.

## FILLAGGRIN GENETICS ANALYSES

### Saliva testing for mutations on the gene encoding for filaggrin (*FLG*)

A sub-group analysis based on presence or absence of mutation(s) in the *FLG* will be conducted. Mutations in *FLG* are commonly found in eczema patients (25 -50% depending on the population([Thomas, Armstrong et al. 2002](#)), and has been associated with disruption of skin barrier function and dry skin([Palmer, Irvine et al. 2006](#)). As a result, there is a strong theoretical basis for thinking that children with at least one *FLG* mutation would be more likely to benefit from clothing, which potentially acts to improve the barrier function of the skin.

In light of this we plan to include *FLG* genotype as a possible predictor of treatment response in the current study.

For the sub-group analysis, study participants will be tested for four prevalent *FLG* loss-of-function mutations (R501X, 2282del4, R2447X and S3247X) and categorised into two groups according to *FLG* status:

Group 1: *FLG* +/+ (no mutations) – control cohort

Group 2: *FLG* +/- (carrying one *FLG* null mutation) and *FLG* -/- (carrying two *FLG* null mutations)

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

### Methodology

To determine *FLG* genotype it will be necessary to obtain DNA from individuals entering the study. Following additional written informed consent, participants will be asked to provide a saliva sample at enrolment (or at their subsequent appointments if more practical). If children are unable to spit into the container, swabs taken from inside the cheek will be used to collect the sample.

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

The containers will be shipped to Dr Sara Brown at the Centre for Dermatology & Genetic Medicine, University of Dundee. DNA will be extracted by standard techniques and *FLG* genotyping for the four most prevalent null-alleles (R501X, 2282del4, R2447X and S3247X) will be carried out according to published protocols ([Sandilands, Terron-Kwiatkowski et al. 2007](#)). Samples will be securely stored within the University of Dundee for future testing of genes associated with atopic eczema. If new techniques become available, consent will be obtained for this.

FLG genotype status will be recorded and returned to the Nottingham Clinical Trials Unit again using the study number and date of birth.

## STATISTICS

### Methods

All analyses will be carried out in accordance with CONSORT guidelines using Stata/SE 11.2 or MLwiN v2.2. Appropriate descriptive statistics will be used to compare randomised participants with those who were eligible and not randomised, and to compare the randomised arms at baseline. The primary approach to analysis will be intention-to-treat (ITT) without imputation. The primary analysis of EASI 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 group) as covariates

Supportive analyses of the primary end point, analyses of secondary and safety end points, planned sub-group analyses, sensitivity analyses including imputation of missing outcome data and accounting for varying adherence with allocation, and any further exploratory analyses will be conducted using appropriate multivariable regression models and documented in the Statistical Analysis Plan (SAP) which will be finalised prior to unblinding of the study. Any changes in the planned statistical methods will be documented in the trial report.

### 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 SD 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.

Participants will be recruited from six recruiting centres over an 18 month recruitment period. Recruitment is expected to increase gradually over the first 6 months of the trial to allow for staggered site set-up.

### Procedures for missing, unused and spurious data

Every effort will be made within the trial to minimise the occurrence of missing data. All missing data items will be tabulated by treatment arm and reasons given where possible. We will examine the plausibility that data are missing at random (MAR) and multiple imputation techniques will be used to handle missing values as appropriate.

## COST-EFFECTIVENESS ANALYSIS

### Objective:

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.

The cost analysis will compare the overall costs for the intervention to standard care, measuring resource use such as primary care contacts, medication prescribed, secondary care contacts and patient costs. Health and family resource use data will be recorded by research nurses. The patients will be asked to collect data on a diary which will serve as an aid memoire.. Resource use will be valued using published unit costs (e.g. Curtis and Netten ([PSSRU 2004](#)), BNF 2005, and NHS reference costs and patient reported estimates. The costs to the NHS and patient will be reported separately as well as in combination.

The primary measures of effectiveness for the cost effectiveness analysis will be the difference in number of participants who achieved “treatment success” (defined as those with at least a 50% improvement in EASI at 6 months compared to baseline). Secondary analyses will be conducted using continuous data from the EASI scale; the Dermatitis Family Impact Scale; eczema specific utility measures (Stevens 2005) and generic measures of health utility as measured using the EQ-5D-3L (for the main carer) and the Children’s Health Utility Index 9D (CHU-9D) for children. 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 (using linear interpolation and area under the curve with baseline adjustment).

If non-dominance occurs an incremental cost-effectiveness ratio will be produced. Sensitivity analysis will be undertaken to test the robustness of results in the face of any uncertainties or assumptions made in the analysis.

### ADVERSE EVENTS

It is unlikely that silk clothing will result in any adverse effects.

A worsening of eczema and infected eczema will not be considered as adverse events as these data will be collected as specific endpoints for the trial. A worsening of eczema will be detected using the scores from EASI.

Hospitalisation due to eczema will be captured as a Serious Adverse Event (SAE).

#### Trial Intervention-related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed **directly related to or suspected to be related to the trial intervention** shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment or intervention.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.

- If the event is deemed related to the trial treatment or intervention shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

## **ETHICAL AND REGULATORY ASPECTS**

### **ETHICS COMMITTEE AND REGULATORY APPROVALS**

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

### **INFORMED CONSENT AND PARTICIPANT INFORMATION**

The process for obtaining assent and parent / guardian informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Informed Consent Form before the person can participate in the study. Children who wish to do so, will also be able to provide “assent” to participation in the trial on the same form.

The participant (or parent/guardian) will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant’s medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant (where appropriate) and their parent/guardian of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.



If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

## **RECORDS**

### **Case Report Forms and patient diaries**

Each participant will be assigned a trial identity code number, allocated at randomisation if appropriate, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mmm/yyyy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required. CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be completed and collected in line with GCP. The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

### **Sample Labelling**

Each participant will be assigned a trial identity code number for use on the samples, consent forms and other study documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mmm/yyyy).

### **Source documents**

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records and diaries. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

### **Direct access to source data / documents**

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall be made available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

## **DATA PROTECTION**

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password

protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

## **QUALITY ASSURANCE & AUDIT**

### **INSURANCE AND INDEMNITY**

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

### **TRIAL CONDUCT**

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

### **TRIAL DATA**

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

### **RECORD RETENTION AND ARCHIVING**

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

### **DISCONTINUATION OF THE TRIAL BY THE SPONSOR**

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee as appropriate in making this decision.

### **STATEMENT OF CONFIDENTIALITY**

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

### **PUBLICATION AND DISSEMINATION POLICY**

During the period of the trial, press releases will be issued from the Centre of Evidence Based Dermatology. No party will be entitled to submit any publicity material without prior approval from the co-ordinating centre.

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

All participants will receive a copy of the trial results in the form of a participant newsletter. Neutral or negative results will not constitute a reasonable justification to delay publication

### **USER AND PUBLIC INVOLVEMENT**

The public and patients have been involved in the prioritising of this research questions as outline in the Eczema Priority Setting Partnership([Batchelor, Ridd et al. 2013](#)). In addition there has been public involvement in the trial design, the patient information, on-line questionnaires and diary cards. There will be at least one member of the public with an interest in eczema on the trial steering group

### **STUDY FINANCES**

#### **Funding source**

This study is funded by NIHR Health Technology Assessment - Ref 11/65/01

#### **Participant stipends and payments**

Participants will not be paid to participate in the trial. Travel expenses will be offered for any hospital visits in excess of usual care and small gifts, sticker incentives will be given to children in order to encourage continued participation and completion of study diaries.

SUPERSEDED

## SIGNATURE PAGES

Signatories to Protocol:

**Chief Investigator:** (name) \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

**Co- investigator:** (name) \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

**Trial Statistician:** (name) \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

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