CLOTHES Trial

FINAL Health Economic Analysis Plan

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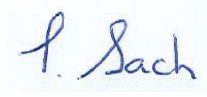
The following people have reviewed the Health Economic Analysis Plan and are in agreement with the contents			
Name	**Role**	**Signature**	**Date**
Tracey Sach	Author		**13.01.16**
Prof Alan Montgomery	Trial Statistician		**19 Jan 2016**
Prof Kim Thomas	Chief Investigator		**13.01.16**

The HEAP has also been reviewed by Lisa Irvine, Senior Research Associate in Health Economics at the University of East Anglia.

Objective

This economic analysis plan aims to provide a detailed description of the economic evaluation to be conducted alongside the CLOTHES trial. It describes how the data will be collected, analysed and reported.

Summary of clinical trial

Eczema is a chronic skin condition that can have a large impact on the quality of life of patients and their families. Non-pharmacological therapies are often appealing to people suffering eczema, and so silk therapeutic garments represent an attractive therapy for many. Silk therapeutic garments are included in the British National

Formulary meaning that doctors can prescribe these items to patients should they deem it necessary. However, the effectiveness and cost-effectiveness of these garments in the management of eczema is as yet unproven. The CLOTHES trial will test the hypothesis that 'silk therapeutic garments plus standard eczema care' is superior to 'standard care alone' for children with moderate to severe eczema.

It will be a parallel group, observer-blind, pragmatic, multi-centre randomised controlled trial of 6 months' in length. Three hundred children aged 1 to 15 years with moderate to severe eczema will be randomised (1:1) to receive silk therapeutic garments plus standard eczema care, or standard eczema care alone. The primary outcome is eczema severity at 2, 4 and 6 months, using the validated Eczema Area and Severity Index (EASI) recommended by the HOME initiative. Secondary outcomes include: patient-reported eczema symptoms (collected weekly for 6 months to capture long-term control); global assessment of severity; quality of life of the child, family and main carer; use of standard eczema treatments (emollients, topical corticosteroids, calcineurin inhibitors and wet wraps); frequency of infections; and cost-effectiveness. The acceptability and durability of the clothing will also be assessed, as will adherence in wearing the garments. A nested qualitative study will assess the views of children wearing the garments, and those of healthcare providers and commissioners.

Recruitment started in November 2013, and the trial is expected to be completed by June 2016. The trial was funded as part of the NIHR HTA programme and sponsored by the University of Nottingham. Full details of results will be published in the National Institute for Health Research Journal series.

Comparators to be included

<u>100% silk garments made from antimicrobially protected knitted sericin-free silk used in addition to standard eczema care</u>

The specific products being used are Dreamskin™ and Dermasilk™. Participants will be asked to wear the clothing as much as possible including at night, and when possible during the day. Participants will receive three sets of garments (long-sleeved vest and leggings, or body suits and leggings depending on the age of the child). Replacement clothing is also available as required should the child grow or garments get spoiled.

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

<u>Standard care</u>

All participants (active and control groups) will continue with standard eczema care in line with NICE guidance (NICE, 2007). A child's standard eczema care will not change unless the research nurse thinks that the skin may be infected. If an infection

is suspected the research nurse will recommend that the patient contact their normal medical team (GP, Nurse, dermatologist) as appropriate.

Standard advice about what clothing to use for a child with eczema will be provided (avoid wool, and wear cool loose clothing – especially cotton and linen), but specific products will not be recommended.

If a child is currently using "specialist" cotton clothing (e.g. special sleep suits with built-in mittens), the use of these garments will be recorded, but will not be grounds for exclusion. However, participants in the control group will be asked to refrain from using prescription clothing (including silk clothing and synthetic garments used for wet wrapping) during the trial.

Study design – Economic evaluation

Guidelines for economic evaluations`

The economic evaluation will adhere to published and well accepted guidelines for the economic evaluation of health care interventions as appropriate. [1-3]

Study Question

To estimate the within trial cost-effectiveness of silk therapeutic clothing with standard care compared to standard care alone from an NHS perspective in the base case and from an NHS and family perspective in secondary analyses.

Blinding

The health economics analysis will be undertaken blinded to intervention group as much as is possible. Thus the majority of resource use items can be valued and utility values scored along with estimation of QALYs without knowledge of intervention group. It will be possible to conduct some preliminary analysis to examine costs and outcomes in the two (unidentified) groups at this point. However the costs of the intervention, i.e. the silk clothing costs are specific to group. Assigning these costs would require knowledge of intervention group and the health economist would need to become unblinded at this point. Final analysis, including the cost of intervention, will therefore not be carried out blinded to intervention group.

Form of economic analysis

Two types of economic evaluation will be conducted as part of this within trial economic evaluation: A cost-effectiveness analysis and Cost-utility analysis.

Perspective

The analysis will primarily take an NHS perspective, reflecting that Personal Social Services costs are unlikely to be relevant for childhood eczema. A secondary analysis will capture costs incurred by the family to assess whether the intervention makes a significant difference to these.

Resource use: identification, measurement and valuation

The range of resource use and costs captured will be in keeping with the chosen perspective.

Intervention resource use

The cost of the intervention will include the cost of silk clothing and replacement garments needed due to growth or wear and tear. The unit costs for this will be taken from the HSCIC Prescription Cost Analysis as the Net Ingredient Cost per Item (NIC) which does not include any discounts, costs/fees of dispensing nor adjust for income from prescription payments. An alternative method of costing the NHS cost of prescribed medications will be explored in sensitivity analyses.

Resource use associated with wider health care contacts related to eczema

The resource use is recorded on the diary card and entered by the research nurse at each of the study visits. To aid memory an online/paper questionnaire prompts participants to complete their diary if a health care professional is visited for eczema in the last week. Resource use will focus on those resources consumed as a result of the child's eczema and will include health care visits (number of appointments to GP, practice nurse, outpatients, other and nights in inpatient care), prescriptions (topical corticosteroids, topical calcineurin inhibitors, emollients (including bath emollients), wet/dry wraps, antibiotics/antivirals for skin infections, other eczema-related prescriptions). This resource use will be recorded at study visits at baseline, 2, 4, 6, and 8 months.

Resource use will be valued using published national sources of unit costs (UK£sterling for the most recent year available)(Curtis 2014, NHS reference costs 2013-14, HSCIC 2014).

Resource use incurred by the family related to their child's eczema

The resource items recorded in this component reflect a family or more societal perspective.

Figure 1 shows the types of resource use items families were asked about at study visits but families were not limited to these examples. Respondents were asked to place a monetary value on the additional cost incurred as a result of eczema, for instance if they bought a more expensive washing detergent because it is kinder on the persons with eczema skin they were asked to state the amount over and above that which they would have paid for a normal washing detergent.

In addition families were asked to record time off work and school as a result of eczema. The time of parents will be valued using the mean gross hourly wage rate for all employee jobs in the UK as reported in the Annual Survey of Hours and Earnings (ASHE) in 2014 since we will not know the respondents personal earnings. [Accessed online on 5th January 2016: http://www.ons.gov.uk/ons/rel/ashe/annual-survey-of-hours-and-earnings/index.html] This approach is known as the human capital approach and assumes a person's productivity is equal to their wage rate to place a maximum cost on the time off work. Time off school will be reported in hours and minutes and not valued due to a lack of evidence about the cost of lost schooling.

Presentation of cost results

To ensure transparency and reproducibility the unit costs used to attach monetary costs to resource use will be clearly displayed in tabular format with source of unit cost displayed in addition to the actual unit cost used. (see appendix 1 for an example)

Resource use and costs will be presented clearly in tabular format to ensure transparency in the final figures reported. Mean and SD resource use and costs will be presented by intervention group and health sector (Primary care, secondary care, Family costs). (see appendix 2 for an example)

Outcomes: effectiveness and utility

The primary measure of effectiveness for the cost effectiveness analysis will be the difference in the number achieving treatment success at 6 months – defined as those with at least a 50% improvement compared to baseline on the primary outcome measure Eczema Area and Severity Index (EASI) (Barbier et al 2004). Secondary analyses will be conducted using continuous data from the Dermatitis Family Impact Scale.

A cost utility analysis, where effectiveness is measured in terms of the Quality Adjusted Life Years (QALYs) for child and main carer, will be undertaken. Utility will be measured in all children using the disease specific Atopic Dermatitis Quality of Life scale (ADQoL), and in those aged 5 or over by the generic health-related quality of life instrument the Child Health Utility index (CHU-9D). The CHU-9D is being used

with children aged 7 and over self-completing and parental proxy completion for 5 and 6 year olds. In addition, the main carer will record their own utility using the EQ-5D-3L. All three utility instruments will be measured at baseline and 6 months and used to estimate QALYs for the trial period by using linear interpolation and area under the curve with and without baseline adjustment (Manca et al, 2007). The primary cost-utility analysis will report the incremental cost per QALY based on the ADQoL since we will have this completed for all children in the study. Secondary analyses will report the cost per QALY based on the CHU-9D for those aged 5 and over. Statistical modelling will explore the potential to impute values for those children too young to complete the instrument but some strong assumptions are made in such an analysis, including that the utility values of those aged under 5 in a similar disease state as the 5 and overs will be the same irrespective of the age difference. In addition, a cost per QALY for the main carers using their EQ-5D-3L values will be estimated separately. Previous work has not explored the ability of the EQ-5D to detect impacts on carers quality of life for this condition. (see appendix 3 for example tables).

Length of follow-up

Since this is a within-trial analysis the trial period will be used (6 months) for both costs and outcomes in the base case. Therefore costs and benefits will not be discounted, reflecting the short time horizon.

Statistical analysis and analysis of uncertainty

In line with statistical analyses an intention to treat population will be used in primary analyses. The economic evaluation will be a 'within trial analysis'. This means that costs and benefits will only be evaluated for the trial follow-up period (6 months). Costs in both arms of the study will be estimated using the methods described above. We will calculate outcomes and QALYs again as described above. This information on costs and benefits will be used to conduct incremental economic analysis comparing the silk therapeutic clothing in addition to usual care to usual care alone. This will be done for both the cost-effectiveness and cost-utility analyses. Conclusions will be based on results achieved. If one arm is clearly dominant (less costly and more effective) a recommendation can be made on this basis. If non-dominance occurs (that is if costs are greater and the intervention is more effective or if the intervention is cheaper and less effective), an incremental cost-effectiveness ratio (ICER) will be produced and a value judgement about value for money will need to be made. ICERs will be calculated using accepted methodology (Ramsey et al 2015, Drummond et al 2005).

Since costs and benefit data may be skewed we will use non-parametric bootstrapping to estimate mean costs, mean QALY estimates, and net benefit. Estimates of cost and benefits will be placed upon cost-effectiveness planes. Bootstrapping will also be used to estimate cost-effectiveness acceptability curves (CEACs)(Glick et al, 2007), these will show the probability that each of the

intervention groups is the most cost-effective option at different monetary valuations of the outcome variable. A range of ceiling ratio (or willingness to pay per QALY) values will be tested but this will include £20,000 and £30,000 per QALY given thresholds used by NICE in cost-utility calculations (NICE, 2013).

The analysis will be undertaken unadjusted and adjusted to control for differences in baseline characteristics (e.g. costs, age, baseline EASI score) using regression methods to estimate differences in costs and QALYs between intervention groups.

Assumptions will need to be made in the estimation of costs and QALYs in this analysis. There may also be cases where there is uncertainty over the best values to use in the analysis. These assumptions and sources of uncertainty will be recorded. Where these are likely to affect results we will carry out sensitivity analysis. Sensitivity analysis tests the robustness of results in the face of any uncertainties. It also improves the generalisability of results by indicating what could happen with different values of a parameter. The sensitivity analysis will include the following:

- Imputing missing values – the base case will be a complete case analysis but if there is significant (>10%) missing data it may bias results. If there is missing data, the extent and nature of the missingness will be explored in order to choose an appropriate approach to deal with the missing data. If missing data is a significant issue multiple imputation will be used to impute missing values and presented as secondary analyses.
- Run a per protocol economic analysis to estimate the cost-effectiveness of the intervention for those participants who complied with the protocol to wear the silk clothes as much as possible day and night. Participants will be classified as adherent if they wear the trial clothing for at least 50% of the days or nights where the diary had been completed, provided that at least 50% of the diary had been completed.
- If the statistical analysis finds a significant difference in effectiveness on the primary outcome measure for those with mutations in the gene encoding for filaggrin FLG as defined on page 17 of the Statistical Analysis Plan, the economic evaluation will be re-run as part of a subgroup analysis for presence of the FLG genotype.
- The cost of the silk therapeutic garments may be a major cost driver affecting the likely cost-effectiveness or not of the garments. To test this the unit cost of the garments will be varied to find the unit cost at which it would change the decision about cost-effectiveness.
- We are also collecting utility information from the main carer. Since the evidence about how to analyse this in addition to the child's utility is limited (Al-Janabi et al 2011) we will present cost per QALY for the child as the base case and cost per QALY per carer (since only one carer completed the EQ-5D an assumption that any change in utility might be double for two parents families could be tested) separately in sensitivity analyses.
- Method of estimating prescription costs will be tested. The main analysis will rely on the HSCIC Prescription Cost Analysis as the Net Ingredient Cost per

Item (NIC). In sensitivity analysis an alternative based on the NHS Business Services Authority formula to estimate the actual cost to the NHS:

Actual Cost = (Net Ingredient Cost less the discount) + Payment for Consumables + Payment for Containers (10p for splitting packs) + Out of Pocket Expenses

Source:www.nhsbsa.nhs.uk/documents/prescriptionservices/gp_faqsver4.doc. Accessed 5th January 2016.

Will be used employing the methods outlined in a personal communication from Kirsty Garfield at the University of Bristol to cost eczema prescriptions in the NIHR RfPB funded "Choice Of Moisturiser in Eczema Treatment (COMET): A feasibility study of pragmatic, single blind, randomised clinical trial to compare the clinical and cost effectiveness of leave-on emollients in treat" study.

- If feasible, a sensitivity analysis will consider the resource use data collected in the observational period (8 months) in order to assess the likely costs of the intervention over an 8-month period of time to reflect more fully the wear and tear of the garments and growth of children. However, health outcomes will not be measured at 8 months so it will not be possible to repeat the economic evaluation for an 8 months period.

All statistical analysis will be undertaken in STATA 14 64-bit SE.

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Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, Briggs A, Sullivan SD. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. Value Health. 2015 Mar;18(2):161-72. doi: 10.1016/j.jval.2015.02.001

FIGURE 1: CLOTHES Examples of out of pocket expenditure related to eczema

During the study we are asking you to make a note of anything you pay for out of pocket as a result of your child having eczema that you would not otherwise have had to purchase.

Based on experience some parents/carers find it difficult to know what type of items we are interested in them recording. This leaflet gives some examples of the type of things we would like you to record purchasing and the price you paid. This list is not exhaustive, there may be other items you think are relevant that are not on the list. Equally there may be things on this list which you haven't had to purchase any differently as a result of your child having eczema and thus you should not record these.

We are interested in the difference in cost of looking after a child with eczema to a child without eczema thus you should only put the whole price down if the item is something you would not have bought if your child did not have eczema (e.g. an emollient). Some items you may have bought even if they had not had eczema (e.g. sun cream, washing powder) but have to buy a more expensive make/brand in order to get one that does not irritate your child's eczema, in this case please record an estimate of how much more you think you have had to pay for the item.

Please only record those items actually purchased during the time you are involved in the study.

Clothing	**Special food**
Night wear, underwear, school uniform, and day wear made from natural fibres such as cotton	Nut-free foods Special milk e.g. goats, oat or lacto free milk
Over the counter products	**Laundry and bedding**
Emollients, moisturiser, bio oil, sun cream Special shampoos, shower or bath gels Vitamins & mineral supplements, anti-histamines, herbal remedies Bandages, tubi-grips	Purchased bedding (sheets, pillow cases, duvet cases) made of natural fibres Anti-allergic pillows and duvets Bath towels made from natural fibres Special laundry powder/liquid undertake more laundry increasing electricity bills & amount of liquid used
Equipment	**Appointments**
Air cooler Water softener	Travel and parking costs to NHS or private visits Appointments with alternative medicine practitioners e.g. allergy testing, homeopath etc

Appendix 1: Example of the "Unit costs in 2014/15 UK pounds sterling" table

Table 1: Example of the "Unit costs in 2014/15 UK pounds sterling" table

Resource Item	Unit cost	Source
Intervention		
Silk therapeutic garments (Various)	£	PCA
Primary health care	£	PSSRU
GP (Per surgery consultation lasting 11.7 minutes)	£	PSSRU
Practice nurse (per consultation)	£	PSSRU
Pharmacist (per home visit)	£	DH
Secondary health care		
A&E (per visit)	£	PSSRU
Outpatients first visit (dermatology, non consultant led)	£	DH
Outpatients follow up visit (dermatology, non consultant led)	£	DH
Cost per bed day on a general medical ward	£	DH
Medications		
Various	£	PCA

Appendix 2: Examples of tables for mean resource use and costs

Table 2: Example of the "Mean (Standard Deviation) Resource Use and Mean Difference in Resource Use per Patient (95% Confidence Interval)" table

Resource use item	**Silk therapeutic clothing (n=)** Number (SD)	**Usual care (n=)** Number (SD)	**Mean difference (95% CI)**
Intervention			
Silk therapeutic garments (number)			
Primary health care			
GP (number of visits)			
Practice nurse (number of visits)			
Pharmacist (number of visits)			
NHS walk-in centre (number of visits)			
Secondary health care			
Inpatients (number of bed days)			
A&E (number of visits)			
Outpatients first and follow-up visit (number)			
Medications			
Prescription items (number)			

Table 3: Example of the "Mean (Standard Deviation) Cost and Cost Difference (95% Confidence Interval) Per Patient over the 6 months Intervention arm compared to usual care arm (in 2014/15 UK pounds sterling)" table

Resource use item	**Silk therapeutic clothing (n=):** **mean (SD) £'s**	**Usual Care (n=):** **mean (SD) £'s**	**Mean difference** **(95% CI) £'s**
Intervention resource use			
Silk therapeutic garments		**0.00** **(0.00)**	
Primary health care			
GP			
Practice nurse			
District nurse			
NHS walk in centre			
Total Primary health care costs			
Secondary health care			
Cost of inpatients			
A&E			
Outpatients first and follow-up visit			
Day hospital visits			
Total prescription costs			
Total health care costs			

This table will include considerably more resource items than those illustrated here and will be presented for children and for adults with and without asthma as a co-morbidity.

Appendix 3: Examples of tables reporting outcomes

Table 4: Mean (SD) utility values for intervention and control group at baseline and follow-up for the ADQoL, CHU-9D (both for childrens HRQL) and EQ-5D-3L for parental HRQL

	Intervention Group		Control Group	
	Baseline	**6 Months**	**Baseline**	**6 Months**
ADQoL all				
ADQoL under 5's				
ADQoL 5 and overs				
CHU-9D 5 and overs				
EQ-5D-3L for parents HRQL				

Table 5: Quality-adjusted Life Years (SD) for intervention and control group at baseline and follow-up for the ADQoL, CHU-9D (both for children's HRQL) and EQ-5D-3L for parental HRQL

	Intervention Group	**Control Group**
ADQoL all		
ADQoL under 5's		
ADQoL 5 and overs		
CHU-9D 5 and overs		
EQ-5D-3L for parent's HRQL		