Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial

Health Economics Analysis Plan

Content:

Section 1: Administrative Information

1.1 Title: Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): Health Economic Analysis Plan

1.2 Trial registration number: ISRCTN21528841

1.3 Source of funding:

This trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project number 12/67/12). The food allergy and food sensitisation assessments are funded by external grants from Goldman Sachs (gives no reference number) and the Sheffield Children's Hospital Research Fund (reference CA15008). Neither funder had any role in the trial design, the writing of this paper or decision to submit. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, THE NIHR, THE NHS or the Department of Health.

1.4 Purpose of HEAP:

This document will outline the methods to be used in the economic evaluation to be conducted alongside the BEEP Trial, including how data will be collected, analysed and reported. It will be finalised and reviewed prior to the trial database being locked to ensure it is appropriate to the aims of the trial and reflective of current practice. This HEAP has been written in line with the trial protocol and SAP in order to ensure there is consistency.

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

1.5 Trial protocol version*:*

This document has been written based on information contained in the trial protocol version 6.1, dated 20th October 2017.

1.6 Trial statistical analysis plan (SAP) version

SAP version: Draft Version 0.2/Final version 1.0, Date: 26 Sept 2018

1.7 Trial HEAP version

HEAP version: 1.0, Date: 26th Sept 2018

1.8 HEAP revisions

Protocol Version	Updated HEAP version No	Section number changed	Description of and reason for change	Individual making the change	Individual making the change

1.9 Roles and responsibilities

This HEAP was written by the senior health economist (TS), who is a co-applicant on the grant, and Emma McManus (EM), the Research Associate for the project. TS has inputted into the design of the wider trial as well as taken the lead on designing all aspects of the health economics analysis attached to the BEEP trial. TS will be analysing and writing up the within-trial economic evaluation in addition to advising and checking on the economic modelling component. The research associate (EM) will check the within-trial analyses, undertake the modelling economic evaluation if it is appropriate to include this component given clinical results, and contribute to and review the write-up for accuracy. EM has also reviewed and commented on the HEAP.

1.10 Signature(s):

The following people have reviewed the Health Economic Analysis Plan and are in agreement with its contents			
Name	**Role**	**Signature**	**Date**
Tracey Sach	Lead Health Economist	T. Sach	17/12/18
Emma McManus	Research Associate (Health Economics)		17 Dec 2018
Prof Alan Montgomery	Trial Statistician	A Montgomery	5 Dec 2018
Prof Hywel Williams	Chief Investigator		5/12/18

1.11 Abbreviations/glossary of terms/definitions

List any abbreviations and/or acronyms used within the HEAP alongside their meanings/definitions

Abbreviation	Meaning
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CHU-9D	Child Health Utility - Nine Dimensions
CUA	Cost Utility Analysis
EQ-5D-5L	EuroQol Five Dimensions Five Levels
HEAP	Health Economic Analysis Plan
ICER	Incremental Cost Effectiveness Ratio
NHS	National Health Service
POEM	Patient-Oriented Eczema Measure
QALY	Quality-Adjusted Life Year

SECTION 2: TRIAL INTRODUCTION AND BACKGROUND

2.1 Trial background and rationale

The primary objective of the BEEP trial is to determine whether advising parents to apply an all over body application of emollient to their child's skin during the first year of life in addition to best practice infant skin care advice can prevent the onset of eczema in high-risk children compared with a control group who are just given the best practice infant skin care advice. A range of secondary objectives are included to capture any difference in the time to onset of eczema, the severity of eczema, the risk of food allergy, the risk of allergic sensitisation to food or non-food allergens, the onset of other allergic diseases, safety issues associated with the emollient, cost effectiveness and long term effects of the intervention.

The BEEP trial is a pragmatic, randomised, controlled, parallel group, multicentre assessor-blind trial. Parents will be recruited from primary and secondary care as well as through general publicity and advertising and will be asked to follow the skin care advice for their child at home with minimal clinical contact. Up to 1400 children at high risk of developing eczema will be randomised to the intervention or control group in order to detect a relative reduction of 30% in the number having eczema at two years. To be classed as high risk of developing eczema a child must have a first degree relative with parental reported, doctor diagnosis of eczema, hayfever or asthma. Children with severe widespread skin condition that would make the detection and/or assessment of eczema difficult will be excluded as will children with a serious health issue which, at parent or investigator discretion, would make it difficult for the family to take part in the trial.

Best practice infant skin care advice will be given to all parents for their child. Those randomised to the intervention group will, in addition, be advised to apply emollient daily to the child's entire body surface area for the first year of the child's life. There is a choice of two emollients (Doublebase Gel® and Diprobase Cream®) for parents to choose for their child in the intervention group, switches between the two emollients will be allowed throughout the trial. The primary outcome is a diagnosis of eczema between 12 and 24

months of age (defined as meeting the UK Working Party Diagnostic criteria). This will be measured when the child is two years of age and conducted by a researcher blind to treatment allocation as it is not possible to blind parents to treatment group. Children will be followed up annually thereafter until they are five years of age. The primary statistical analysis will be a comparison of the proportion of children with eczema between one and two years of age, summarised using a relative risk with 95% confidence interval, from a generalised linear model adjusting for randomisation stratification factors.

Summary of evidence on cost effectiveness of emollient use to prevent eczema in high risk children

A decision tree model was developed by Xu et al (2017) to estimate the cost effectiveness of seven moisturisers used in the first 6 months of life to prevent eczema in high risk individuals from a health system perspective. The study was a secondary analysis based on limited published evidence about the effectiveness of emollients from the UK (the BEEP pilot study by Simpson et al 2014) and Japan (Horimukai et al 2014) where relative risk was estimated as 50% and 25% respectively. Using these estimates along with assumptions over the amount of emollient that would be used the decision tree was reportedly analysed using a cost utility approach for a 6 month time horizon. Xu et al conclude that daily moisturisation is a cost effective preventative strategy that can reduce the burden of atopic eczema.

The study has a number of limitations, which the authors acknowledge, including that the clinical efficacy of the emollients is based only on preliminary data, that they assume equivalent efficacy across the seven moisturisers included, and that the time horizon of the analysis is short reflecting available evidence. They also do not capture the wider cost changes or longer term changes to costs or health benefits.

2.2 Aim(s) of the trial:

The primary objective of the BEEP trial is to determine whether advising parents to apply emollient to their child's skin during the first year of life in addition to best practice infant skin care advice can prevent the onset of eczema in high-risk children compared with a control group who are just given the best practice infant skin care advice.

2.3 Objectives and/or research hypotheses of the trial

The primary objective of the BEEP trial is to determine whether advising parents to apply emollient to their child's skin during the first year of life in addition to best practice infant skin care advice can prevent the onset of eczema in high-risk children compared with a control group who are just given the best practice infant skin care advice

A range of secondary objectives are included to capture any difference in the time to onset of eczema, the severity of eczema, the risk of food allergy, the risk of allergic sensitisation to

food or non-food allergens, the onset of other allergic diseases, safety issues associated with the emollient, cost effectiveness and long term effects of the intervention.

2.4 Trial population

To be eligible for inclusion a child must have a first-degree relative with parental reported, doctor diagnosis of eczema, hayfever or asthma, be up to 21 days old with a mother aged ≥16 years and with a consenting adult able to understand English.

A child born prematurely (defined as birth prior to 37 weeks gestation); who has a sibling (including twin) previously randomised into this trial (If multiple births the first child will be randomised into the trial); who has severe widespread skin condition that would make the detection and/or assessment of eczema difficult; has a serious health issue which, at parent or investigator discretion, would make it difficult for the family to take part in the trial; or has any condition that would make the use of emollient inadvisable or not possible will not be eligible for participation in the trial.

Up to 1400 children may be randomised following advice from the independent Trial Steering Committee after a planned sample size review after 20 months of recruitment

The sample size calculation assumed that 30% of children in the control group will have eczema between one and two years of age and that a relative reduction of 30% is deemed to be of clinical importance (i.e. 21% of children in the intervention group have eczema between one and two years of age), a total of 1282 children will allow this difference to be detected at the 5% significance level (two-sided) with 90% power. This assumes equal numbers of children randomised to each group and 20% attrition.

2.5 Intervention and comparator(s)

Parents in both the intervention and comparator arms will be given best practice infant skin care advice for their child.

Those randomised to the intervention group will, in addition, be advised to apply emollient daily to the child's entire body surface area for the first year of life. Parents of children in the intervention group will be given a choice of two emollients (Doublebase Gel® and Diprobase Cream®) and may change between the two emollients throughout the trial if they want to.

2.6 Trial design

The BEEP trial is a pragmatic, randomised, controlled, parallel group, multicentre assessor-blind trial. Parents will be recruited from primary and secondary care as well as through general publicity and advertising and will be asked to follow the skin care advice for their child at home with minimal clinical contact. Up to 1400 children at high risk of developing

eczema will be randomised to the intervention or control group in order to detect a relative reduction of 30% in the number having eczema at two years. To be classed as high risk of developing eczema a child must have a first degree relative with parental reported, doctor diagnosis of eczema, hayfever or asthma. Children with severe widespread skin condition that would make the detection and/or assessment of eczema difficult will be excluded as will children with a serious health issue which, at parent or investigator discretion, would make it difficult for the family to take part in the trial.

Best practice infant skin care advice will be given to all parents for their child. Those randomised to the intervention group will, in addition, be advised to apply emollient daily to the child's entire body surface area for the first year of the child's life. There is a choice of two emollients (Doublebase Gel® and Diprobase Cream®) for parents to choose for their child in the intervention group, switches between the two emollients will be allowed throughout the trial. The primary outcome is a diagnosis of eczema between 12 and 24 months of age (defined as meeting the UK Working Party Diagnostic criteria). This will be measured when the child is two years of age and conducted by a researcher blind to treatment allocation as it is not possible to blind parents to treatment group. Children will be followed up annually thereafter until they are five years of age. The primary statistical analysis will be a comparison of the proportion of children with eczema between one and two years of age, summarised using a relative risk with 95% confidence interval, from a generalised linear model adjusting for randomisation stratification factors. This statistical analysis plan and this health economics analysis plan will be finalised prior to database lock and unblinding.

An allergy sub-study was added to the BEEP trial after the start of the trial. Parents provide consent for their child to undergo a Skin Prick test at 24 months of age for egg, milk or peanut allergy. The economic analysis will not incorporate any costs related to allergy as questions on resource use relating to allergy were not included in the original study questionnaires due to this being an addition to the study after the start of the trial.

Full details of the trial can be found in the published protocol (Chalmers et al 2017).

2.7 Trial start and end dates

Trial recruitment started in December 2014 and finished in November 2016. The follow up period will run until November 2020 when all participants will reach 5 years of age.

SECTION 3: ECONOMIC APPROACH/OVERVIEW

3.1 Aim(s) of economic evaluation

The aim of this economic evaluation is to determine the cost-effectiveness, from an NHS perspective, of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children at 2 years.

Cost-effectiveness and cost-utility at 24 months (combining health resource use and health-related quality of life outcomes) will be undertaken. A within trial economic evaluation to 5 years will be undertaken to assess if cost effectiveness differs at this point perhaps due to the effects of the intervention taking longer to materialise. If advice to undertake daily all-over-body application of emollient during the first year of life is found to reduce the risk of being diagnosed with eczema than usual care at either 24 months or 60 months, and if costs and outcomes have not converged between trial arms at 60 months, then we will build an economic model to estimate the cost effectiveness of the intervention from birth to 16 years. This will require sufficient data to be available to populate the parameters of the model.

3.2 Objectives(s)/hypotheses of economic evaluation

The primary objective of the within trial economic evaluation is to estimate the cost-effectiveness of advice to provide daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children over a two year time horizon.

Secondary objectives exist to look at the medium term cost effectiveness at 60 months using a within trial analysis and, if a favourable difference in risk is found at 24 months or 60 months and costs and outcomes have not converged at 60 months, a longer term cost effectiveness analysis from birth to 16 years using a model-based analysis will be undertaken.

3.3 Overview of economic analysis

The base case within-trial economic analysis will use individual participant level data collected over 24 months from the BEEP trial. The base case analysis will undertake a cost effectiveness analysis from an NHS perspective in terms of the number of cases of eczema prevented. A secondary analysis will be undertaken using a cost-utility approach, this has been chosen as the secondary analysis due to uncertainties about how best to capture child health utilities especially in the very young (Griebsch et al 2005, Petrou 2003, Petrou and Gray 2005).

The evaluation will adhere to published guidelines for the economic evaluation of health care interventions as appropriate (Drummond et al 2015; Ramsey et al 2015; Glick et al 2014; Husereau, D., 2013, NICE 2013).

3.4 Jurisdiction

The trial is being conducted in the UK which has a national health service (NHS), providing publicly funded healthcare which is largely free of charge at the point of use.

3.5 Perspective(s)

The analysis will take an NHS perspective in keeping with the NICE reference case (NICE 2013). Disease specific (eczema, asthma, and rhinitis) resource use will be collected. Personal Social Service (PSS) resource use is not being captured explicitly as it is not anticipated that these types of services will be used for the diseases of interest (eczema, asthma and rhinitis). However, there are "other" response spaces given in which participants parents/carers could record such items if relevant. The trial is a light-touch trial as after recruitment there is only one face-to-face contact at 24 months. In keeping with this the health economic evaluation only collects NHS resource use relevant to the diseases of interest and does not collect any costs incurred by the family or wider society to ensure the respondent burden is low.

3.6 Time horizon

The primary economic analysis will compare the costs and consequences over the 2 year follow-up period from randomisation. Secondary analyses will look at 60 months using data collected within the BEEP trial and if the intervention is effective from birth to 16 years via economic modelling.

SECTION 4: ECONOMIC DATA COLLECTION AND MANAGEMENT

4.1 Statistical software used for HE analysis

Stata SE version 14 will be used to conduct the analysis.

4.2 Identification of resources

In keeping with the chosen perspective the base case will capture the intervention costs to the NHS and the participant's wider disease specific resource use of the NHS (including health care visits and prescriptions for eczema, wheezing and nose problems).

4.3 Measurement of resource use data

Use of the intervention emollients is being monitored by the clinical trials unit. Wider NHS disease specific resource use is being recorded by participants in online or postal paper questionnaires at 3, 6, 12, 18, 24, 36, 48 and 60 months.

4.4 Valuation of resource use data

The cost of the intervention will be estimated using data collected by the clinical trials unit and costed using published unit costs for Doublebase Gel® and Diprobase Cream® in the Prescription Cost Analysis (Health and Social Care Information Centre, 2017). It will be assumed that the cost of distribution of the emollients incurred in the trial would not be incurred in the same way in practice, it is unlikely the NHS would send out emollients rather people would collect these via repeat prescription from their GP surgery to take to a

pharmacist for dispensing. As such postage costs incurred in the trial will not be captured in the economic evaluation.

Unit Costs:

Wider disease specific resource use relevant to the NHS perspective will be valued using UK unit costs (in £Sterling) from the most current price year available at the time of the analysis. Unit costs will be identified from published sources, such as Unit Costs of Health and Social Care (PSSRU, 2017), Prescription Cost Analysis (Health and Social Care Information Centre, 2017) and NHS Reference Costs (Department of Health, 2017). A table of unit costs, together with their sources will be produced.

Total Costs:

The cost of all reported resource use (relevant to an NHS perspective) will be calculated for each participant. For each of the different intervention arms, a mean cost per participant will be calculated.

4.5 Identification of outcome(s)

Quality of Life:

The primary economic outcome measure will be incremental cost per eczema case prevented in a cost effectiveness analysis.

Secondary analysis will be a cost-utility analysis using Quality Adjusted Life Years (QALYs) estimated using utility scores obtained using the proxy CHU-9D at 24 months in the analysis.

4.6 Measurement of outcome(s)

Utility measurements will be collected via online or paper based questionnaires at 2, 3, 4, and 5 years.

4.7 Valuation of outcome(s)

In the cost utility analysis, the responses received on the quality of life instruments will be converted to utility scores, the CHU-9D using the valuation set published by Stevens (2012) and parental utility as captured on the EQ-5D using UK preference weights in line with current recommendations at the time of the analysis (NICE 2017; Devlin et al 2016). Following this, the utility values will be used to calculate the number of quality adjusted life years (QALYs) generated over the trial period of 24 (and 60) months, using both linear interpolation and area under the curve analysis with and without baseline adjustment (Manca, 2005). Child utility at baseline will be assumed to be 1, perfect health, at birth, for

all participants given it is not appropriate to ask these instruments at that age. Parental EQ-5D-5L responses will be estimated in the same way and reported separately.

SECTION 5: ECONOMIC DATA ANALYSIS

In this prevention trial a cost effectiveness analysis will be undertaken whatever reduction in risk of eczema is observed even if this is zero. The rationale for this is that even if the risk reduction observed is less than that which was powered to be observed the intervention may still be cost-effective at a population level. If no risk reduction is observed it is still possible the intervention reduced the severity of eczema experienced and associated to this could reduce costs of care or improve quality of life such that it is possible the intervention might be estimated to be cost effective.

5.1 Analysis population

The economic base-case analysis will take an intention to treat principle approach including all randomised participants with data available.

5.2 Timing of analyses

The base case analysis will be a within-trial analysis, taking a 24 month time horizon. Secondary analyses will be undertaken using within-trial data to conduct a 60 month cost effectiveness analysis and a longer term economic model if appropriate.

5.3 Discount rates for costs and benefits

As the time horizon being evaluated is 24 months, costs and benefits in months 13 to 24 will be discounted using recommended rates at the time of analysis, these are currently 3.5% for both costs and benefits (NICE, 2013).

5.4 Cost-effectiveness threshold(s)

The main base case analysis is a cost effectiveness analysis, where decision makers will need to make a value judgement about the acceptable value of cost per eczema case prevented.

For the secondary analysis, the estimated mean costs and QALYs per participant associated with each intervention option will be combined with a feasible range of values for decision makers' willingness to pay (ʎ), to obtain a distribution of net benefits at different levels of ʎ. The economic analysis will use a cost-effectiveness threshold (ʎ) of £20,000 per QALY.

5.5 Statistical decision rule(s)

As appropriate, all statistical tests will be two-sided with the statistical significance level set at 5%.

5.6 Analysis of resource Use

Mean (sd) resource use per participant will be estimated for each randomised group. Mean difference (95% CI) in resource use per participant between arms will be presented.

5.7 Analysis of costs

Mean (sd) cost per participant will be estimated for each randomised group. Mean difference (95% CI) in cost per participant between arms will be estimated unadjusted and adjusted (for centre and number of immediate family members with atopic disease (1, 2 or more than 2)).

5.8 Analysis of outcomes

The primary outcome for the economic evaluation will be cost per eczema case prevented. Secondary analysis will estimate quality-adjusted life years (QALYs) of child participants. Mean (SD) utility and mean (sd) QALYS per participant per randomised group will be presented and mean difference (95% CI) in utility and QALYs between arms will be estimated unadjusted and adjusted (for centre and number of immediate family members with atopic disease (1, 2 or more than 2)). QALYs for the main carer will also be estimated and presented separately.

5.9 Data cleaning for analysis

Before carrying out analyses, plausibility checks will be performed on the relevant data fields, such as resource use and reported outcome measures, such as quality of life. Where problems are identified, the health economist will contact the data manager of the trial for clarification.

5.10 Missing data

The economic analysis will take the broad approach to missing data as the SAP. The base case economic evaluation will not impute missing data, undertaking a complete case analysis. Sensitivity analysis will explore the amount of missing data and the likely mechanism of missingness of trial data. Multiple imputation will be undertaken, assuming data are missing at random (Faria et al 2004). However, in line with the SAP approach we will test the best and worse case scenario in the cost effectiveness analyses with the additional assumption that:

- All participants with missing cost data in the intervention arm have the same cost as that of the lowest cost intervention participant with data available and those in the usual care group with missing data all have the same cost of the usual care participant with the highest cost (Best case)

- All participants with missing cost data in the intervention arm have the same cost as that of the highest cost intervention participant with data available and those in the usual care group with missing data all have the same cost of the usual care participant with the lowest cost (Worst case)

In order to test the robustness of the conclusion if missing data are missing not at random.

5.11 Analysis of cost-effectiveness.

A within trial cost effectiveness analysis will be undertaken whatever the primary outcome of this prevention trial. This is important even if a zero risk reduction is observed since there may be other benefits, such as reduced disease severity, that result in a change in costs or quality of life. Cost and effect data will be combined to estimate an incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) from the NHS perspective comparing advice to provide daily all-over-body application of emollient during the first year of life to usual care for preventing atopic eczema in high-risk children. A regression-based approach (such as seemingly unrelated regression equations for the cost utility analysis if appropriate) (Willan et al 2004) will be used.

The primary clinical outcome measure of the BEEP trial, as described above, will be used in the base case cost-effectiveness analysis. The number of cases of eczema prevented per intervention arm will be totalled and divided by the number of participants allocated in the respective arm. A generalised linear model (GLM) for binary outcome will be fitted and presented as unadjusted and adjusted by centre and number of immediate family members with atopic disease (1, 2 or more than 2).

5.12 Sampling uncertainty

It is likely that costs and outcomes will be skewed, therefore non-parametric bootstrapping will be used to determine the level of sampling uncertainty surrounding the mean ICERs by generating 10,000 estimate of incremental costs and benefits. These estimates will be plotted on a cost-effectiveness plane. In addition, Cost-Effectiveness Acceptability Curves will be produced, which will show the probability that each of the intervention arms is cost effective at different values of willingness to pay.

5.13 Subgroup analysis/Analysis of heterogeneity

We will undertake subgroup analyses for the following where they are shown to be important in terms of the clinical effect: (1) FLG mutation: none, one or two FLG null mutations. This will only be undertaken for the base case cost effectiveness analysis.

5.14 Sensitivity analyses

The following sensitivity analyses will be undertaken to explore key uncertainties around important parameters in the economic evaluation.

1. The impact of missing data will be explored – See section 5.10 for more detail.

2. The base case cost effectiveness analysis will use the same definition of a diagnosis of eczema as the primary outcome. However, diagnosis of eczema can be defined and established in different ways. To explore this uncertainty the difference in risk of being diagnosed with eczema between trial arms will be varied by the lower and upper 95% CI to provide a range around the incremental cost per eczema case prevented.

3. The cost of emollients will be varied to test the impact this has on the incremental cost per case prevented. Values will be varied between £0 (assuming the NHS decides not to reimburse emollients on the NHS in favour of providing advice to parents to buy it over the counter) and the maximum price of any emollient at time of the analysis.

4. The timeframe of the analysis will be tested by using within trial data to repeat cost effectiveness analyses at 60 months. A longer term economic model will also be built (see section 6) if the intervention shows a risk reduction at 24 and/or 60 months.

SECTION 6: MODELLING AND VALUE OF INFORMATION ANALYSES

6.1 Extrapolation or Decision analytic modelling

If either the 24 or 60 months within-trial cost effectiveness analyses show the intervention is likely to be cost effective, a model will be constructed to evaluate the long-term cost-effectiveness of the intervention. To do this, costs and outcomes will be extrapolated beyond the follow-up period of the trial.

6.2 Model type

A Markov model will be used to evaluate the long term cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing eczema in high-risk children. The Markov approach was selected as this method deals best with the chronic nature of eczema. It is also the most common modelling approach used within eczema published eczema studies, as shown by a recent systematic review (McManus, E. et al., 2018). The intended time horizon of the model is 16 years to reflect the whole of childhood. This time period has been chosen as it is the period where eczema is most likely to occur but also since prior systematic reviews suggest the evidence base surrounding eczema in adulthood is limited. The time period for the model will be reconsidered at the point where the model is starting to be developed to check that the evidence base surrounding eczema in adulthood still limits the ability to project forward to a lifetime horizon. Cycles within the model will be 4 weekly in duration to reflect the dynamic nature of the condition. The model will take the perspective of the NHS and an appropriate software will be used to carry out the modelling, for example Microsoft Excel or R.

A cohort of 1000 hypothetical newborn children will be modelled, characterised by a high risk of developing eczema and reflecting the overall the socio-demographics of this population across UK.

6.3 Model structure

The model will be structured using the following health states: Skin clear (or subclinical eczema), mild eczema, mild eczema flare, moderate eczema, moderate eczema flare, and severe eczema. Charman et al (2013) have published research suggesting POEM scores which fit into five bandings: 0-2 clear/almost clear; 3-7 mild; 8-16 moderate; 17-34 Severe; and 25-28 very severe. We propose combining severe and very severe to simplify the model given treatment approaches are unlikely to differ significantly between severe and very severe and as a proportion of total eczema sufferers those at the severe end of the spectrum is small. Whilst work has been published showing there is no consensus definition of what a flare is (Langan, S.M. et al., 2014), feedback from public involvement has shown that eczema patient's associate a flare as more than a temporary increase in severity. Therefore, flare states have been included in the model, which differs from the strategy used within NICE guidance documents where flares are modelled as a step up or down in treatment (NICE Clinical Guidelines, 2007).

The model structure will be reviewed by expert clinicians, to ensure the structure accurately reflects the underlying disease process, and therefore any suggested amendments will be implemented, for example the need to stratify the model according to eczema location.

The disease severity of eczema for each of these health states will be defined using the Patient Oriented Eczema Measure (POEM) as advocated by the HOME initiative. Published literature will be consulted to define the minimal clinically important difference and severity ranges within the POEM scores (Gaunt, D.M., et al., 2016, Charman et al (2013)). Data for POEM is being collected at 2, 3, 4 and 5 years in the clinical trial.

Each health state will have health care costs and health related quality of life associated with it. The model will evaluate the intervention in comparison to usual care / no daily application of emollient during the first year of life, to determine the incremental costs and outcomes associated with the intervention.

The potential model structure is shown in Figure 1.

6.4 Treatment effect beyond the end of the trial

There may be multiple treatment effects associated with the BEEP trial and the daily application of emollients during the first year of life. Primarily, it is expected to prevent the development of eczema, but it is also possible that eczema still develops but the severity of eczema is reduced, alternatively, it is also possible that the intervention delays the onset of eczema, rather than preventing eczema development completely.

As the BEEP trial was only adequately powered to address the first of these treatment effects: Stopping the occurrence of eczema, it is this treatment effect that will considered in the model unless the trial observes no risk reduction, in which case the other treatment effects will be considered. To do this, a hazard ratio will be calculated, representing the risk of developing eczema in the intervention group in comparison to the control. The hazard ratio will be derived from the clinical trial data and will be assumed to persist at the same rate following the trial end.

6.5 Other key assumptions

The key structural assumptions of the model are listed below. These will be subject to expert opinion and clinician approval as well as any suggestions made by public involvement.

- Mortality will not be considered in this model, as the population being modelled are children. This assumption is commonly used in other published decision models evaluating preventions for eczema amongst children.

- A flare can only be experienced for one cycle (currently defined as 4 weeks)

It should be noted that the model structure may be subject to change, following initial exploratory analysis of trial data and the availability of any non-trial data necessary.

6.6 Methods for identifying and estimating parameters

The evidence hierarchy as outlined by Cooper et al. 2005 will be used to identify data to inform the calculation of transition probabilities, with preference being given to those evidence sources cited more highly.

Sources of data will include, data from the trial itself, information from the CPRD study which may help in the identification of flares (through looking at prescribing patterns), to using other published epidemiological studies. Particularly, the management document developed by NICE suggesting guidelines for children with eczema from birth up to the age of 12 (NICE Clinical Guidelines, 2007), will be an invaluable source of relevant epidemiological studies.

<u>Treatment effects:</u>

The preventative effect of all over emollient use in the first year of life will be sourced directly from the clinical trial and will be assumed to persist over the extended time horizon.

<u>Outcomes (utilities):</u>

Utility values will be informed by data collected within the trial, as well as other trial based data where appropriate. These will then be used to calculate quality adjusted life years (QALYs), which will be the main outcome reported by the model.

QALYs will be discounted at the rate recommended by the NICE reference case at the time of analysis, which is currently 3.5% (NICE, 2013).

Cost data source and price year:

Costs will be reported in UK£ Sterling, using data from the most current available price year, as appropriate. Costs will be estimated using trial data and or data from an on-going Clinical Practice Research Datalink (CPRD) study, seeking to estimate the annual costs of health care for eczema patients. However, where such information is not sufficient expert opinion will be utilised to estimate resource use and unit costs will be sourced from published sources, such as Prescription Cost Analysis for medications (Health and Social Care Information Centre, 2018), the Unit Costs of Health and Social Care (PSSRU, 2018) for primary care appointments and NHS Reference Costs (Department of Health, 2018) for secondary care appointments, and applied. Where it is not possible to identify a nationally published unit cost, it may be necessary to source a unit cost locally, or rely on expert opinion. A table of unit costs, together with their sources will be produced.

It is likely that various assumptions will be required about the type and amount of treatments and healthcare resource use used within each health state. These assumptions will be informed by existing literature, for instance NICE (2007), and by expert opinion. All assumptions and evidence for their use will be documented clearly.

Costs will be discounted at the rate recommended by the NICE reference case at the time of analysis, which is currently 3.5% (NICE, 2013).

6.7 Model uncertainty

Parameter uncertainty will be accessed by varying parameters within stated ranges and the results displayed on a tornado diagram. As well as this, probabilistic sensitivity analysis will be conducted (which involves fitting probability distributions to each parameter) and running Monte Carlo simulations.

It may also be appropriate to examine the structural uncertainty inherent within the model, which can be explored by running alternative versions of the model, with different structural assumptions, for example removing flare states and assuming that a flare is equivalent to eczema severity increasing.

Other uncertainties that could be explored include changing to different treatment strategies associated with the disease states or changing the assumptions on how the eczema is managed (primary or secondary care). The utility values used in the model could also be varied, for instance by using published sources (Stevens et al 2005).

6.8 Model validation

A variety of methods will be used to check the validity of the model produced, these will be

guided by the AdViSHE tool (A validation-assessment tool of health-economic models for decision makers and model users) (Verner, P. et al., 2016) and are referred to below:

The validity of the conceptual model will be tested by confirming with expert clinicians that the appropriate comparators have been selected and that the model accurately reflects the underlying disease process.

Cross-validation will be carried out by comparing the results of the model to the results of other published models (if such publications exist).

Furthermore, to ensure that the mathematical logic of the model has been tested, a second modeller will review the model to ensure that there are no obvious coding errors or calculation errors (referred to as external review).

The face validity of the model will be tested by carrying out extreme value testing, which will facilitate the identification of coding errors and any counterintuitive results will be explored.

6.9 Subgroup analyses/Heterogeneity

In keeping with the SAP we will undertake subgroup analyses for the following where they are shown to be important in terms of the clinical effect: (1) FLG mutation: none, one or two FLG null mutations; (2) number of immediate family members with atopic disease (one, two, three or more); (3) number of immediate family members with eczema (zero, one, two or more).

SECTION 7: REPORTING/PUBLISHING

The 24 month economic analysis will be published alongside the 24 month clinical analysis in a peer-reviewed journal. Subsequent longer term analyses will be published separately in later peer reviewed publications

7.1 Reporting standards

The CHEERS reporting quality guidelines will be followed when writing up the health economic evaluation.

7.2 Reporting deviations from the HEAP

Any deviations necessary from the HEAP will be described and justified in the main study report (HTA monograph).

SECTION 8: Appendices

Appendix 1: Example Tables

Unit Costs Table (UK£ sterling, Price Year)

Cost Item	Unit Cost (£)	Source
Intervention		
Doublebase Gel®		
Diprobase Cream®		
NHS Care		
GP		
Practice Nurse		
Pharmacist*		
Hospital Doctor		
Hospital Nurse		
Therapist (assume psychologist)		
Other		
Medication		

*Note assumed to be a community pharmacist

Mean (sd) resource use and mean (95% CI) difference in resource use at 24 months

Cost Item	Intervention (n=)	Usual care (n=)	Mean difference (95% CI)
Intervention			
Doublebase Gel®			
Diprobase Cream®			
NHS Care			
GP			
Practice Nurse			
Pharmacist*			
Hospital Doctor			
Hospital Nurse			

Therapist (assume psychologist)			
Other			
Medication			

Mean (sd) cost and mean difference in cost at 24 months

Cost Item	**Intervention (n=)**	**Usual care (n=)**	**Mean difference (95% CI)**
Intervention			
Doublebase Gel®			
Diprobase Cream®			
NHS Care			
GP			
Practice Nurse			
Pharmacist*			
Hospital Doctor			
Hospital Nurse			
Therapist (assume psychologist)			
Other			
Medication			

Utility and QALYs

	Intervention (n=)		**Usual Care (n=)**		
	Mean	**Std dev**	**Mean**	**Std dev**	**n**
Child participants					
CHU-9D 24 months					
CHU-9D 36 months					
CHU-9D 48 months					
CHU-9D 60 months					
QALYs at 24 months					

QALYs at 36 months					
QALYs at 48 months					
QALYs at 60 months					
Main carer					
EQ-5D-5L at baseline					
EQ-5D-5L at 24 months					
EQ-5D-5L at 36 months					
EQ-5D-5L at 48 months					
EQ-5D-5L at 60 months					
QALYs at 24 months					
QALYs at 36 months					
QALYs at 48 months					
QALYs at 60 months					

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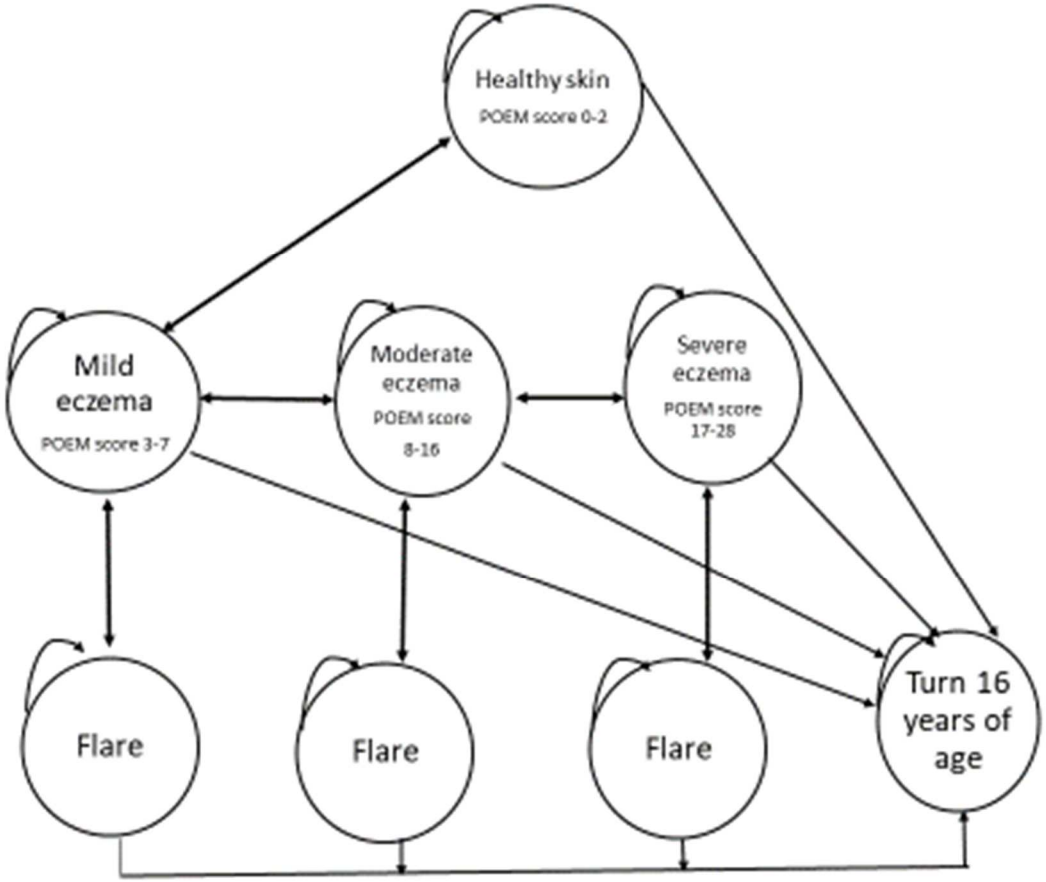
Figure 1: *Potential* model structure for longer term economic evaluation (birth to 16 years)



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