DR TRACEY H SACH (Orcid ID : 0000-0002-8098-9220)

MISS EMMA MCMANUS (Orcid ID : 0000-0002-3442-8721)

PROFESSOR NICK J LEVELL (Orcid ID : 0000-0003-3393-8305)

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Understanding economic evidence for the prevention and treatment of atopic eczema

T. H. Sach[1*]

e-mail: T.Sach@uea.ac.uk

E. McManus[1]

e-mail: Emma.Mcmanus@uea.ac.uk

N. J. Levell[2]

e-mail: nick.levell@nnuh.nhs.uk

[1] Health Economics Group, Norwich Medical School, University of East Anglia, Norwich, NR4 7TJ.

[2] Dermatology Department, Norfolk and Norwich University Hospitals NHS Foundation Trust, Colney Lane, Norwich, NR4 7UY

*corresponding author: Professor Tracey Sach, Health Economics Group, Room 2.37, Norwich Medical School, University of East Anglia, Norwich, NR4 7TJ. E-Mail; T.Sach@uea.ac.uk

Running title: Economic evidence for the prevention and treatment of atopic eczema

Competing interests

NL is a trustee and an officer of the British Association of Dermatologists, which owns the British Journal of Dermatology. TS is an author on several of the papers included in the review but these were assessed by other members of the research team. Otherwise the authors declare that they have no competing interests.

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What's already known about this topic?

- Resources available for health care are limited and their efficient allocation should be informed by robust economic evidence about value for money.
- The scale and quality of economic evidence available for atopic eczema has not previously been examined.

What does this study add?

- By comparison with the considerable clinical evidence for interventions to prevent and treat eczema, there is limited economic evidence available.
- The economic evidence available is limited in scope with regard to the types and range of interventions evaluated.
- The quality of future economic studies could be improved by greater collaboration between economists and clinicians.

Abstract

Background

Atopic eczema is an inflammatory skin condition, with a similar impact on health-related quality-of-life as other chronic diseases. Increasing pressures on resources within the NHS increase the importance of having good economic evidence to inform their allocation. This paper aims to educate dermatologists about economic methods with illustration to currently available economic evidence on eczema.

Methods/design

The type and role of different types of economic evidence is illustrated by evidence found in a systematic literature search conducted across 12 online databases published until 22nd May 2017. Primary empirical studies either reporting the results of a cost of illness study or evaluating the cost, utility or full economic evaluation of interventions for preventing or treating eczema were included. Two reviewers independently assessed studies for eligibility and performed data abstraction, with disagreements resolved by a third reviewer. Evidence tables of results were produced for narrative discussion. The reporting quality of economic evaluations was assessed.

Results

78 studies (described in 80 papers) were deemed eligible. 33 (42%) were judged to be economic evaluations, 12 (15%) cost analyses, 6 (8%) utility analyses, 26 (34%) cost-of-illness studies and 1 feasibility study (1%). The calcineurin inhibitors: tacrolimus and pimecrolimus, as well as barrier creams had most economic evidence available. Partially hydrolysed infant formula was the most commonly evaluated prevention.

Conclusions

The current level of economic evidence for interventions aimed at preventing and treating eczema is limited compared to that available for clinical outcomes suggesting that greater collaboration between clinicians and economists might be beneficial.

Registration

PROSPERO registration number: CRD42015024633

Keywords:

Eczema; Economics; Costs; Health-related quality of life; Cost-effectiveness

BACKGROUND

Economic evidence is important, particularly in the current climate of limited healthcare resources. The impact on this within dermatology can be seen, for instance, in the NHS consultation on reducing prescribing of over-the-counter medications in which around a third of medications considered are dermatological in

nature.[1] To challenge such strategies, if appropriate, and ensure that treatments offering value for money remain available, requires both clinical and economic evidence.

Atopic eczema, (atopic dermatitis) herein referred to as eczema has a highest incidence in the first year of life[2] (13.8 per 100 person-years; 95% CI, 13.7-13.9[3]). Eczema is largely managed in primary care, with treatments aiming to control eczema in remission and to manage flare-ups. Eczema may have a similar impact on health-related quality of life for patients and families[4] as asthma and diabetes.[5] Those with eczema are more likely to develop asthma and allergic rhinitis.[6] Given the scale of the condition and its consequences, it is likely to have large cost implications for health systems and families.

Much is already known about the clinical efficacy of interventions for eczema, shown by the scale of evidence included in The Global Resource of Eczema Trials (GREAT) database[7] which details over 900 systematic reviews and randomised controlled trials to date. However, it does not include any economic evidence on eczema. It is important to identify, assess and understand the existing economic evidence in order to inform future economic research in this area. This is particularly important given the emergence of biologic therapies for moderate to severe eczema.[8,9]

METHODS

The review informing this paper was registered in the International Prospective Register of Systematic Reviews (PROSPERO) CRD42015024633 and the protocol, containing more detailed information on the search strategy and methods used, published.[10]

Literature search

An electronic search using the following databases was undertaken from their inception dates through to 22nd May 2017: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database (ceased adding records March 2015), Econ Lit, Scopus, Health Technology Assessment, Cost-Effectiveness Analysis Registry and Web of Science.

Studies were eligible for inclusion if they included primary data on cost and/or economic outcomes (utility or willingness to pay) on eczema. There was no restriction on study design, although only full text articles published in English were included. Two independent reviewers screened abstracts before accessing the full text of eligible papers to determine inclusion within the review. The references of eligible studies were screened to ensure all relevant literature was identified.

Data Extraction

Two reviewers (TS, EM), independently extracted data using a data extraction form. Reporting quality was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[11] In this paper, only the quality assessment for full economic evaluations is reported, since many of the items are irrelevant for partial studies. For three publications where TS was an author[12-14], the data extraction and quality assessment was completed by NL and EM.

Analysis

The narrative synthesis considered the findings in three ways. Firstly, the studies were categorised by type of economic analysis in order to highlight the range of methods used. Secondly, for those studies conducting full economic evaluations the findings in terms of the cost effectiveness of the interventions evaluated was considered. In this section studies were categorised into those in which the new intervention was found dominant (more effective and less expensive), those where a judgment was made about value for money (more costly but also more effective), and those where the new intervention was dominated (more expensive and less effective). The third section considers the reporting quality of studies in order to highlight the importance of critically appraising the available evidence before using it.

RESULTS

The review found that the quantity of economic evidence available is limited. Figure 1 details the results of the literature search. In total, 78 unique studies were detailed within 80 publications (Papers [12] and [13] reported on the same study, as did [15] and [16]. We included the HTA monograph for each[13, 15]). The number of economic studies

being published each year is small and relatively static with between 3 and 8 papers published per year since 2002.

The variety of interventions considered were relatively limited when compared to the 240 intervention groups listed on the GREAT database. Of the studies found within this review, the most commonly evaluated intervention type were topical calcineurin inhibitors (14: [15-28]), followed by infant formula feeds intended to prevent eczema from developing (10: [29-38]). Six studies evaluated a change of service delivery – including the use of web based consultations[39], delivering care by a nurse practitioner[40-42] , the development of a paediatric dermatology service (although what this entailed was not described)[43] and the use of interdisciplinary group sessions with an educational counterpart.[44] Mason et al. also evaluated an educational support programme which included the provision of an educational DVD and telephone support.[45] Moisturisers or barrier creams were evaluated in six studies.[46-51] Other preparations evaluated included fluticasone propionate ointment,[52] topical prednicarbate[53] and some oral preparations including montelukast[54], bacterial lysate[55], cyclosporine A[56] and antibiotics (compared to an antibiotic cream) for infected eczema[57]. Homeopathic interventions were evaluated in three studies.[58-60] One study examined the use of ion-exchange water softeners for the treatment of eczema in children.[14] One study, discussed in two publications[12,13] evaluated the use of silk clothing by children with moderate to severe eczema.

Economic methods used by studies

This section describes the type of methods used in the papers found, different methods can inform different types of questions. Under half of the studies undertook full economic evaluations, those studies which compare both costs and outcomes for two or more interventions, (cost benefit, cost utility, or cost effectiveness analyses). The remainder looked only at partial economic aspects including costs, outcomes or cost of illness studies. These studies alone cannot inform decisions about the efficient allocation of resources, as they do not provide relative estimates of costs and effects of alternative provisions. They do still have value as a source of evidence that can inform the design of future studies or provide evidence to inform parameters for economic models, for instance.

Partial Economic Studies

Outcome Only Studies:

Six studies that just considered outcomes were identified.[57,61-64] These studies may help to inform the design of future economic evaluations or to parameterise economic models. Two papers[61,62] conducted a willingness-to-pay (WTP) study amongst Germans with eczema, both studies found that patients would be willing to spend in the range of €50 (for controlled eczema) to €150 (for uncontrolled eczema) per month to achieve a complete cure.

Stevens et al.[65] developed a disease specific preference based health measure, ADQoL (Atopic Dermatitis Quality of Life), for economic evaluation of children with eczema. Parental interviews generated items that formed 16 unique health states, which were then valued using standard gamble methods which presents

respondents with two alternatives, one a certain outcome in some sub-optimal health state and the other a probability of being in perfect health or immediately dead. The probability is varied until the respondent is indifferent between the two alternatives. Mean estimates for the 16 health states ranged from 0.36 (SD 0.36) for the worst state to 0.84 (SD 0.19) for the best health state. ADQoL has been used in few trial evaluations, although the estimates in the paper have been more widely used in economic modelling studies. Only three trial-based full or feasibility stage economic evaluations in this review used the ADQoL descriptive system to elicit a health state description for each participant.[13,50,57] Francis et al.[57] tested the construct and face validity of ADQoL[65] completed by parents of children with eczema, in comparison to the clinical measures POEM (Patient Oriented Eczema Measure), EASI (Eczema Area and Severity Index) and IDQoL (Infants' Dermatitis Quality of Life Index).[57] This study supported the use of ADQoL but noted that parents of the youngest participants found it harder to complete. Only two studies[57,65] considered outcome studies in a paediatric population. Since eczema often starts in childhood there is a need to have measures of utility that are suitable and validated in the very young.

Cost Studies:

The majority of cost analyses were performed alongside clinical trials, where costs were not combined with outcome data[17,19,39,41,44,45,54,58] and some had weaknesses in their methodological approach. For example, Staab et al.[44] looked at the treatment costs of participants, however failed to cost the intervention that was being evaluated. Furthermore, Bergmo et al.[39] only reported the cost of baseline resource use, not the cost of any subsequent resource use. Kernick et al.[41] were also limited in the costs disclosed, stating only a few costs associated with the intervention.

Whilst Boguniewicz et al.[17] did perform a cost analysis, the study focused more-so on the development of a framework for assessing outcomes, intended to inform future research. There were four studies that completed retrospective cost analyses using administrative databases[21,22,43,60] and one feasibility study that identified potential cost drivers for a future trial.[50]

Only one study explored the potential methodological challenges in costing eczema interventions and care. Mason et al.[45] compared methods used to estimate emollient resource use, contrasting daily diary recording of emollient use to estimates of time taken to use a 500g container of emollient. However, the method chosen was found to have only a small effect on the estimated cost. See Table 1 for further details of these studies.

Cost of Illness:

Cost of illness studies estimate the financial burden of a condition for a defined population.[66] These studies show decision makers the size of the problem relative to other conditions so can help inform the planning of services and care. Such studies vary in how different costs are captured and the complexity of methods used.[67] A total of 26 studies (34%) were considered to have conducted a form of cost of illness study[68-93], one of which used a model developed in Excel.[68] Most of these studies evaluated the cost of eczema within children,[68-79] with only two papers stating explicitly that they were evaluating adults with eczema.[80,81] Other papers did not specify the population age, with 11 stating a population of eczema patients.[82-92] Filanovsky et al.[93] studied the carers of children with eczema.

Seven studies compared the eczema cohort to other groups, mainly those without eczema or allergic disease[69,70,83-85] to calculate an incremental cost of treatment.[94] One study compared eczema patients to those with diabetes.[79] Table 2 provides further details of these studies.

The most recent cost of illness figures published in the UK were by Herd et al. in 1996[92], based on self-reported data for a sample of 155 people with eczema. These old estimates require updating, with analysis using real-world observational data and methods to better inform current policies for eczema in the UK.

Feasibility study

One feasibility randomised controlled trial[50] was found, which included an economic evaluation component and looked at four different leave-on emollients in those aged under 5 years. Such studies are primarily undertaken to help inform design decisions for full trials, including to identify appropriate outcomes, items of resource use to collect and the completeness of this data by data collection methods.

Full Economic Evaluations

Full economic evaluations, accounted for 42% of the unique studies found. Of these, 24 were model based economic evaluations. 10 studies were conducted alongside a trial[12-14,18,20,40,42,46,52,56,59] and were from the UK (3 studies, one reported in two papers), multi-site in Europe (2), the Netherlands (2), Finland (1), Germany (1) and the USA (1).

Cost benefit studies:

Cost benefit analyses are the broadest type of economic evaluation, as they seek to value the consequences of an intervention in monetary terms to enable comparisons between interventions across as well as within sectors of the economy. No studies detailing cost benefit analyses were found.

Cost Utility Analyses:

Cost Utility Analyses (CUA) measure the consequences of an intervention in terms of healthy years, which are typically measured as Quality-Adjusted Life-Years (QALYs). This is the most commonly used method to inform resource allocation decisions within the NHS, as advocated in the NICE reference case.[95] The generic outcome measure enables comparisons to be made across disease areas. Only four CUA's that were not model based were found in the review,[12-14,18,20] one of which was described in two papers.[12,13] The method of generating utilities in these studies varied. Poole et al.[18] used answers from the SF-12, and then a mapping algorithm[96] to predict EQ-5D responses, from which the UK tariff was used to generate utility values. In comparison, Wollenberg et al.[20] also used SF-36 responses but used a mapping algorithm developed by Brazier et al.[97] Thomas et al.[14] used the youth version of the EQ-5D (EQ-5D-Y) for children aged over 3 years generating utility values using the UK tariff derived from an adult population (acknowledged as a potential weakness in the study). Only one study, as described in [12,13] used the ADQoL.

Cost Effectiveness Analyses:

Cost Effectiveness Analyses (CEA) value the consequences on an intervention in terms of natural units (for example the number of eczema flares prevented). CEAs are mainly designed to inform resource allocation decisions within the same condition. Six studies conducted a CEA.[40,42,46,52,56,59] The majority of these focused on clinical outcomes, including the percentage improvement in EASI score,[46] number of remission days per patient,[56] number of successfully treated flares,[52] and eczema severity assessed using SCORAD (Scoring Atopic Dermatitis).[59] By contrast, two studies considered a health-related quality of life measure, with Schuttelaar et al.[40] using the IDQoL for children aged less than 4 years and the CDLQI (Children's Dermatology Life Quality Index) for children aged 4-16 years. Os-Medendorp et al.[42] used the IDQOL for children and the DLQI (Dermatology Life Quality Index) for adults.

Modelling studies:

24 papers used a model to evaluate a prevention or intervention for eczema[15,16,24-27,29-38,47-49,51,53,55,98,99], 11 of which used CUA, 9 CEA, 3 both CEA and CUA, and 1 both cost minimisation analysis (CMA) and CEA. The economic methods used in these studies and their quality are examined elsewhere[100] so these studies will not be discussed further.

Cost-effectiveness results for interventions to prevent and treat eczema

Ten studies (described in 11 papers) undertook full economic evaluations[12-14,18,20,40,42,46,52,56,59]. Interventions estimated to be dominant (more effective and less expensive) included tacrolimus ointment[20], ciclosporin [56], care by a nurse

practitioner[40], and care package with access to an electronic eczema portal[42]. Two interventions were judged cost effective (that is they had higher costs that were justified by greater effectiveness given societies willingness to pay for health gain): fluticasone propionate – twice daily application[52], and tacrolimus ointment[18]. Silk clothing along with standard care[13], ion exchange water softener[14], homeopathy[59], atopiclairand epiceram[46], were dominated (cost more and less effective than their comparators). It should be noted that such statements lack usefulness without knowing the perspective, timeframe, precise detail of the comparator, country of study etc. for each study. That different economic evaluations of the same intervention can reach different answers is illustrated here by tacrolimus ointment. In the study[18] that required a judgment to be made about cost effectiveness tacrolimus ointment was compared to hydrocortisone ointment whereas the economic evaluation[20] finding tacrolimus ointment dominant was comparing to usual care. Therefore, we provide fuller details in table 3 to aid interpretation of the results.

It is clear from Table 3 that the range of interventions fully evaluated is limited. This inevitably limits the ability of decision makers to use such evidence to inform their resource allocation decisions both about how to allocate resources. This affects both allocation between different eczema interventions but also between eczema and other disease areas. The best resource allocation decisions are likely to be made where an array of evidence exists which can be integrated to inform an economic model. Economic decision models often facilitate this but in the area of eczema these models tend to be of insufficient timeframe and quality[100]. The evidence in table 3 suggests that current decisions are likely to be made either on the basis of no evidence (where none exists) or based on a single influential trial. The CLOTHES

trial[13], for example, seems to be the sole evidence justifying guidance suggesting silk garments should not be routinely prescribed in any circumstance in primary care in the NHS [101]. In the absence of good economic evidence, good decisions will not be made about resource allocation in eczema.

Reporting quality of the economic evidence available

The reporting quality of the full economic evaluations was assessed using the CHEERS checklist[11], detailed in Table s4. This checklist was developed as part of an initiative to consolidate and update existing health economic checklists into one checklist. No study met all the CHEERS criteria, with the percentage of applicable items fulfilled ranging from 42% (Green et al.[52]) to 95% (Thomas et al.[14]). The checklist items least often met were checklist items 6 (Study perspective), 20a (Characterising uncertainty), and 21 (Characterising heterogeneity). Study Perspective is the viewpoint taken in the analysis (eg from the point of view of the patient, NHS Institution or of society), which is important as the cost effectiveness of an intervention may depend on which viewpoint is taken;. Four of the eleven full economic evaluations did not explicitly state the perspective being used within their analysis requiring the reader to make inferences based on the resource use/costs and outcomes reported.[18,46,52,56] By not stating the perspective of the evaluation, it was difficult to assess if all of the appropriate resource use and costs had been included. . Eight of the studies did not conduct subgroup analyses to examine how observable characteristics of the patients might influence results (referred to as characterising heterogeneity), this may have been appropriate but justification for this omission was not provided in the papers.[13,14,18,42,46,52,56,59] Moreover, 5 of the 11 full economic evaluations did not report a price year.[18,20,46,52,59] In order to compare

different cost effectiveness estimates, often you need to inflate them to a common price year (which without knowing the original price year) is difficult to do. The majority of full economic evaluations clearly reported the source of funding for the study (with the exception of Green et al.[52]) and conflicts of interest (with the exception of Green et al.[52], Miller et al.[46] and Witt et al.[59]).

DISCUSSION

This study has used results from a systematic review to demonstrate the type and quality of economic research currently available to support evidence based decisions for eczema. It appears insufficient to inform decision makers about how to allocate limited resources between eczema and other disease areas, nor how best to use resources allocated to eczema to maximise health outcomes. The current evidence base surrounding the economics of eczema has gaps, which if filled, could help to inform future research efforts in this area.

It was encouraging to find that economic evaluations were the most commonly found study type. The majority used decision modelling. The low number of economic evaluations conducted alongside randomised controlled trials was surprising given the number of clinical trials that have been conducted for eczema[7]. Those undertaking trials may not be aware of the importance of incorporating economic outcomes within their study or may lack skills in this area. Cost of illness studies were the second most common type found, covering a range of countries and methods. They demonstrated the range of costs incurred by health care systems, families and society as a result of eczema. However the UK relevant estimates are out of date and require updating.[92] It is important that future cost of

illness studies must have good methodology including a control group to obtain realistic estimates.

The range of interventions with economic evidence available is also limited. The majority of studies were conducted over short time horizons and so indicate little about the long-term value for money of the interventions. Clinicians and economists might be able to improve this by working together to identify where important economic questions exist. The new high-cost treatments for eczema, such as biologics,[102] must be evaluated appropriately and for a sufficient duration.

Since eczema often starts at a young age, measures of utility must be suitable and validated in the very young. Similar to other disease areas in children, further economic research is needed.[103] The Harmonising Outcome Measures for Eczema (HOME) initiative has so far been unable to reach consensus on a single quality of life measure to be included in the core outcome set.[104,105] Consequently no one instrument has been well tested which exacerbates problems in eczema health economic assessments.

Strengths and Limitations

To the authors' knowledge, this is the first collation of all types of economic evidence on the topic of eczema. It is informative in identifying interventions, populations and methodological gaps where further research is needed. However, there are limitations, particularly, that the search only covered published research and therefore, may have missed guidance documents relevant to the economic evidence of eczema. The data extraction was dependent on the subjective view of those

extracting the information and at points, it was difficult to classify some studies, particularly those that performed partial cost analyses. Whilst the inclusion criteria only included English language articles, the search was not restricted by publication language and consequently 12 foreign language papers were identified that, based on the English abstract and title, appeared potentially relevant.[106-117] We reference them here in case they are of use to multilingual researchers. We also recognise that since the search was undertaken further relevant economic studies have been published[118-126]. Our primary aim, however, was to use available literature to increase understanding about the range of economic methods available as with understanding may come more appropriate use of these methods.

Conclusion

At a time where access to public health services are being more overtly restricted, economic evidence is important to help inform that process and ensure transparent justification. This study has found a paucity of economic evidence for interventions aimed at preventing and treating eczema, suggesting the need for clinicians to incorporate health economics within their study design more frequently. The evidence that is available is of variable quality such that not only is there a need for more research, but also for more methodologically robust research.

Abbreviations

ADQoL: Atopic Dermatitis Quality of Life; CDLQI: Children's Dermatology Life Quality Index; CBA: Cost Benefit Analysis; CEA: Cost Effectiveness Analysis; CMA: Cost Minimisation Analysis; CHEERS: Consolidated Health Economic Evaluation Reporting Standards; CUA: Cost Utility Analysis; DLQI – Dermatology of Life Quality

Index; EASI: Eczema Area and Severity Index; EQ-5D: EuroQol five Dimensions; EQ-5D-Y: EuroQol Five Dimensions Youth version; GREAT: Global Resource for Eczema Trials; ICER: Incremental Cost Effectiveness Ratio; IDQoL: Infants' Dermatitis Quality of Life Index; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; QALYs: Quality-Adjusted Life Years; SCORAD: Scoring Atopic Dermatitis; SF-12: 12-item Short-form Health Survey; SF-36: 36-item Short-Form Health Survey; UK: United Kingdom; WTP: Willingness to pay.

Authors' contributions

TS conceptualised and designed the research, carried out the screening and data extraction, contributed to interpretation of data, and drafted and critically reviewed the manuscript. EM contributed to the design of the study, carried out the searches, screening and data extraction, and contributed to interpretation of data, drafting and critically reviewing the manuscript. NL contributed to the design of the study, provided expertise on eczema, carried out data extraction, and critically reviewed the manuscript. All authors reviewed the manuscript for important intellectual content and approved the final manuscript. TS is the guarantor.

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Table 1: Characteristics of the cost analyses, outcome studies and feasibility study

Study	Study Overview	Country	Population	Sample Size	Time Horizon	Currency (Price Year)	Methods	Results	Conclusions
Outcome Studies									
Beikert 2014 [61]	Willingness to Pay	Germany	Adults with eczema (Aged 18 years≤)	N=384	One off postal questionnaire.	-	DLQI, EQ-5D. WTP was elicited using 3 questions 1) The absolute sum a patient would pay to achieve a complete cure (open question). 2) The absolute sum patients would be willing to spend per month for complete healing - in 9 predefined categories. 3) The percentage of the patient's monthly income that they would be willing to pay to obtain a cure.	Patients were willing to pay €1000 (median) for a sustainable healing of their eczema.	This study demonstrated a large number of eczema patients have some limitations in their quality of life, and have moderate to high WTP values.
Francis 2016 [5]	Utiliy	United Kingdom	Children with clinically infected eczema (Aged <8 years)	N=113	12 weeks	-	Parent completed paper-based questionnaire including ADQoL, POEM and EASI.	The trial was prematurely stopped due to poor recruitment.	The evaluation showed encouraging results for the preference based measure (ADQoL) in terms of the construct and face validity.
Schmitt 2008 [62]	Utility	Germany	Adults with eczema (Aged 18 years≤)	N=139 (of which n=62 had eczema)	One off computer assisted interview	-	Utilities measured using WTP, TTO and VAS. Severity of eczema measured using EASI, DLQI.	Using the TTO method utilities were 0.97 for controlled eczema; 0.64 for uncontrolled eczema. Median monthly WTP for an eczema cure was €50 for controlled and €150 for uncontrolled eczema.	This study did not recommend the use of VAS in future economic evaluations.
Simpson	Utility	Canada,	Adults with	N=380	One off	-	SCORAD, POEM, DLQI,	Median EQ-5D VAS	Moderate to severe

Study	Study Overview	Country	Population	Sample Size	Time Horizon	Currency (Price Year)	Methods	Results	Conclusions
2016 [63]		Czech Republic, Germany, Hungary, Japan, Poland, United States	moderate to severe eczema (Aged 18 years≤)		questionnaire		EQ-5D questionnaire and VAS	score was 60.0. The overall health index score was 0.659.	eczema in adults affects quality of life and places a multi-dimensional burden on sufferers. The EQ-5D domain most affected was pain/discomfort.
Stevens 2005 [65]	Utility	United Kingdom	Members of the general population (Aged 18 years≤)	N=150	One off interview	-	Interview respondents were asked to value 10 health states using the standard gamble technique.	Utility values ranged from 0.36 (worst health state) to 0.84 (best health state) - there were 16 health states overall.	This study has estimated utility weights for different eczema health states, which can now be used in economic evaluations to produce QALYs.
Vinding 2014 [64]	Utility	Denmark	Adults with eczema (Aged 20 years≤)	N=439 (of which n=36 had eczema)	One off questionnaire	-	DLQI, Skindex-29, EQ-5D questionnaire and VAS	The EQ-5D domain most affected in eczema patients was pain/discomfort (with 54.3% reporting a 2 or a 3).	This study indicated that patients with eczema had a lower quality of life in comparison to controls.
COST STUDIES									
Beal 2016 [43]	Cost analysis of pre/post establishment of a paediatric dermatology service	United States	Children with moderate to severe eczema (Aged <21 years)	Not stated	1 year prior to the service being established, 3 years after the service was established for 1 year.	US $ (2007)	Emergency department charges, dermatology visits and primary care, measured through electronic medical records.	Total emergency department charges were $142,885 (pre service) and $90,610 (post service setup), a $52,275 decrease.	The paediatric dermatology service reduced emergency department usage.
Bergmo 2009 [39]	Cost analysis of web based consultation software compared to usual care	Norway	Children with moderate to severe eczema (Age range not stated – but population <7 years)	N=98	1 year	Euro (2007)	Household expenses and days off work, parental self-reported.	Only baseline costs were reported, although it was stated no significant differences were found in resource use, family costs or loss of employment.	No effect of the intervention was found.

Study	Study Overview	Country	Population	Sample Size	Time Horizon	Currency (Price Year)	Methods	Results	Conclusions
Boguniewicz 2007 [17]	Cost analysis of topical tacrolimus ointment	Not stated	Moderate to severe eczema patients (Adults (age range not stated), children (aged 5-16 years))	N=40	6 months	US $ (Not stated)	Physician visits and prescription costs. Resource use measured via questionnaires.	Following tacrolimus treatment, out of pocket costs decreased over time, although these reductions were not statistically significant.	This study developed a framework for use in future eczema therapy evaluations.
Chang 2005 [21]	Database cost analysis of pre/post introduction of pimecrolimus	United States	Eczema patients (Age range not stated)	N=80119 (patients identified within the database)	1 year pre, 1 year post	US $ (2003)	Medication and physician visits (resource use measured from claims database)	Before pimecrolimus was introduced, the total cost per member per month was approximately $0.362. After the introduction, total costs increased by $0.002 per member per month (0.7% increase).	The analysis demonstrated that pimecrolimus was responsible for a minimal incremental budget impact.
Delea 2007 [22]	Cost analysis of pimecrolimus, tacrolimus compared to topical corticosteroids	United States	Eczema patients (Aged over 2 years)	N=314 (n=157 with eczema)	12 months	US $ (Not stated)	Costs of eczema related visits and medications, (sourced from health insurance records).	Total eczema related expenditure was not significantly different between groups: $308 for pimecrolimus, $376 for tacrolimus.	Only a small difference in total eczema related costs was observed between pimecrolimus and tacrolimus (less than $100 per year).
Ehlayel 2008 [54]	Cost analysis of oral montelukast compared to placebo	Qatar	Children with moderate to severe eczema (Aged 2-16 years)	N=25 (n=9 montelukast, n=16 placebo)	12 weeks	US $ (Not stated)	Medication use measured over 6 clinic visits, held every 2 weeks.	The average monthly cost per patient was $50.08 for placebo group compared to $49.46 for montelukast group, excluding the cost of montelukast tablets ($68.25 per month).	Montelukast does not have any drug sparing capacities, nor does it reduce treatment costs.
Kernick	Cost analysis	Not stated	Adults with	N=109	4 months	£ (Not stated)	Nurse and GP time,	Limited economic	No significant differences

Study	Study Overview	Country	Population	Sample Size	Time Horizon	Currency (Price Year)	Methods	Results	Conclusions
2000 [41]	of practice nurse consultations compared to routine GP care		eczema (Aged 18-65 years)	(n=59 with eczema, n=5 with eczema and psoriasis)			along with training.	analysis was carried out (costs were only reported in a table).	were found when compared to the control group.
Mason 2013 [45]	Cost analysis of educational support programme compared to usual care	United Kingdom	Children with mild to moderate eczema (Aged 3 months to 6 years)	N=136	12 weeks	£ (2011)	Number of GP visits and concurrent medications recorded in parental diaries, telephone questionnaires	A difference in cost of emollient was found, depending on whether the diary method or 'time-in-use' method was used.	At 12 weeks the educational support programme was cost-neutral.
Ostermann 2015 [60]	Cost analysis of homeopathic care compared to usual care	Germany	Patients with eczema (Age range not stated)	N=44500 (of which n=1488 had a diagnosis of eczema (with a matched control of n=1488))	12 months prior to subscription, 18 months post homeopathy subscription	Euro (Not stated)	Outpatient and inpatient care, medications and productivity losses. Costs were assigned using insurer claims databases.	The homeopathy group had an adjusted mean total cost of €4256.71 compared to €3426.10 in the usual care group.	Patients who used additional homeopathic treatment had significantly higher costs compared to patients who received usual care alone.
Roll 2013 [58]	Cost analysis of homeopathic care compared to usual care	Germany	Children with mild to moderate eczema (Aged 1-14 years)	N=135	36 months	Euro (Not stated)	Resource use measured from patient questionnaires and diaries.	Differences in total costs were found at long-term follow-up: homeopathic group: €216.99, usual care group: €99.93.	Homeopathic treatment had higher costs and was clinically similar to conventional doctors.
Staab 2002 [44]	Cost analysis of structured educational programme compared to waiting list control	Not stated	Children with moderate to severe eczema (Aged 5 months to 12 years)	N=204	1 year	Not stated (Not stated)	Eczema treatments assessed via questionnaire	Cost reduction was greater in the intervention group compared to the control.	The education programme was concluded to be a helpful addition to eczema treatment.
Thaci 2010 [19]	Cost analysis of tacrolimus	Pan-European	Children with mild to	N=267 (n=146 with	12 months	Euro (Not stated)	Out of pocket expenses, productivity loss	For moderate (severe) eczema,	Twice-weekly treatment was found to be superior

Study	Study Overview	Country	Population	Sample Size	Time Horizon	Currency (Price Year)	Methods	Results	Conclusions
	ointment compared to vehicle, twice weekly	(10 countries)	severe eczema (Aged 2-15 years)	resource data)				mean total annual cost per patient was €1233 (€1571) for twice weekly tacrolimus, compared to €1136 (€2002) with vehicle.	to standard treatment and was stated as likely to decrease costs.
FEASIBILITY STUDIES									
Ridd 2016 [50]	Feasibility of collecting resource use associated with 4 different emollients	United Kingdom	Children with eczema (Aged 1 month to 5 years)	N=197	12 weeks	£ (2014)	GP, nurse and hospital visits, medications captured using parent diaries and electronic medical records. Health-related quality of life measured using the ADQoL.	No considerable difference in healthcare costs were found between treatment arms. Annual QALYs were estimated to be 0.799.	This study may inform future studies looking to address the question of which emollient is the most effective and safe in treating eczema.

Abbreviations: ADQoL: Atopic Dermatitis Quality of Life; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; GP: General Practitioner; POEM: Patient Oriented Outcome Measure; QALYs: Quality-Adjusted Life Years; SCORAD: Scoring Atopic Dermatitis; TTO: Time trade off; VAS: Visual Analogue Scale; WTP: Willingness to pay.

Table 2: Cost of Illness study characteristics

Study	Country	Type	Population	Comparator	Sample Size	Time Horizon	Costs included	Resource use data source	Price Year	Currency	Results
COST OF ILLNESS STUDIES IN CHILDREN											
Alanne 2012 [69]	Finland	Prospective	Children who developed allergic disease by the age of 2 years	No atopic disease	N=60 (control: n=56)	24 months	Primary and secondary care visits, private services, examinations, treatment, medications, travel, parental time off work, disability allowances, infant formula.	Insurance databases (National and private insurance companies, health care providers), questionnaire (Paper based, self-completed)	2006	Euro	The median cost in cases of eczema was €275. Median family costs were €0 in healthy cases, and €131 for those with eczema.
Arnold 2007 [77]	United States	Retrospective	Children with eczema (Aged 2-12 years)	N/a	N=414	2 years	Unscheduled medical visits.	Medical record review, case report forms and billing database	Not stated	US $	It was found that as the severity of eczema increased, the likelihood of unscheduled clinic visits also increased.
Emerson 2001 [71]	United Kingdom	Retrospective	Children with eczema (Aged 1-5 years)	N/a	N=1761	12 months	Primary and secondary care visits, prescription costs, family costs associated with changing the home environment, over the counter medications, transport, private consultations, and income loss.	Questionnaire (Single, paper based, self-completed)	1995	£	Total mean disease costs were estimated to be £75.59 per child over the 12-month study period.

Study	Country	Type	Population	Comparator	Sample Size	Time Horizon	Costs included	Resource use data source	Price Year	Currency	Results
Hammer-Helmich 2016 [70]	Denmark	Retrospective	Children with allergic disease (Aged 3, 6, 11, 15 years)	No atopic disease	N=1583 (control: n=9720)	1 year	Primary and secondary care visits, prescribed medications.	Questionnaire (single, paper based, self-reported. Responses were linked to administrative registers – name not given)	2009	Euro	The mean annual cost of those experiencing eczema symptoms was €908 compared to €537 for those who had no atopic disease.
Handa 2015 [72]	India	Prospective	Children with eczema (Aged 0-10 years)	N/a	N=37	6 months	Parental time off work and expenditure on travel, lodging, food, paperwork, investigations, over the counter medications and treatments. Provider costs: hospital services and medications.	Hospital database and questionnaire (2 monthly, paper based, self-completed)	Not stated	Indian Rupees (Rs)	The total cost (caregiver, provider and indirect costs) over 6 months was Rs 6235.
Hughes 2007 [78]	Not stated	Retrospective	Children with eczema (Age range not stated)	N/a	N=80	Not stated	Alternative therapy treatments	Questionnaire (Single, paper based, self-completed)	Not stated	Euro, £	The cost of treatments ranged from €0 to €4000 with an average cost of €321.80.
Lapidus 1993 [73]	United States	Retrospective	Children with eczema (Age range not stated)	N/a	Not stated	6 months	Ambulatory care, emergency department care, inpatient care and pharmaceutical supplies.	Administrative database (National Centre for Health Statistics, National Inpatient Profile)	1990	US $	The annual total treatments costs for eczema was estimated to be $364million.

Study	Country	Type	Population	Comparator	Sample Size	Time Horizon	Costs included	Resource use data source	Price Year	Currency	Results
Misery 2014 [74]	France	Retrospective	Children with eczema (diagnosed in their first year of life)	Children without eczema	N=1163 (control: 1163)	9 years	Primary care visits and prescriptions.	Administrative databases	2012	Euro	The average cost of medications during the first year of follow-up was €140 in the eczema cohort compared to €94 in the controls.
Ngamphaibo on 2012 [68]	Thailand	Model based	Children with eczema (Aged 0-5 years)	N/a	N/a (model based)	1 year	Treatments, inpatient and outpatient care, diagnostic tests and monitoring.	Expert opinion	2010	Thai baht (THB)	Assuming a prevalence rate of 10.1%, the average yearly cost per treated patient was 5432 THB.
Ricci 2006 [75]	Italy	Retrospective	Children with eczema (Aged 1-9 years)	N/a	N=33	12 months	Healthcare consultations, medications, specialist laundry detergent, specialist dietary items, alternative therapies, parental time off work.	Questionnaire (Single, paper based, self-reported)	Not stated	Euro	The average annual family cost was €694, €1172, €1809 for those with mild, moderate and severe eczema respectively.
Su 1997 [79]	Australia	Retrospective	Children with eczema (Aged 4 months to 15 years)	Children with Type 1 diabetes (only for family impact scores, not costing)	N=48 (control: n=46)	3 month	Medication, visits to health professionals, days of hospital admission, parental time off work, time taken to apply treatments.	Questionnaire (Single, paper based, self-completed)	Not stated	AUS $	The annual total cost associated with eczema was $480, 1712, and 2545, for mild, moderate and severe eczema respectively.

Study	Country	Type	Population	Comparator	Sample Size	Time Horizon	Costs included	Resource use data source	Price Year	Currency	Results
Weinmann 2003 [76]	Germany	Retrospective	Children with eczema (Aged 0-8 years)	N/a	N=91	8 years	Inpatient services, physician visits, hospital outpatient services, medications, atopy related diagnostics.	Medical record review	1996	Deutsche Mark (DM), US $	Total costs for eczema per disease year were $219.
COST OF ILLNESS STUDIES IN ADULTS											
Fitton 1985 [80]	United Kingdom	Prospective	Adults with eczema (Aged 16 years and over)	N/a	N=19	Maximum 8 weeks follow-up	Patient prescription charges, travel to appointments, loss of work, self-help items, over the counter medication.	Patient interview, semi-structured questionnaires, patient diary	1979	£	The average cost per patient for eczema was found to be £2.12, over the 8-week follow-up period.
Silverberg 2015 [81]	United States	Retrospective	Adults with eczema (Age range not stated)	N/a	N=27157 (2010) N=34613 (2012)	1 year	Physician visits, emergency department visits, out of pocket costs for healthcare, time off work.	Questionnaire (Single, paper based, self-completed)	2010 and 2012	US $	Adults with eczema paid $37 762 442 054 and $29 341 828 250 in out-of-pocket health care costs in 2010 and 2012, respectively.
COST OF ILLNESS STUDIES (NO AGE RESTRICTION)											
Barbeau 2006 [88]	Canada	Retrospective	People with eczema (Age range not stated)	N/a	N=76	12 months	Medical visits, prescriptions, over the counter medications, household expenses, work absenteeism.	Questionnaire (Single, paper based, self-reported)	Not stated	CAN $	The average annual cost of eczema per patient varied from $282 to $1242 (depending on severity).

Study	Country	Type	Population	Comparator	Sample Size	Time Horizon	Costs included	Resource use data source	Price Year	Currency	Results
Bickers 2004 [82]	United States	Retrospective	People with eczema (Age range not stated)	N/a	Prevalence estimated as 15.2 million	1 year	Inpatient and outpatient visits, prescriptions, over the counter medications, time off work for medical visits, days off work, restricted activity days, caregiver lost workdays.	Claims database (National Centre for Health Statistics was the primary source for disease prevalence and health services use data, Medicare Standard Analytic File for costing information)	2004	US $	Assuming a prevalence of 15.2 million: annual direct costs associated with eczema were estimated to be $1009 million and annual indirect costs due to lost productivity estimated as $619million.
Ellis 2002 [83]	United States	Retrospective	People with eczema (Age range not stated)	No eczema	N=124,795 (Out of 3.2million identified in the database)	1 year	Costs associated with an eczema code (medications and medical visits)	Claims database (Private insurer, Medicaid)	1997	US $	The projected annual cost of illness for eczema is $0.9 billion.
Fivenson 2002 [86]	United States	Retrospective	People with eczema (Age range not stated)	N/a	N=274	12 months	Outpatient and emergency visits, medications, hospitalisations, productivity losses	Claims database (Medicaid, Private insurer), Medical chart review, Questionnaire (Single, paper based, self-reported)	1997	US $	The total annual burden of eczema was $609 per patient.

Study	Country	Type	Population	Comparator	Sample Size	Time Horizon	Costs included	Resource use data source	Price Year	Currency	Results
Fowler 2007 [84]	United States	Retrospective	People with eczema (Age range not stated)	No eczema	N=13,749 (control: 41247) Work loss data only available for n=1616 (control: 3950)	Variable (when they left the health plan or when the study ended)	Direct health care costs paid by the employer (inpatient and outpatient services, outpatient pharmacy prescriptions), time taken off work.	Claims database (name not stated)	2005	US $	The mean incremental cost per eczema patient per month was $88.
Gieler 1999 [89]	Germany	Retrospective	People with eczema (Age range not stated)	N/a	N=148	2 years	Prescription costs of corticosteroids, antihistamines and alternative therapies. Treatments, time taken off work, travel.	Questionnaire (Two, paper based, self-reported)	Not stated	Deutsche Mark (DM)	An annual cost per eczema patient to society was calculated as DM 4827 and the personal cost estimated as DM 468.
Herd 1996 [92]	United Kingdom	Prospective	People with eczema (Age range not stated)	N/a	N=155	2 months	Prescriptions, over the counter medications, primary and secondary care consultations, time off work, specialist expenses such as laundry detergents.	Self-reported (patient diary)	Not stated	£	The mean annual cost to eczema patients was £153 compared to the mean annual cost to the UK NHS of £97 per patient.

Study	Country	Type	Population	Comparator	Sample Size	Time Horizon	Costs included	Resource use data source	Price Year	Currency	Results
Jenner 2004 [91]	Australia	Prospective	People with eczema (Aged 14 years and over)	N/a	N=85	1 year	Specialist items such as soap, shampoo, bedding or clothes. Eczema medications.	Self-reported (Patient diaries)	1999	AUS $	Using only the complete cases (n=45) the average out-of-pocket expense on products was calculated to be $425.30, ranging from $13.50 to $2105.64 for the year.
Kim 2015 [87]	Korea	Prospective	People with eczema (Age range not stated)	N/a	N=32	3 months	Consultation fees, medical tests and procedures, prescription and dispensing fees, sick leave taken or days of work absent by the family or guardians of eczema patients.	Self-reported (Questionnaire and patient diary)	Not stated	Korean won (KRW)	The direct cost of eczema, over 3-months was 541,280 KRW per patient. Thus, the annual direct cost per patient of eczema was found to be 2,646,372 KRW.
Suh 2007 [85]	United States	Retrospective	People with eczema and atopic manifestations (Age range not stated)	People with eczema prior to atopic manifestation	N=5,599 (control: n=5,599)	1-year prior to atopic manifestation, 1-year post.	Hospitalisations, outpatient visits and prescriptions.	Claims database (Marketscan)	2005	US $	The annual cost per patient of eczema was found to be $338 prior to the development of atopic manifestations and $820 after the development.
Verboom 2002 [90]	The Netherlands	Retrospective	People with eczema (Age range not stated)	N/a	N=2809	Mean follow-up 11 months	GP visits, prescription costs and cost of referrals to a dermatologist or laboratory.	Medical record review	1999	US $	The total mean health-care costs per eczema patient was US$71 (mean follow-up was 11 months).

Study	Country	Type	Population	Comparator	Sample Size	Time Horizon	Costs included	Resource use data source	Price Year	Currency	Results
COST OF ILLNESS STUDIES IN CARERS OF CHILDREN WITH ECZEMA											
Filanovsky 2016 [93]	USA	Prospective	Carers of children with eczema (Parents or guardians of children aged 6 months to 12 years)	N/a	N=79	3 years	Medical visit co-payments, hospitalisation charges, prescriptions and over the counter medications, carer time off work and childcare.	Questionnaire (Multiple, paper based, self-reported)	Not stated	US $	The average personal cost of eczema in the month before an office visit, including direct and indirect costs was calculated as $274 per patient ($75 direct costs, $199 indirect costs).

Abbreviations: N/a: not applicable; NHS: National Health Service; UK: United Kingdom.

Table 3: Overview of the Economic Evaluations of interventions for Eczema

Study	Evaluation Type	Intervention	Comparator	Country	Perspective	Population	Time Horizon	Price Year	Outcome measure used in economic analyses	Reported Cost-Effectiveness	
Wollenberg 2008 [20]	CUA	Tacrolimus ointment	Usual care	Multisite (13 European countries)	Third party payer, and Societal	Adults with eczema (16 years≤) with mild to severe eczema	12 months	Not stated	Quality of life (SF-36)	Maintenance with tacrolimus ointment was the dominant strategy.	Dominant
Salo 2004 [56]	CEA	Cyclosporin	UVAB Phototherapy	Finland	Not stated	Patients with severe eczema (mean age 33 years)	12 months	1997	Number of remission days (where SCORAD was 50% at or below baseline score)	The incremental cost-effectiveness ratio was $27 for cyclosporin A in comparison to UVAB. However when total costs were considered, as it was both more effective and less costly an ICER was appropriately not reported.	Dominant (when considering total costs) Cost-effective when considering direct costs
Schuttelaar2011 [40]	CEA	Care by a nurse practitioner (NP)	Usual care by a dermatologist	Not stated	Societal	Children with eczema (≥16 years)	12 months	2008	Disease specific quality of life (IDQOL, CDLQI)	"The costs of care provided by the NPs were lower than care provided by the dermatologists with comparable effectiveness."	Dominant / cost-effective
Os-Medendorp 2012 [42]	CEA	Care package with access to an electronic eczema portal	Usual Care	The Netherlands	Societal	Adults (18 years≤) and Children (0-6) with moderate eczema	12 months	2009	Disease specific quality of life (DLQI)	Both interventions were equally effective; e-health is expected to reduce costs.	Cost-effective / dominant
Green 2005 [52]	CEA	Fluticasone Propionate – twice daily application	Fluticasone Propionate – once daily application	United Kingdom	National Health Service	Patients with eczema (Age range not stated)	Not stated	Not stated	Treatment success (Method of measurement not stated)	"72% success in the once-daily group compared with 84% success in the twice-daily group, p=0.031)" "£38.50 cost per additional successfully treated flare (assuming a total of 4 flares per year)"	Cost-Effective
Poole 2010	CUA	Tacrolimus ointment	0.1% Hydrocortiso	Multisite (12	Not stated	Adults with eczema (18	6 months	Not stated	Quality of life (SF-36)	An ICER of £10458 per QALY was generated for the	Cost-Effective

Study	Evaluation Type	Intervention	Comparator	Country	Perspective	Population	Time Horizon	Price Year	Outcome measure used in economic analyses	Reported Cost-Effectiveness	
[18]			ne ointment	European countries)		years≤) with moderate to severe eczema				tacrolimus ointment.	
Thomas 2017 [13]	CUA	Silk clothing along with standard care	Standard care	United Kingdom	National Health Service (family and employer in secondary analyses)	Children with moderate to severe eczema (aged 1-15 years)	6 months	2014	Quality of Life (ADQoL)	The ICER was £56,811 per QALY in the base case, whereas taking a wider NHS/family/employer perspective the ICER was £61,385 per QALY.	Not cost-effective
Thomas 2011 [14]	CUA	Ion exchange water softener	Usual care	United Kingdom	National Health Service	Children with eczema (aged 6 months to 16 years)	12 weeks	2009	Quality of life (EQ-5D)	Ion-exchange water softeners were dominated by usual care alone.	Dominated
Witt 2009 [59]	CEA	Homeopathy	Usual care	Germany	Societal	Children with mild to moderate eczema (aged 1-14 years)	12 months	Not stated	Severity of eczema (SCORAD)	Homeopathic treatment was not superior to conventional treatment and the costs were higher.	Dominated
Miller 2011 [46]	CEA	Atopiclair, Epiceram	Over the counter Aquaphor healing ointment	United States	Not stated	Children with mild to moderate eczema (aged 2-17 years)	3 weeks	Not stated	Severity of eczema (IGA, EASI)	Atopiclair and epiceram were dominated by Aquaphor.	Dominated

Abbreviations: ADQoL: Atopic Dermatitis Quality of Life; CUA: Cost utility analysis; CEA: Cost Effectiveness Analysis; EASI: Eczema Area and Severity Index; IGA: Investigators Global Assessment; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality adjusted life year; SCORAD: Scoring Atopic Dermatitis; UK: United Kingdom.