REVIEW ARTICLE

BJD
British Journal of Dermatology

Understanding economic evidence for the prevention and treatment of atopic eczema*

T.H. Sach,[1] E. McManus[1] and N.J. Levell[2]

[1]Health Economics Group, Norwich Medical School, University of East Anglia, Norwich, NR4 7TJ, U.K.
[2]Dermatology Department, Norfolk and Norwich University Hospitals NHS Foundation Trust, Colney Lane, Norwich, NR4 7UY, U.K.

Correspondence
Tracey H. Sach.
E-mail: t.sach@uea.ac.uk

Accepted for publication
24 January 2019

Funding sources
This systematic review is independent research arising from T.S's Career Development Fellowship (CDF-2014-07-006) supported by the National Institute for Health Research (NIHR). The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care.

Conflicts of interest
N.J.L. is a trustee and an officer of the British Association of Dermatologists, which owns the British Journal of Dermatology. T.H.S. is an author on several of the papers included in the review, but these were assessed by other members of the research team.

*Plain language summary available online

DOI 10.1111/bjd.17696

Summary

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 National Health Service increase the importance of having good economic evidence to inform their allocation.

Objectives To educate dermatologists about economic methods with reference to currently available economic evidence on eczema.

Methods The role of different types of economic evidence is illustrated by evidence found in a systematic literature search conducted across 12 online databases up to 22 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 Seventy-eight studies (described in 80 papers) were deemed eligible. Thirty-three (42%) were judged to be economic evaluations, 12 (15%) cost analyses, six (8%) utility analyses, 26 (33%) cost-of-illness studies and one a feasibility study (1%). The calcineurin inhibitors tacrolimus and pimecrolimus, as well as barrier creams, had the 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 with that available for clinical outcomes, suggesting that greater collaboration between clinicians and economists might be beneficial.

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.

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 National Health Service (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 its highest incidence in the first year of life (13·8 per 100 person-years; 95% confidence interval 13·7–13·9).[2,3] 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 as asthma and diabetes.[4,5] 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, to date, details > 900 systematic reviews and randomized controlled trials. 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 biological therapies for moderate-to-severe eczema.[8,9]

Materials and 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 of the following databases was undertaken from their inception dates through to 22 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 (stopped 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 (T.H.S, E.M.) 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, as many of the items are irrelevant for partial studies. For three publications where T.H.S. was an author,[12–14] the data extraction and quality assessment were completed by N.J.L. and E.M.

Analysis

The narrative synthesis considered the findings in three ways. Firstly, the studies were categorized 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 categorized into those in which the new intervention was found to be dominant (more effective and less expensive than the comparator), those where a judgement 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) by the comparator. 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 (Thomas *et al.*[12] and Thomas *et al.*[13] reported on the same study, as did Garside *et al.*[15] and Pitt *et al.*[16]). We included the *Health Technology Assessment* monograph for each.[13,15] The number of economic studies being published each year is small and relatively static with between three and eight papers published per year since 2002.

The variety of interventions considered were relatively limited when compared with the 240 intervention groups listed on the GREAT database. Of the studies found within this review, the most commonly evaluated intervention types were topical calcineurin inhibitors (n = 14),[15–28] followed by infant formula feeds intended to prevent eczema from developing (n = 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

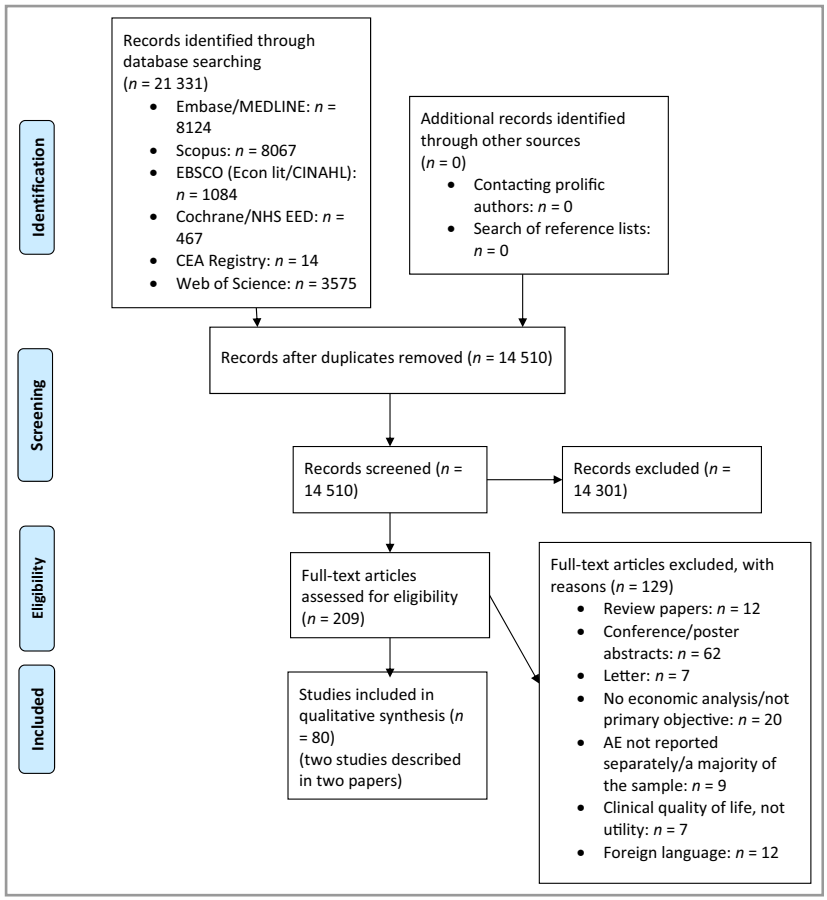

Fig 1. PRISMA flow diagram. NHS, National Health Service; EED, Economic Evaluation Database; CEA, Cost-Effectiveness Analysis; AE, atopic eczema.

provision of an educational DVD and telephone support.[45] Moisturizers 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] ciclosporin A[56] and antibiotics (vs. 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. Fewer than half of the studies undertook full economic evaluations – those studies comparing as in comparing 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.[57,61–65] These studies may help to inform the design of future economic evaluations or to parameterize economic models. Two papers conducted a willingness-to-pay study in Germans with eczema.[61,62] 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.* developed a disease-specific preference-based health measure, Atopic Dermatitis Quality of Life (ADQoL), for economic evaluation of children with eczema.[65] 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 suboptimal 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 ± SD estimates for the 16 health states ranged from 0·36 ± 0·36 for the worst state to 0·84 ± 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.* tested the construct and face validity of the ADQoL completed by parents of children with eczema vs. the clinical measures Patient Oriented Eczema Measure (POEM), Eczema Area and Severity Index (EASI) and Infants' Dermatitis Quality of Life Index (IDQoL).[57,65] This study supported the use of ADQoL but noted that parents of the youngest participants found it harder to complete. Only two studies considered outcome studies in a paediatric population.[57,65] As 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.* looked at the treatment costs of participants but failed to cost the intervention that was being evaluated.[44] Furthermore, Bergmo *et al.* only reported the cost of baseline resource use, not the cost of any subsequent resource use.[39] Kernick *et al.* were also limited in the costs disclosed, stating only a few costs associated with the intervention.[41] While Boguniewicz *et al.* did perform a cost analysis, the study focused more so on the development of a framework for assessing outcomes, intended to inform future research.[17] Four studies completed retrospective cost analyses using administrative databases,[21,22,43,60] and one feasibility study 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.* compared methods used to estimate emollient resource use, contrasting daily diary recording of emollient use to estimates of time taken to use a 500-g container of emollient.[45] However, the method chosen was found to have only a small effect on the estimated cost. See Table S1 (see Supporting Information) 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 (33%) were considered to have conducted a form of cost-of-illness study,[68–93] one of which used a model developed in Excel (Microsoft, Redmond, WA, U.S.A.).[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 patients with eczema.[82–92] Filanovsky *et al.* studied the carers of children with eczema.[93]

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 patients with eczema to those with diabetes.[79] Table S2 (see Supporting Information) provides further details of these studies.

The most recent cost-of-illness figures published in the U.K. were by Herd *et al.* in 1996,[92] based on self-reported data from 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 U.K.

Feasibility study

One feasibility randomized controlled trial was found,[50] which included an economic evaluation component and looked at four different leave-on emollients in those aged < 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. Ten studies were conducted alongside a trial and were from the U.K. (three studies, one reported in two papers) and multiple sites in Europe (n = 2), the Netherlands (n = 2), Finland (n = 1), Germany (n = 1) and the U.S.A. (n = 1).[12–14,18,20,40,42,46,52,56,59]

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 measure the consequences of an intervention in terms of healthy years, which are typically measured as quality-adjusted life-years. This is the most commonly used method to inform resource-allocation decisions within the NHS, as advocated in the National Institute for Health and Care Excellence reference case.[95] The generic outcome measure enables comparisons to be made across disease areas.

Only four cost–utility analyses 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 Short Form (SF) 12 (SF-12), and then a mapping algorithm to predict EuroQoL-5D (EQ-5D) responses,[96] from which the U.K. tariff was used to generate utility values. In comparison, Wollenberg *et al.* also used SF-36 responses but used a mapping algorithm developed by Brazier *et al.*[20,97] Thomas *et al.*[14] used the youth version of the EQ-5D (EQ-5D-Y) for children aged > 3 years, generating utility values using the U.K. tariff derived from an adult population (acknowledged as a potential weakness in the study). Only one study, as described in Thomas *et al.*,[12,13] used the ADQoL.

Cost-effectiveness analyses

Cost-effectiveness analyses value the consequences on an intervention in terms of natural units (e.g. the number of eczema flares prevented). Cost-effectiveness analyses are mainly designed to inform resource-allocation decisions within the same condition. Six studies conducted a cost-effectiveness analysis.[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 SCORing Atopic Dermatitis (SCORAD).[59] By contrast, two studies considered a health-related quality-of-life measure, with Schuttelaar *et al.* using the IDQoL for children aged < 4 years and the Children's Dermatology Life Quality Index for children aged 4–16 years.[40] van Os-Medendorp *et al.* used the IDQoL for children and the Dermatology Life Quality Index for adults.[42]

Modelling studies

Twenty-four 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 cost–utility analyses, nine cost-effectiveness analyses, three both cost–utility analyses and cost-effectiveness analyses, and one both cost minimization analysis and cost-effectiveness analyses. The economic methods used in these studies and their quality are examined elsewhere and so will not be discussed further.[100]

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 to be cost-effective (i.e. 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] Atopiclair and EpiCeram,[46] were dominated (cost more and were less effective than their comparators). It should be noted that such statements lack usefulness without knowing the perspective, time frame, precise detail of the comparator, country of study, etc., for each study. That different economic evaluations of the same intervention can reach different conclusions is illustrated here by tacrolimus ointment. In the study that required a judgement to be made about cost-effectiveness,[18] tacrolimus ointment was compared with hydrocortisone ointment, whereas the economic evaluation finding tacrolimus ointment to be dominant was comparing it with usual care.[20] Therefore, we provide fuller details in Table S3 (see Supporting Information) to aid interpretation of the results.

It is clear from Table S3 that the range of interventions evaluated fully is limited. This inevitably limits the ability of decision-makers to use such evidence to inform their resource-allocation decisions about how to allocate resources. This affects not only allocation to 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 time frame and quality.[100] The evidence in Table S3 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 provide the sole evidence justifying guidance suggesting silk garments should not be routinely prescribed in any circumstance in NHS primary care.[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 (see Supporting Information). 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 (e.g. 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 11 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 whether 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 characterizing 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, five 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.*, Miller *et al.* and Witt *et al.*).[46,52,59]

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 maximize 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 randomized 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 healthcare systems, families and society as a result of eczema. However, the U.K.-relevant estimates are out of date.[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.

As 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 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] No single instrument has been well tested, which exacerbates problems in eczema health economic assessments.

To our 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. While 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 recognize that since the search was undertaken, further relevant economic studies have been published.[118–126] However, our primary aim was to use the available literature to increase understanding about the range of economic methods available as with understanding may come more appropriate use of these methods.

At a time where access to public health services is 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.

Acknowledgments

The following individuals are acknowledged as providing advice as research mentors (Professor Kim Thomas and Professor Nicky Welton) and as part of the annual advisory panel (Dr Tom Kenny, Professor Nick Levell, Fiona McOwan, Jo Parris, Amanda Roberts, Professor Lee Shepstone, Professor Fujian Song and Dr Edward Wilson), and for contributing to data extraction (Miss Amy Dymond) and the search strategy and data extraction (Mr Christopher McMonagle).

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Characteristics of the cost analyses, outcome studies and feasibility study.

Table S2 Cost-of-illness study characteristics.

Table S3 Overview of the economic evaluations of interventions for eczema.

Table S4 Reporting quality assessment of the full economic evaluations according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

Video S1 Author video.