TITLE PAGE

Title

The use of decision-analytic models in Atopic Eczema: A systematic review and critical appraisal.

Running title Decision-analytic models in Atopic Eczema

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Highlights

What is already known about the topic?

There are a large number of published clinical trials evaluating preventative interventions and treatments in eczema, as evidenced in the Global Resource for EczemA Trials (GREAT) database (see http://www.greatdatabase.org.uk). Currently no similar resource or review of the economic evidence of preventative interventions or treatments in eczema exists.

What does the paper add to existing knowledge?

This paper provides a critical appraisal of current economic models evaluating preventions or treatments for eczema.

Only a limited range of eczema interventions have been evaluated using economic decision modelling.

There is scope to improve the quality of economic decision models in the area of eczema.

Conflicts of Interest (http://www.elsevier.com/conflictsofinterest**)**

The authors declare that they have no conflicts of interests.

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Contribution of authors

EM contributed to the design of the study, carried out the searches, screening and data extraction, contributed to interpretation of data, and drafted and critically reviewed the paper. TS contributed to the design of the study, carried out the screening and data extraction, contributed to interpretation of data, and drafted and critically reviewed the paper. NL contributed to the design of the study and critically reviewed the paper.

ABSTRACT

Objective

To identify and assess the quality of published economic decision-analytic models within atopic eczema against best practice guidelines, with the intention of informing future decision-analytic models within this condition.

Methods

A systematic search of the following online databases was performed: 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, EconLit, Scopus, Health Technology Assessment, Cost-Effectiveness Analysis Registry and Web of Science. Papers were eligible for inclusion if they described a decision-analytic model evaluating both the costs and benefits associated with an intervention or prevention for atopic eczema. Data was extracted using a standardised form by two independent reviewers, whilst quality was assessed using the model specific Philips criteria.

Results

24 models were identified, evaluating either preventions (n=12) or interventions (n=12). 14 reported using a Markov modelling approach, 4 utilised decision trees and 1 a discrete event simulation, whilst 5 did not specify the approach. The majority, 22 studies, reported that the intervention was dominant or cost-effective, given the assumptions and analytical perspective taken. Notably the models tended to be short-term (16 used a time horizon of one year or less), often providing little justification for the limited time horizon chosen. The methodological and reporting quality of the studies was generally weak, with only 7 studies fulfilling more than 50% of their applicable Philips criteria.

Conclusions

This is the first systematic review of decision models in eczema. Whilst the majority of models reported favourable outcomes in terms of the cost-effectiveness of the new intervention, the usefulness of these findings for decision making is questionable. In particular, there is considerable scope for increasing the range of interventions evaluated, for improving modelling structures and reporting quality.

Key words

Atopic eczema, decision-analytic model, decision analysis, systematic review, economic evaluation.

Key Points

This paper is the first to identify and critically appraise current economic models evaluating preventions or treatments for eczema.

Only a limited range of eczema interventions have been evaluated using economic decision modelling.

There is scope to improve the quality of economic decision models in the area of eczema.

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Compliance with Ethical Standards

Conflicts of Interest

The authors, EM, TS and NL, declare that they have no conflicts of interests.

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1 INTRODUCTION

Atopic eczema, also known as atopic dermatitis and from herein referred to as eczema, is a chronic disease characterised by dry, red, itchy skin, which sometimes blisters, weeps or crusts [1]. Eczema primarily affects children, with an onset in the first few months of life, although it can also be experienced in adulthood [2]. There is currently no cure for eczema, and thus treatments are twofold: to control the eczema during periods of remission and to treat the eczema when it becomes exacerbated. Individuals with eczema are likely to develop other atopic diseases such as asthma or allergic rhinitis, for example, it is estimated that 30% with eczema develop asthma, and 35% develop allergic rhinitis [3].

Alongside the physical symptoms, sufferers may also experience emotional stress, depression or sleep deprivation; resulting in a diminished quality of life [4]. In the United Kingdom, the lifetime prevalence of eczema is estimated to be between 12.5 and 20% [5, 6]. The annual personal cost for the UK population suffering with eczema, including the costs of purchasing over-the-counter preparations, special clothing or laundry detergents, as well as salary losses, has been estimated as £297m (price year not stated) [7]. In comparison, the annual cost to the National Health Service is estimated to be £125m (price year not stated) [7]. These estimates, paired with the reduced quality of life of sufferers, indicate the importance of economic decision making in this area.

There are currently no published reviews of decision-analytic models pertaining to eczema. Therefore, this study aims to systematically identify and review such models, comparing their results and evaluating their strengths and limitations relative to the Philips criteria [8], using the three broad categories of ‘data’, ‘structure’, and ‘uncertainty and consistency’. In doing so, this study will act as a resource for decision makers and interested clinicians, signposting to existing models. It may also inform the development of future decision-analytic models within eczema, which may utilise any strengths and improve upon any weaknesses identified within this review.

2 METHODS

The methods used within this systematic review, have been developed and reported according to the suggested methods in “Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015” [9].

2.1 Literature search

A systematic search was conducted of the following electronic databases, from database inception 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, EconLit, Scopus, Health Technology Assessment, Cost-Effectiveness Analysis Registry and Web of Science. The complete protocol and search strategy is published elsewhere [10], although key search terms included: “eczema,” “dermatitis,” “cost,” “QALY” and “econ*”. In addition to the electronic search, the reference lists of review papers and eligible studies were inspected, and the authors of any relevant conference abstracts were, where possible, contacted. No restriction was made on the publication language within the electronic search.

2.2 Eligibility Criteria

As the electronic search strategy was used as part of a wider body of work [10], it was designed to identify papers reporting primary data on cost and/or outcome (utility or willingness to pay) data on eczema. Thus, this systematic review reflects a subset of the results, with the additional eligibility criteria that a full economic evaluation be conducted using a decision-analytic modelling approach. In this instance, we defined a decision-analytic model to be a mathematical framework that uses data from multiple sources to evaluate the long-term costs and benefits of an intervention and its comparators, with the aim of informing decision-making [11, 12]. Despite the search strategy not being restricted by publication language, only papers in English were considered within the review.

2.3 Study Selection

Study selection occurred in two stages and was performed by two independent reviewers. Initially, the titles and abstracts of the search results were screened. Following this, the full papers of the potentially eligible abstracts were accessed and reviewed, to determine inclusion within the review. Where disagreement occurred, a third reviewer was used.

A flow diagram of the systematic literature search and study selection can be found in **Figure 1**.

2.4 Data Extraction

Data extraction was carried out with the aim of capturing the main results and identifying key points about the decision-analytic model, these included, but were not limited to: type of model used, population studied, intervention evaluated, time horizon, and source of clinical and cost data.

Data was extracted using a standardised form, by two independent reviewers and where disagreement occurred, resolution was sought through reviewer discussion. Where any clinical questions arose, these were discussed with a consultant dermatologist. Reporting quality was assessed using the detailed decision-analytic model specific, Philips Criteria [8]. This criteria is commonly used to assess model quality in the existing literature [13-15], and so was deemed the most appropriate to be used within this review.

The data extraction and quality assessment forms can be found in Supplementary Material 1.

3. RESULTS

Results are presented using a narrative approach, as it was not appropriate to synthesise the findings, due to the heterogeneity of populations, interventions and comparators considered.

3.1 Description of included models

A total of 24 models, published between 1997 and 2016, were identified, the general characteristics of which are detailed in Table 1. To facilitate comparison, studies are grouped into those evaluating preventions and interventions and where possible the same intervention. Also reported are the cost-effectiveness results using the original price year and currency, as well as an inflated result for a common price year (2016) and currency (UK£sterling) using a web-based tool [16]. Where the price year was not stated it was assumed, for the purposes of this estimate, to be the year of publication. Notably, some of the studies used the same decision model structure [17-20], [21, 22], [23-26] to conduct analyses for different countries, whilst the same model was discussed in a HTA monograph and within a journal article, albeit narrower in scope [27, 28].

Overall, it was judged that nine studies conducted cost-effectiveness analyses [17, 18, 20-23, 29-31], 11 conducted cost-utility analyses [27, 28, 32-40], three conducted both cost-effectiveness and cost-utility analyses [24-26], and one carried out a cost-minimisation and cost-effectiveness analysis [19].

An equal number of studies evaluated preventions and treatments. Of those evaluating preventions for eczema, nine [17-20, 23-26, 31], evaluated partially hydrolysed formula milk, given to at risk

infants, where ‘at risk’ was defined as having first degree atopic heredity. The comparator for all but one of these studies was standard cows’ milk formula, with one study [19], comparing with extensively hydrolysed formula milk instead. The remaining three papers considered a mixture of prebiotics [37], oral application of bacterial lysate [30] and various prophylactic moisturisers, which included sunflower seed oil [40]. In comparison, studies of eczema treatments evaluated a wider range of interventions. Four evaluated tacrolimus ointment [21, 22, 34, 36], three considered pimecrolimus ointment [27, 32, 33], whilst Garside et al. [28] evaluated both tacrolimus and pimecrolimus. Three studies evaluated emollient or barrier preparations [35, 38, 39]. Finally, one Spanish study evaluated a topical corticosteroid preparation [29]. Notably no modelling studies were found evaluating a broader range of interventions (e.g. education programmes, psychological therapy, or different service configurations) beyond medications and formula milk.

Due to the large number of studies evaluating hydrolysed infant formulas, the most common population considered in 12 studies [17-20, 23-26, 30, 31, 37, 40] was infants at risk of developing eczema. A further four papers [27, 28, 32, 34] considered subjects of all ages, four [21, 29, 36, 39] considered “patients” with eczema without stating the age range, two studies [33, 38], considered paediatric patients and two studies [22, 35], looked solely at adults.

The most common decision-analytic approach was a Markov modelling process, used in 14 studies [21-28, 32, 33, 35-38]. Within these, the cycle length ranged from one week [25] to one year [37], whilst four studies [21, 26, 32, 33] did not specify the cycle length used. A decision-tree was used in four studies [29-31, 40], and only one study was found to use a discrete event simulation model [39]. Five papers [17-20, 34], did not explicitly state the methodology used, referring to a “decision-analytic model,” although it could be inferred that a Markov modelling approach was used. The majority of studies, 14 [17-22, 27, 28, 33-36, 38, 39], used a time horizon spanning a year, and most were reportedly conducted using a societal [23, 25, 26, 29, 35, 38, 39] or third party payer [21, 22, 27, 28, 33, 34, 36, 37] perspective. Other studies report taking multiple perspectives, for example, two studies conducted analysis from both third party and societal perspectives [31, 32] and four studies considered three different perspectives, the ministry of health, the subject’s family and a societal perspective (which combined the two former perspectives) [17-20]. Kiencke et al. failed to report the perspective used [30] and Bhanegaonkar et al. reported to use the perspective of “urban populations” [24] within their analyses.

It was found that 22 studies reported that the intervention was dominant or cost-effective, given the assumptions made and the analytical perspective taken. Only two papers [22, 27], found that the intervention evaluated was not cost-effective, evaluating tacrolimus and pimecrolimus in comparison to topical corticosteroids respectively. Reported incremental cost-effectiveness ranged from $353 [40] (equivalent to £246.39 in 2016 prices) per QALY gained, comparing petrolatum cream to usual care which in this case was seemingly no treatment, to $40,000 [32] (equivalent to £34,728.01 in 2016 prices, assuming a price year of 2004) per QALY gained, comparing pimecrolimus ointment to usual therapy. A total of seven (29%) studies [17-20, 23-25], were either partially or fully funded, by the manufacturer of the evaluated product.

[INSERT TABLE 1]

3.2 Quality Assessment

The Philips Criteria [8] consists of 56 items intended to assess the reporting quality of decision models across three broad categories: ‘structure’, ‘data’ and ‘uncertainty and consistency’. In this review, each item was answered using “yes”, “no”, “partial” or “not applicable”. A response of “yes” indicated the question was appropriately answered, “no” indicated it was not answered or not enough detail was given, “partial” was used when only some elements of the criteria were satisfied. When an item was not relevant to the model, “not applicable” was used. Supplementary Material 2 shows the responses given for each of the studies. These broad categories and the item responses, form the basis of the following discussion.

3.2.1 Structure

It is important when constructing a model to decide which modelling approach to use, as different model types are best used in different circumstances [41]. However, a number of papers omitted justification for the modelling approach selected and only five papers [22, 25, 27, 28, 37] gave full or partial justification regarding the model structure. Of these, Ellis et al. [22] provided a comprehensive justification for using a Markov model, stating that “it is able to represent more accurately the cyclic, recursive nature of AD. Markov models simulate how patients might experience periods of remission and recurrence, and treatment and response,” whilst also citing other published papers that used this

modelling approach within other dermatological conditions. Only four papers explicitly discussed the implications of using alternative modelling structures [22, 27, 28, 37]. Overall, the selected modelling approaches were relatively similar, with the majority of studies using a Markov cohort approach, and fewer using decision tree analysis. Interestingly, no studies used a whole disease modelling process [42]. Only one study used a discrete event simulation [39], although this was rudimentary, having only two health states, eczema and eczema-free, and using data from a single randomised controlled trial. The lack of more complex modelling methods, may indicate that a Markov approach is sufficient for modelling eczema, without the need for incorporating individual level interaction. Alternatively, it could reflect an absence of appropriate data to inform a more complex model, as suggested by Pitt et al., "An alternative modelling approach, such as discrete event simulation which could do justice to the conditional aspects of treatment might be preferred if such treatment pathway data for eczema were available" [27]. In comparison to other similar dermatological conditions, such as psoriasis, there are a similarly limited number of modelling approaches used. Findings from a recent systematic review within psoriasis found only decision trees and Markov models used [43].

To evaluate the appropriateness of the modelling approach, the decision problem and objective of the evaluation should be described, which was clearly outlined by all but three [29, 39, 40] of the papers. In line with the stated objectives, for the majority of papers the costs and outcomes measured were also consistent with the perspectives taken. Where a third party perspective was used, primarily the costs included were limited to the intervention and wider healthcare costs. By comparison, for studies taking a societal perspective, the range of costs included was more varied. Most common was the expected productivity losses associated with time off work, or time required to look after children, with this cost included in 14 studies [17-20, 23-26, 29, 31, 32, 35, 38, 39]. Less frequently included were the transportation costs associated with visiting a physician, included in only six studies [17-20, 23, 24], as well as the costs of over the counter medications [31, 32], childcare costs [20] and the time taken to apply emollients [20]. Of the papers that took a societal perspective, Mertens et al. [31] took the most comprehensive view of costs, taking into account productivity losses, the cost of additional household expenses such as bed encasings and special diet, as well as any homeopathic treatments and over the counter medications required.

Only one of the studies was thought to have used an inappropriate modelling approach [37], using the following four health states: no eczema, eczema, no asthma, asthma, and stating them as "mutually

exclusive." These states are not mutually exclusive and therefore one of the requirements of a Markov model is violated [44]. A further nine studies [17-19, 29-32, 34, 40] provided insufficient detail to decide if the modelling approach was appropriate. Two studies, using decision trees, [30, 31] had relatively long time scales: three and six years respectively, despite decision trees being recommended to consider short term events [11].

In models using a Markov process, the structure usually centred on progression through different treatment states, [17-28]. Alternatively, eight studies used disease severity states [32-39]. Of these, three studies, [32, 33, 38], used the Investigator's Global Assessment (IGA) score for eczema [45]. The Harmonising Outcome Measures for Eczema (HOME) initiative [46], recommends using Eczema Area and Severity Index (EASI) for clinician-reported signs of disease severity, to facilitate comparison between trials. Within the review, only two papers referred to the EASI. Abramovits et al. [21] calculated percentage improvement using EASI scores at baseline and post treatment defining a disease controlled day as >67% improvement, whilst Garside et al. [28] reported changes in EASI score within their effectiveness data.

Given these different approaches, the strengths and weaknesses of using either treatment or disease severity states should be considered, however this evaluation was not found in the current literature. We consider that the use of treatment states would facilitate understanding by end users of the evaluation process, as the different treatment pathways are clearly displayed. It may also be easier to evaluate different pathways using this structure, for example in comparing the introduction of a therapy as first-line or second-line treatment, which within a severity state model would be harder to achieve. However, as disease severity is not included within treatment states, individuals within the same state are assumed to have the same utility and associated costs, despite potentially having different eczema severities, unless an adjunct is used. Pitt et al. [27, 28], proposed a model within which treatment states are used along with a severity matrix for each state, which states the percentage suffering with mild, moderate and severe eczema, allowing for different utilities to be assigned accordingly.

Weinstein et al. [47] suggested that the time horizon for analysis should capture all important benefits and consequences. Whilst, eczema is not life limiting, patients can experience periods of remission, or may develop the condition for the first time in adulthood [2]. Therefore, whilst a lifelong time horizon

may not be necessary, characteristics of the condition indicate the need for an extended time period to be modelled. Moreover, the rationale of using a modelling approach is often to go beyond the limited time horizons of clinical trials [47]. Therefore, it is surprising that the majority of studies found within this review used only a one year time horizon [17-22, 27, 28, 33-36, 38, 39], particularly when considering adults: for example, “A shorter time horizon of 1 year was modelled; this duration was sufficient to capture the cyclical response and relapse characteristics of eczema,” [27]. In comparison, for paediatric populations, the shortest time horizon considered was six months (notably this was a decision tree) [40] ranging to 16 years [37], with the majority using a time horizon of six years [23-26, 30, 31].

Of the models where it was applicable, very few papers adequately defined and justified the cycle length chosen [27, 36, 38]. More commonly, the cycle length was stated but not justified, with this occurring within 10 of the studies [17-20, 23-25, 28, 35, 37]. For the six remaining, the cycle length used was either unclear or not explicitly stated, thus reducing the overall transparency of the models. For example, a cycle length of one year was used by Lenoir-Wijnkoop et al. [37] evaluating a preventative infant formula, with no justification. Given that the cycle length of any model should reflect the “minimum interval over which pathology and symptoms is expected to alter,” [8] this is a weakness of the current literature. For the majority of models it was not applicable to apply a half-cycle correction, given the short cycle lengths chosen [48]. However where it was applicable, very few papers discussed using a half-cycle correction or provided justification for why it had not been used. Ellis et al. did report using a half cycle correction although the exact cycle length used was not explicitly stated [33], whilst Pitt et al. provided justification for not performing a half cycle correction [27].

3.2.2 Data

Data sources were consistently underreported, particularly when describing how data was identified, which in 13 papers [21-26, 30, 31, 33, 35, 36, 38, 39], was not discussed. Moreover, the quality of the data was not assessed in 16 of the papers [20, 21, 23-27, 29, 30, 32, 33, 35-38, 40]. It was also found that of the papers which utilised the same model structure for evaluations in different countries [17-20], [21, 22], [23-26], very few adaptations were made in terms of the data inputs or model structure. Largely,

the only change that was made was to the unit cost sources and currency used, with the clinical data inputs remaining unchanged.

In addition to identified data, a large majority of studies used expert opinion to inform some aspect of the decision-analytic model, with only five papers reporting no reliance on expert opinion [30, 33, 36, 39, 40]. Whilst it is not detrimental to use expert opinion, according to the hierarchy of evidence, as outlined by Cooper et al. [49], it is advised that other data sources are consulted before resorting to expert opinion. However, by not stating how data were identified, it is unclear whether other sources, higher in the hierarchy, were overlooked or if there were simply no other data sources available.

Of the papers that did use expert opinion to inform parameters, the level of detail as to how opinion was elicited was minimal, going against the reporting advice proposed by Leal et al. [50]. In some studies, the members of the clinical expert panel were not described, making it difficult to assess whether appropriate experts were used, or if their opinions were valid within the population group being studied. To demonstrate, Tang et al. [38] considered 12 different countries and relied heavily on expert opinion to inform transition probabilities as well as resource use, however, failed to list the members of the expert panel and their expertise. Particularly when considering such a wide geographical area, it is especially important to provide detail of who the expert panel was, to enhance the transparency of assumptions made and to allow judgement of their validity. Three studies provided details on the experts used and the methods employed to elicit expert opinion, perhaps due to the sizable reliance on expert opinion within the developed models [17-19], although they did not appear to follow formal elicitation methods [51]. The most common uses of expert opinion in the studies were to inform treatment pathways, approaches and discontinuation rates, as well as estimating levels of resource use across different eczema severity levels.

There were 10 papers [23-25, 30, 31, 33, 34, 36, 39, 40], that used only one source of clinical data for treatment effects, only one of which provided justification, stating that only one trial was found in their literature search [33]. Of the papers that used more than one source of data, the method of data synthesis was consistently underreported, with six papers [26, 27, 32, 35, 37, 38], providing little to no detail. In comparison, six studies used a meta-analysis to synthesise treatment effects [17-20, 22, 29], ranked as the best source for eliciting clinical effects [49]. Whilst two, [21, 28], were clear in providing the calculations and data sources used.

Of the 14 studies that conducted a cost-utility analysis, and thus included quality of life as an outcome measure, all but one, [34], which utilised unpublished data, provided references to the source of the utility weights. One study [40], assumed the same utility values across all of the evaluated moisturisers, effectively making the inclusion of utilities redundant. Two studies were also judged to have included inappropriate utilities. Coyle & Barbeau [32], considered both an adult and paediatric population, however sourced utilities based solely on a paediatric study, without discussing whether this was appropriate for an adult population. Similarly, Lenoir-Wijnkoop et al. [37], considered a paediatric population, but sourced utilities from a study by Poole et al. [52] which estimated health related utilities with the EQ-5D, by mapping responses from adults, using the SF-12. Using adult utilities amongst a paediatric population was justified by the authors, stating "there is no evidence that utilities for children may be different from those for adults", but neither does there appear to be any evidence to support the use of adult utilities amongst a paediatric population. Despite the other modelling studies using appropriate utilities, the method for deriving the utility weights was consistently underreported, and it was often necessary to consult referenced papers. Thus, this is one of the areas that future researchers could improve in the reporting of their models. One paper that did report this well, by Hjalte et al. [35], considered the base case utilities achieved by a Visual Analogue Scale (VAS) and used two different methods of derivation, time trade off and standard gamble, within sensitivity analyses. Half of the utility studies referenced in some way to Stevens et al. [53]. This study involved 150 members of the general population valuing 10 out of 16 possible health states using the standard gamble technique, a disease-specific preference based instrument later referred to as the ADQoL (Atopic Dermatitis Quality of Life) [54]. Interestingly, these utility values have not yet been validated alongside a trial with another validated health related quality of life instrument.

3.2.3 Uncertainty and Consistency

One of the main incentives for modelling, is the ability to analyse the uncertainty surrounding a result [47]. Thus, it is suggested that sensitivity analysis is performed not only to assess the uncertainty in parameters used, but also for the methodological, structural and heterogeneity components [8].

All papers considered some form of uncertainty within their model, however none appeared to address all of the types of uncertainty identified above. Most consistently omitted was the assessment of both methodological and structural uncertainties.

Assessment of parameter uncertainty was generally well completed, with the majority of papers performing at least a one-way sensitivity analysis. Moreover, 11 papers [17-20, 23-28, 34], reported performing probabilistic sensitivity analysis (PSA), arguably the most appropriate way to assess parameter uncertainty [55]. However, within these, the distributions used were often not justified, without which the usefulness of the analysis was reduced. Only seven papers [21, 29-31, 36, 37, 39], were judged to have not assessed parameter uncertainty appropriately. This was primarily due to not performing sensitivity analyses on all parameters and also not reporting the ranges used.

Uncertainty associated with heterogeneity, was only assessed within four papers [27, 28, 34, 36], which primarily involved looking at the results of the model according to different severities of eczema, as well as differences according to subgroups of the population.

When reporting the internal consistency of models, no study reported testing the mathematical logic of the model before use, as recommended by ISPOR [47]. The process of internal validation is key to enhancing the trustworthiness of results and ensuring the model is fit for purpose [56]. Similarly, between-model validation was only discussed in three papers [25, 26, 39]. For example, Bhanegaonkar et al. [25], who presented contradictory results produced from the model and discussed why they may have arisen. There was also only one paper by Garside et al. [28] who reported calibrating their model against independent data. Other models, stated comparisons were not made due to the model being the first of its kind to assess the certain intervention [18, 19], and others [22-24, 31, 34], did compare some of the model outputs against existing literature, however not decision-analytic models. The remaining 13 studies [17, 20, 21, 27, 29, 30, 32, 33, 35-38, 40] did not compare results or offer justification for why this did not occur.

4 DISCUSSION

This review has demonstrated the variety of modelling approaches used within eczema, the majority being Markov models. Largely, it was found that the rationale for using a modelling approach as opposed to any other method of economic evaluation was not well explored, especially given the limited time horizon used within many of the studies. Nor was justification for the modelling approach selected routinely outlined. As well as this, the associated advantages and disadvantages of using either treatment or disease states were not commonly discussed, despite having important implications in the modelling process. The treatment state models have the advantage of being more

transparent, in that it is easy to see how a patient can progress through the model, however, with the development of new treatments and guidelines, it is likely that these models may quickly become outdated. Alternatively, in using disease states, it is unlikely that the disease process will drastically alter, however, it may be more difficult for the reader to grasp how the interventions being modelled affect the transitions, and thus to appreciate the inner workings of the model. This systematic review is believed to be the first to review decision-analytic models within eczema. A sizeable number of models were identified, comparable to the number found in other reviews in different disease areas, for example 18 in Parkinson's disease [57] and 16 in lower extremity artery disease [58], indicating that eczema is certainly not an under researched condition. However, the literature is small in contrast to the number of clinical trials available within eczema [59] and the range of interventions evaluated, limited in contrast.

Future modelling studies should consider using routinely collected clinical data to inform parameters instead of relying on expert opinion alone. Where this is not feasible, it is important to provide sufficient detail on the methods of eliciting expert opinion, including who the experts are and how their opinion was elicited. The time horizon of future models should be extended and an effort should be made to evaluate a greater range of eczema interventions. There is also no common modelling approach currently being implemented, nor is there consensus on the best methodological approaches to take. Therefore, there is scope for future research to develop a consensus approach, where assumptions and modelling approaches are agreed upon by interested clinicians and expert modellers. This has in fact been carried out in other disease areas, such as Rheumatoid Arthritis, with the objective to "assist model development and review to inform future policy decisions" [60]. Having now identified all published models within eczema, a similar initiative could be implemented.

Whilst every effort was made to conduct this review in a systematic manner and according to published guidelines [9], it is acknowledged that there are some limitations. For example, the search strategy only covered published research articles and therefore it is possible that some guidance or policy documents relevant to this review, may have been missed. As well as this, despite having two reviewers independently extracting data, when assessing the quality of the reporting, the decision as to whether criteria were satisfied was subject to individual interpretation of checklist items and the relative importance placed on each aspect within it. It is also acknowledged that due to strict journal word limits, it is often difficult for authors to include all relevant details of their modelling approach.

However, with the increased ability to publish supplementary material, it is likely that in the future this difficulty will be reduced.

The Philips criteria [8] is frequently now used as the standard for assessing model reporting, but it was not developed to be used as a checklist and was written with a focus on cumulating all available evidence on reporting criteria. Several of the studies in this review were published before the Philips criteria [21, 22, 29], thus it may be unfair to assess them based on current standards, given that modelling techniques have developed substantially since the original manuscripts were published. The Philips criteria have 56 assessment items, so the task of synthesising these for the included studies was challenging, meaning only a subset of items have been reported, although the detailed assessments can be viewed in Supplementary Material 2.

5 CONCLUSION

This review indicates that there are currently no models that satisfy the majority of points within the Philips criteria, showing there is scope for improvement. As a result of this review, it can be seen that any future model should consider a longer time horizon for both adults and children, in order to ensure that all relevant costs and benefits have been considered.

Data Availability Statement

The search strategy used to conduct the systematic literature search is published elsewhere [10]. The unpopulated data extraction form used within this review, as well as the quality assessment form based on the Philips Criteria can be found in Supplementary Material 1. The completed data extraction table for all of the studies included within this review can be found in Supplementary Material 2.

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Table

Table 1: Characteristics of included studies.

Authors, year	Study type	Intervention / Comparator	Population / Country	Perspective / Price Year	Analytic Approach (Time horizon/cycle length)	Primary outcome measure	Sensitivity Analysis	Incremental Cost-Effectiveness results	Cost-Effectiveness adjusted for Price Year (2016) and Currency (£)
STUDIES FOCUSING ON PREVENTION									
Bhanegaonkar et al. 2015 [23]	CEA	Partially hydrolysed formula – whey / cow's milk formula	High risk infants / United States	Societal / 2013	Markov (6 years / 2 weeks)	Reduction in eczema risk	One way and probabilistic	Partially hydrolysed formula was dominant compared to cow's milk formula.	Not applicable
Bhanegaonkar et al. 2015 [24]	CEA/ CUA	Partially hydrolysed formula – whey / cow's milk formula	High risk infants / Malaysia	"Urban populations" / 2013	Markov (6 years / 2 weeks)	Reduction in eczema risk, QALY (standard gamble)	One way and probabilistic	Partially hydrolysed formula was dominant compared to cow's milk formula.	Not applicable
Bhanegaonkar et al. 2014 [25]	CEA/ CUA	Partially hydrolysed formula – whey / cow's milk formula	High risk infants / The Philippines	Societal / 2013	Markov (6 years / 1 week)	Reduction in eczema risk, QALY (standard gamble)	One way, scenario and probabilistic	Partially hydrolysed formula was dominant compared to cow's milk formula.	Not applicable
Botteman & Detzel, 2015 [26]	CEA/ CUA	Partially hydrolysed formula – whey / cow's milk formula	High risk infants / Singapore	Societal / 2013	Markov (6 years / not stated)	Reduction in eczema risk, QALY (standard gamble)	One way, scenario and probabilistic	Partially hydrolysed formula was dominant compared to cow's milk formula.	Not applicable
Iskedjian et al. 2012 [19]	CMA/CEA	Partially hydrolysed formula - whey / Extensively hydrolysed formula (EHF-Whey or Casein)	High risk infants / Denmark	Danish Ministry of Health, Family of the child, Societal / not stated	"Decision-analytic model" (12 months / 3 months)	Avoided cases of eczema	One way and probabilistic	Partially hydrolysed whey based formula was found to dominate extensively hydrolysed formula from all 3 perspectives.	Not applicable

Authors, year	Study type	Intervention / Comparator	Population / Country	Perspective / Price Year	Analytic Approach (Time horizon/cycle length)	Primary outcome measure	Sensitivity Analysis	Incremental Cost-Effectiveness results	Cost-Effectiveness adjusted for Price Year (2016) and Currency (£)
Mertens et al. 2012 [31]	CEA	Hydrolysed formula (partially hydrolysed whey, extensively hydrolysed whey and extensively hydrolysed casein) / cow's milk formula	High risk infants / Germany	German statutory health insurance, Societal / not stated	Decision Tree (6 years)	Avoided cases of eczema	One way	All 3 hydrolysed formulas were found to be dominant from a societal perspective, in comparison to regular cow's milk.	Not applicable
Iskedjian et al. 2012 [17]	CEA	Partially hydrolysed formula – whey / cow's milk formula	High risk infants / Switzerland	Swiss Ministry of Health, Family of the child, Societal / not stated	"Decision-analytic model" (12 months / 3 months)	Avoided cases of eczema	One way and probabilistic	Incremental cost per avoided case of eczema was: €982 (Ministry of health perspective). From the family and societal perspective, partially hydrolysed whey formula dominated standard cow's milk formula.	£511.39 per avoided case of eczema. [Assumed price year of 2012]
Iskedjian et al. 2010 [18]	CEA	Partially hydrolysed formula – whey / cow's milk formula	High risk infants / France	French Ministry of Health, Family of the child, Societal / not stated	"Decision-analytic model" (12 months / 3 months)	Avoided cases of eczema	One way and probabilistic	Incremental cost per avoided case of eczema was: €1342 from Ministry of health perspective and €719 from societal perspective. From a family perspective, partially hydrolysed whey formula was found to dominate standard cow's milk formula.	Incremental cost per avoided case of eczema was: £1201.03 (Ministry of health perspective) and £643.47 (Societal perspective) [Assumed price year of 2010]

Authors, year	Study type	Intervention / Comparator	Population / Country	Perspective / Price Year	Analytic Approach (Time horizon/cycle length)	Primary outcome measure	Sensitivity Analysis	Incremental Cost-Effectiveness results	Cost-Effectiveness adjusted for Price Year (2016) and Currency (£)
Su et al. 2012 [20]	CEA	Partially hydrolysed formula - whey / cow's milk formula	High risk infants / Australia	Australian Public Health Care, Family of the child, Societal / not stated	"Decision-analytic model" (12 months / 6 months)	Avoided cases of eczema	One way and probabilistic	ICERs reported were: AU$496 per case avoided (public health care perspective), AU$1243 per case avoided (societal perspective). From a family perspective, the partially hydrolysed whey formula dominated standard cow's milk formula.	Incremental cost per avoided case of eczema was: £246.37 (Public health care perspective) and £617.41 (Societal perspective) [Assumed price year of 2012]
Lenoir-Wijnkoop et al. 2012 [37]	CUA	Prebiotics infant formula / No prebiotics	High risk infants / The Netherlands	"Health insurance" / 2009	Markov (16 years, 1 year)	QALY (Unclear)	Not clear	Reported ICER of €472 per QALY gained.	£429.13 per QALY gained.
Kiencke et al. 2013 [30]	CEA	Prophylactic treatment with sterile bacterial lysate / placebo	High risk infants / Germany	Not stated / not stated	Decision Tree (3 years)	Avoided cases of eczema	One way	Bacterial lysate was found to dominate the placebo.	Not applicable
Xu et al. 2016 [40]	CUA	5 Prophylactic Moisturisers and sun flower seed oil / "Usual Care"	High risk infants /United States	Not stated / 2016	Decision Tree (6 months)	QALY (Standard gamble)	One way	Cost effectiveness ranged from $353/QALY (Petrolatum) to $8386/QALY (Vaniply ointment)	£246.39/QALY (Petrolatum) to £5853.43/QALY (Vaniply ointment)

Authors, year	Study type	Intervention / Comparator	Population / Country	Perspective / Price Year	Analytic Approach (Time horizon/cycle length)	Primary outcome measure	Sensitivity Analysis	Incremental Cost-Effectiveness results	Cost-Effectiveness adjusted for Price Year (2016) and Currency (£)
STUDIES FOCUSING ON INTERVENTION									
Healy et al. 2011 [34]	CUA	Tacrolimus maintenance regime / reactive tacrolimus treatment	Adults and children / United Kingdom	U.K. National Health Service / not stated	"Decision-analytic model" (1 year / not stated)	QALY (Standard gamble for children, unpublished data for adults)	One way and probabilistic	Tacrolimus maintenance treatment was dominant compared to tacrolimus reactive treatment.	Not applicable
Abramovits et al. 2003 [21]	CEA	Tacrolimus / pimecrolimus	Eczema patients / Country not stated	Third party payer / 2002	Markov (52 weeks / not stated)	Disease controlled days (DCD)	One way	Average cost effectiveness ratio for tacrolimus was $7.34 per DCD, $11.34 per DCD for pimecrolimus.	£6.68 per DCD, £10.32 per DCD for pimecrolimus.
Hjelmgren et al. 2007 [36]	CUA	Tacrolimus / Standard treatment (Emollients and topical corticosteroids)	Adults / Sweden	Swedish healthcare sector / 2004	Markov (1 year / 3 weeks)	QALY (Visual Analogue Scale)	One way	ICERs reported of £12300 (severe eczema) and £8300 (moderate eczema) per QALY gained using tacrolimus ointment compared to standard treatment.	£15896.53 for patients with severe eczema, and £10726.93 for patients with moderate eczema, per QALY gained.
Ellis et al. 2003 [22]	CEA	Tacrolimus /High-potency topical corticosteroids	Adults / Country not stated	Third party payer / not stated	Markov (1 year / 2 weeks)	Disease controlled days (DCD)	One way	Average cost effectiveness ratio (instead of incremental). 4 week high-potency topical corticosteroids	Not applicable

Authors, year	Study type	Intervention / Comparator	Population / Country	Perspective / Price Year	Analytic Approach (Time horizon/cycle length)	Primary outcome measure	Sensitivity Analysis	Incremental Cost-Effectiveness results	Cost-Effectiveness adjusted for Price Year (2016) and Currency (£)
								dominated tacrolimus, whereas tacrolimus dominated 2 weekly high-potency topical corticosteroids.	
Coyle and Barbeau, 2004 [32]	CUA	Pimecrolimus/ "Usual Therapy"	Adults and children / Canada	Societal and health care / not stated	Markov (360 days (children), 169 days (adults) / not stated)	QALY (Visual Analogue Scale)	One way	Healthcare perspective: ICER value of $40000 per QALY (children) and $37000 (adults). Societal perspective: ICER value of $38000 per QALY (children) and $35000 (adults).	Incremental cost per QALY gained for children and adults respectively: £28465.35, £26330.45 (Healthcare perspective) £27042.08, £24907.18 (Societal perspective) [Assumed price year of 2004]
Ellis et al. 2006 [33]	CUA	Pimecrolimus / "Conventional Therapy"	Children (2-17 years) / Country not stated	Third party payer / 2004	Markov (1 year / not stated)	QALY (Visual Analogue Scale)	One and Two way	ICER of US$38231 per QALY gained.	£33192.16 per QALY gained.
Pitt et al. 2006 [27]	CUA	Pimecrolimus / Topical corticosteroids	Adults and children / United Kingdom	U.K. National Health Service / 2003	Markov (1 year (adults) 14 years (children) / 1 month)	QALY (Standard gamble)	One way and probabilistic	Topical corticosteroids dominated pimecrolimus.	Not applicable

Authors, year	Study type	Intervention / Comparator	Population / Country	Perspective / Price Year	Analytic Approach (Time horizon/cycle length)	Primary outcome measure	Sensitivity Analysis	Incremental Cost-Effectiveness results	Cost-Effectiveness adjusted for Price Year (2016) and Currency (£)
Garside et al. 2005 [28]	CUA	Pimecrolimus and tacrolimus / Topical corticosteroids	Adults and children / United Kingdom	U.K. National Health Service / 2003	Markov (1 year (adult) 14 years (children) / 4 weeks)	QALY (Standard gamble)	One way and probabilistic	(Not all ICERs presented as there were approximately 8 models with different treatment pathways) For pimecrolimus as first line treatment, in children, corticosteroids were found to dominate. For tacrolimus as first line treatment, in children, the ICER value was £35,669 per QALY gained.	£47436.14 per QALY gained, for tacrolimus as first line treatment.
Hjalte et al. 2010 [35]	CUA	Moisturising cream / No treatment	Adults / Sweden, Denmark, Norway and Finland	Societal / 2008	Markov (1 year / 3 weeks)	QALY (Visual Analogue Scale)	One way	Reported ICER of €5479 per QALY gained for treatment with moisturising cream in comparison to no treatment, within Sweden, €26908 within Denmark, €26118 within Norway, €9518 within Finland.	£4671.43(†) per QALY gained, within Sweden, £20428.62(†) within Denmark, £19163.98(†) within Norway, £8243.44 within Finland.
Norrlid et al. 2016 [39]	CUA	Moisturiser containing 5% urea / Moisturiser with no active ingredients	"Patients with AD" / Finland, Norway, Sweden	Societal / 2014	"Discrete Event Model" (1 year / Not applicable)	QALY (Not stated)	One way	The barrier-strengthening moisturiser was found to dominate the moisturiser with no active ingredients.	Not applicable

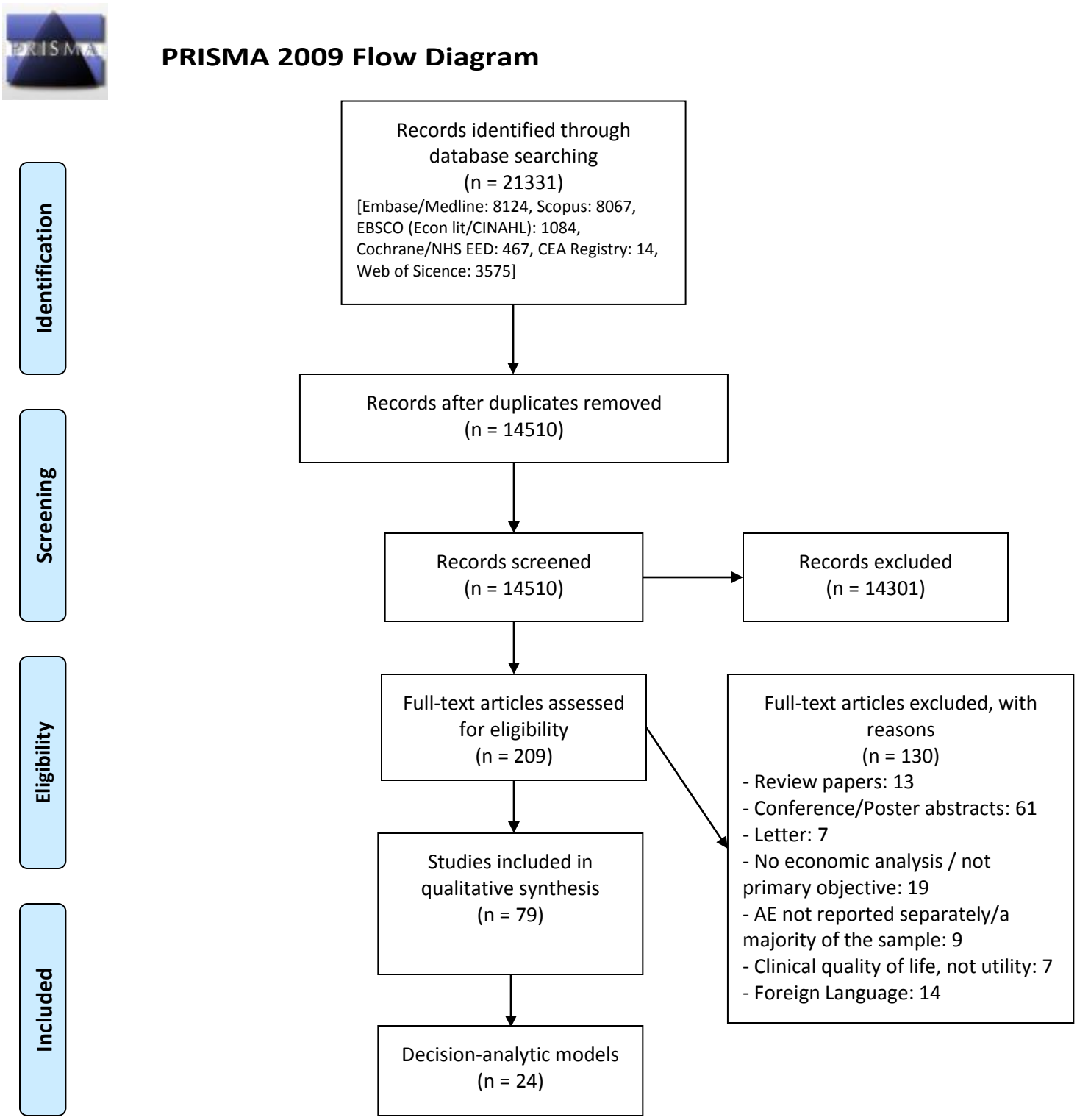
Authors, year	Study type	Intervention / Comparator	Population / Country	Perspective / Price Year	Analytic Approach (Time horizon/cycle length)	Primary outcome measure	Sensitivity Analysis	Incremental Cost-Effectiveness results	Cost-Effectiveness adjusted for Price Year (2016) and Currency (£)
Tang et al. 2015 [38]	CUA	Non-steroidal barrier cream / regular emollient	Children / Asia (12 countries)	Societal / 2013	Markov (1 year / 22 days)	QALY (Multiple sources, some Visual Analogue Scale, others Standard gamble)	One way and scenario	The non-steroidal barrier cream dominated regular emollient cream.	Not applicable
De Tiedra et al. 1997 [29]	CEA	Topical prednicarbate 0.25% / fluocortin 0.75%	Patients with “inflammatory dermatoses” / Spain	Societal / 1996	Decision tree (not stated)	Patients achieving a therapeutic success	One way	"The cost per patient successfully treated was Pta 5608 for prednicarbate and Pta 8680 for fluocortin."	£53.56 for prednicarbate and £82.90 for fluocortin.

(†) Note: This paper converted results into a common currency, Euros, without providing the exchange rate used. Thus to convert these results into 2016 prices, using UK£Sterling, it was necessary to convert the prices back into the original country’s currency, using the average exchange rate for the 2008 price year, sourced from the European central bank, using this value to then inflate and convert to 2016, UK£Sterling, prices, using a web based tool [16].

Abbreviations: CEA: Cost-effectiveness analysis, CMA: Cost-minimisation analysis, CUA: Cost-utility analysis, QALY: Quality adjusted life year

Figure

Click here to download Figure FIGURE 1.doc



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Article Title: The use of decision-analytic models in Atopic Eczema: A systematic review and critical appraisal.

Journal Name: Pharmacoeconomics

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Supplementary material 1: Data Extraction Table

General Information	
Review ID	
Author, Year	
Title	
Reviewer	
Date of review	
Publication type	
Population and setting	
Type of study	
Stated type of economic analysis	

Actual type of economic analysis (if different)	
Country of study	
Study setting	
Population	
Study size	
Method of recruitment	
Recruitment time period	
Inclusion criteria	
Exclusion criteria	
Study design	
Primary intervention	
Secondary intervention(s)	
Comparators	
Time horizon (for follow up)	
Outcomes	
Outcomes measure (1)	
Method of measurement (1)	
Outcome measure (2)	
Method of measurement (2)	
Outcome measure (3)	

Method of measurement (3)	
Secondary outcome measure(s)	
Method of measurement(s)	
For utility studies: what value set or direct method of measurement has been used?	
Timing of measurements	
Discount rate, outcomes	
Method of dealing with missing data - outcomes	
Resource and Cost information	
Cost perspective	
Intervention costs	
Direct cost items	
Method of capturing direct cost items	
Direct cost data sources	
Indirect cost items	
Method of capturing indirect cost items	
Indirect cost data sources	
Resource items collected	
Resource use, recall period	
Method of dealing with missing data - cost	
Price year	

Currency	
Inflation rate, cost	
Discount rate, cost	
Results	
Resource use and costs	
Reported cost effectiveness	
Appropriateness of ICER	
Sensitivity analysis	
Major Result(s)	
Conclusions	
Funding source	
Model specific information	
Type of decision analytic model	
Model perspective	
Model population	
Cohort or individual?	
Model assumptions	
Model exclusions	
Method for dividing disease severity	
Distinction between body/face eczema?	

Interventions included	
Time horizon	
Cycle length	
Value of any parameters used	
Source of parameters	
Software used for model	
Type of sensitivity analysis performed	
Method of model validation	
Author specified limitations	

Philips Criteria

Dimensions of quality		**Questions for critical appraisal**	**Response (Yes/No/Partial//NA)**	**Comments**
Structure				
Statement of decision problem / objective	1	Is there a clear statement of the decision problem?		
	2	Is the objective of the evaluation and model specified and consistent with the stated decision problem?		
	3	Is the primary decision maker specified?		

Statement of scope / perspective	4	Is the perspective of the model stated clearly?		
	5	Are the model inputs consistent with the stated perspective?		
	6	Has the scope of the model been stated and justified?		
	7	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?		
Rationale for structure	8	Has the evidence regarding the model structure been described?		
	9	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?		
	10	Have any competing theories regarding model structure been considered?		
	11	Are the sources of data used to develop the structure of the model specified?		
	12	Are the causal relationships described by the model structure justified appropriately?		
	13	Are the structural assumptions transparent and justified?		

Structural assumptions	14	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?		
Strategies/ comparators	15	Is there a clear definition of the options under evaluation?		
	16	Have all feasible and practical options been evaluated?		
	17	Is there justification for the exclusion of feasible options?		
Model type	18	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?		
Time horizon	19	Is the time horizon of the model sufficient to reflect all important differences between options?		
	20	Is the time horizon of the model, and the duration of treatment and treatment effect described and justified?		
	21	Has a lifetime horizon been used? If not, has a shorter time horizon been justified?		
Disease states/ pathways	22	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the		

		disease in question and the impact of interventions?		
Cycle length	23	Is the cycle length defined and justified in terms of the natural history of disease?		
Data				
Data identification	24	Are the data identification methods transparent and appropriate given the objectives of the model?		
	25	Where choices have been made between data sources, are these justified appropriately?		
	26	Has particular attention been paid to identifying data for the important parameters in the model?		
	27	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?		
	28	Has the quality of the data been assessed appropriately?		
	29	Where expert opinion has been used, are the methods described and justified?		
Pre-model data	30	Are the pre-model data analysis methodology based on justifiable		

		statistical and epidemiological techniques?		
Baseline data	31	Is the choice of baseline data described and justified?		
	32	Are transition probabilities calculated appropriately?		
	33	Has a half cycle correction been applied to both cost and outcome?		
Treatment effects	34	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?		
	35	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified? Have alternative assumptions been explored through sensitivity analysis?		
	36	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified? Have alternative assumptions been explored through sensitivity analysis?		

Quality-of-life weights (utilities)	37	Are the utilities incorporated into the model appropriate?		
	38	Is the source for the utility weights referenced?		
	39	Are the methods of derivation for the utility weights justified?		
Data incorporation	40	Have all data incorporated into the model been described and referenced in sufficient detail?		
	41	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?		
	42	Is the process of data incorporation transparent?		
	43	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?		
Assessment of uncertainty	44	Have the four principal types of uncertainty been addressed?		
	45	If not, has the omission of particular forms of uncertainty been justified?		
Methodological	46	Have methodological uncertainties been addressed by running		

		alternative versions of the model with different methodological assumptions?		
Structural	47	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?		
Heterogeneity	48	Has heterogeneity been dealt with by running the model separately for different sub-groups?		
Parameter	49	Are the methods of assessment of parameter uncertainty appropriate?		
	50	Has probabilistic sensitivity analysis been done, if not has this been justified?		
	51	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated and justified?		
Uncertainty and Consistency				
Internal consistency	52	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?		
External consistency	53	Are the conclusions valid given the data presented?		
	54	Are any counterintuitive results from the model explained and justified?		

	55	If the model has been calibrated against independent data, have any differences been explained and justified?		
	56	Have the results of the model been compared with those of previous models and any differences in results explained?		

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Supplementary material 2: Philips Criteria responses

Included within the tables below are the responses to the Philips checklist items [8], for each of the studies included within the review, divided into structure, data and certainty. The full questions are coded within the data extraction form, provided in Appendix 3. Here, 'Y' means yes, 'N' means no or not enough information provided to judge, 'P' means partial and 'N/A' means not applicable.

Structure:

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Abramovits, W. (2003) [21]	Y	Y	N	Y	Y	Y	Y	N	Y	N	N	Y	P	Y	Y	Y	N/A	Y	P	P	N	Y	N
Bhanegaonkar, A. (2015) [23]	Y	Y	N	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	N/A	Y	Y	Y	N	Y	P
Bhanegaonkar, A. (2015) [24]	Y	Y	N	P	N	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	N/A	Y	Y	Y	N	Y	P
Bhanegaonkar, A.(2014) [25]	Y	Y	N	Y	Y	Y	Y	P	Y	N	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	N	Y	P
Botteman, M. (2015) [26]	Y	Y	N	Y	Y	Y	Y	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N
Coyle, D. (2004) [32]	Y	Y	Y	Y	Y	P	Y	N	Y	N	Y	N	N	N	Y	Y	N/A	P	N	N	N	P	N
de Tiedra, A. (1997) [29]	P	Y	N	Y	Y	N	Y	N	N	N	N	N	N	N	Y	Y	N/A	N	N	N	N	P	N/A
Ellis, C. N., et al. (2003) [22]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N/A	Y	P	P	N	Y	P
Ellis, C. N., et al. (2006) [33]	Y	Y	N	Y	Y	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	N/A	Y	N	N	N	Y	N

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Garside, R. (2005) [28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P
Healy, E., et al. (2011) [34]	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Y	Y	N/A	N	P	P	Y	N	N
Hjalte, F. (2009) [35]	Y	Y	N	Y	Y	P	Y	N	P	N	N	N	P	N	Y	Y	Y	Y	Y	Y	N	N	P
Hjelmgren, J. (2007) [36]	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	N	N	Y	Y	Y	N/A	Y	P	N	N	Y	Y
Iskedjian, M. (2012) [17]	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	N	Y	Y	Y	N/A	N	Y	P	N	P	P
Iskedjian, M. (2010) [18]	Y	Y	Y	Y	Y	Y	Y	N	P	N	Y	N	N	N	Y	Y	N/A	N	Y	P	N	P	P
Iskedjian M. (2012) [19]	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	N	Y	Y	Y	N/A	N	P	P	N	P	N
Kiencke, P. (2013) [30]	Y	Y	N	N	N	P	Y	N	P	N	N	Y	Y	Y	Y	N	N	N	Y	P	Y	Y	N/A
Lenoir-Wijnkoop, I. (2010) [37]	Y	Y	Y	Y	P	Y	Y	Y	N	Y	N	N	N	N	Y	Y	N/A	N	P	N	N	N	P
Mertens, J. (2012) [31]	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	N/A	N	Y	N	N	Y	N/A
Norrlid, H. (2016) [39]	Y	P	N	Y	Y	P	Y	N	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	P	N	P	N/A
Pitt, M. (2006) [27]	Y	Y	Y	Y	Y	Y	Y	P	Y	P	N	Y	Y	Y	Y	Y	Y	Y	P	Y	P	Y	Y
Su, J. (2012) [20]	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	N/A	Y	N	Y	P	Y	P
Tang, M. B. Y. (2015) [38]	Y	Y	N	Y	Y	P	Y	N	Y	N	N	N	Y	Y	Y	Y	N/A	Y	N	P	N	Y	Y

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Xu, S. (2016) [40]	Y	N	N	N	N	N	N	N	N	N	Y	N	P	Y	Y	N	N	N	N	N	N	P	N/A

Data:

	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Abramovits, W. (2003) [21]	N	N	N	N	N	N	P	P	N	N	P	N	P	N/A	N/A	N/A
Bhanegaonkar, A. (2015) [23]	N	N/A	N	N	N	N	N	Y	N	N	N/A	N/A	Y	N/A	N/A	N/A
Bhanegaonkar, A. (2015) [24]	N	N/A	N	N	N	N	N	Y	N	N	N/A	N/A	Y	Y	Y	N
Bhanegaonkar, A.(2014) [25]	N	N	N	N	N	N	N	Y	N	N	N/A	N/A	Y	Y	Y	Y
Botteman, M. (2015) [26]	N	N	N	N	N	N	N	P	N	N	N	N/A	N	N	Y	N
Coyle, D. (2004) [32]	P	N/A	N	N	N	N	N	N	N	N	N	N/A	N	P	Y	Y
de Tiedra, A. (1997) [29]	P	N/A	N	P	N	P	Y	Y	N/A	N/A	Y	N	N	N/A	N/A	N/A
Ellis, C. N., et al. (2003) [22]	N	N/A	N	Y	Y	N	N	P	N	N	Y	N/A	Y	N/A	N/A	N/A
Ellis, C. N., et al. (2006) [33]	N	N/A	N	Y	N	N/A	N	P	N	Y	N/A	N/A	N/A	Y	Y	Y
Garside, R. (2005) [28]	Y	Y	Y	Y	Y	P	Y	Y	N	N	Y	Y	Y	Y	Y	Y

	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Healy, E., et al. (2011) [34]	Y	Y	N	N	Y	P	N	Y	N	N	N/A	N/A	N	P	N	N
Hjalte, F. (2009) [35]	N	N/A	N	N	N	N	N	Y	P	P	N	N	N/A	Y	Y	N/A
Hjelmgren, J. (2007) [36]	N	N/A	P	N	N	N/A	N	N	N	N	N/A	N	N/A	Y	Y	Y
Iskedjian, M. (2012) [17]	Y	N	N	Y	Y	Y	Y	Y	N	N	Y	P	N	N/A	N/A	N/A
Iskedjian, M. (2010) [18]	Y	N/A	N	Y	Y	Y	Y	Y	N	N	Y	N	N	N/A	N/A	N/A
Iskedjian M. (2012) [19]	Y	N/A	N	Y	Y	Y	N	Y	N	N	Y	N	N	N/A	N/A	N/A
Kiencke, P. (2013) [30]	N	N/A	N	P	N	N/A	Y	Y	Y	N/A	N/A	P	N	N/A	N/A	N/A
Lenoir-Wijnkoop, I. (2010) [37]	P	N	N	N	N	N	N	N	N	N	N	N	N/A	N	Y	N
Mertens, J. (2012) [31]	N	N/A	N	N	P	N	Y	Y	N	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Norrlid, H. (2016) [39]	N	N/A	N	N	P	N/A	N	N	N/A	N/A	N/A	N	N	Y	Y	N
Pitt, M. (2006) [27]	Y	N	Y	Y	N	N	N	Y	N	N/A	N	P	Y	Y	Y	N
Su, J. (2012) [20]	Y	N/A	N	Y	N	P	N	Y	N	N	Y	Y	N	N/A	N/A	N/A
Tang, M. B. Y. (2015) [38]	N	P	N	P	N	N	N	Y	N	N/A	N	N	P	N	Y	N
Xu, S. (2016) [40]	Y	N/A	N	N	N	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N	N	Y	N

	40	41	42	43	44	45	46	47	48	49	50	51
Abramovits, W. (2003) [21]	N	N/A	N	N/A	P	N	N	N	N	P	N	P
Bhanegaonkar, A. (2015) [23]	P	N/A	Y	N/A	P	N	P	N	N	Y	Y	Y
Bhanegaonkar, A. (2015) [24]	P	N/A	Y	P	P	N	Y	N	N	Y	Y	Y
Bhanegaonkar, A.(2014) [25]	Y	N/A	Y	P	P	N	Y	N	N	Y	Y	P
Botteman, M. (2015) [26]	P	N/A	P	N	P	N	Y	N	N	Y	Y	N
Coyle, D. (2004) [32]	N	N/A	N	N/A	P	N	N	Y	N	Y	N	Y
de Tiedra, A. (1997) [29]	P	N/A	Y	N/A	P	N	N	N	N	P	N	N
Ellis, C. N., et al. (2003) [22]	P	N/A	Y	N/A	P	N	N	N	N	Y	N	P
Ellis, C. N., et al. (2006) [33]	N	N/A	P	N/A	P	N	N	N	N	Y	N	N
Garside, R. (2005) [28]	Y	N/A	Y	P	P	N	N	N	Y	Y	Y	Y
Healy, E., et al. (2011) [34]	Y	N/A	Y	N/A	P	N	N	N	Y	Y	Y	Y
Hjalte, F. (2009) [35]	Y	N/A	N	N/A	P	N	N	N	N	Y	N	N
Hjelmgren, J. (2007) [36]	P	N/A	Y	N/A	P	N	N	N	Y	P	N	N

	40	41	42	43	44	45	46	47	48	49	50	51
Iskedjian, M. (2012) [17]	Y	N/A	Y	P	P	N	P	N	N	Y	Y	Y
Iskedjian, M. (2010) [18]	Y	N/A	Y	P	P	N	P	N	N	Y	Y	Y
Iskedjian M. (2012) [19]	Y	N/A	Y	N/A	P	N	N	N	N	Y	Y	N/A
Kiencke, P. (2013) [30]	P	N/A	P	N/A	P	N	N	N	N	P	N	P
Lenoir-Wijnkoop, I. (2010) [37]	P	N/A	P	N/A	P	N	N	N	N	N	N	N
Mertens, J. (2012) [31]	P	N/A	P	N/A	P	N	N	N	N	P	N	N
Norrlid, H. (2016) [39]	N	N/A	Y	P	P	N	P	N	N	N	N	Y
Pitt, M. (2006) [27]	N	N/A	P	Y	P	N	N	N	Y	Y	Y	Y
Su, J. (2012) [20]	Y	N/A	Y	N/A	P	N	Y	N	N	Y	Y	Y
Tang, M. B. Y. (2015) [38]	Y	N/A	Y	N/A	P	N	Y	N	N	Y	N	P
Xu, S. (2016) [40]	Y	N/A	Y	N/A	P	N	N	N	N	Y	N	Y

Certainty:

	52	53	54	55	56
Abramovits, W. (2003) [21]	N	Y	N/A	N/A	N
Bhanegaonkar, A. (2015) [23]	N	Y	Y	N/A	N
Bhanegaonkar, A. (2015) [24]	N	Y	N/A	N/A	P
Bhanegaonkar, A.(2014) [25]	N	Y	N/A	N/A	Y
Botteman, M. (2015) [26]	N	Y	N/A	N/A	Y
Coyle, D. (2004) [32]	N	Y	N/A	N/A	N
de Tiedra, A. (1997) [29]	N	Y	N/A	N/A	N
Ellis, C. N., et al. (2003) [22]	N	Y	N/A	N/A	N
Ellis, C. N., et al. (2006) [33]	N	Y	N/A	N/A	N
Garside, R. (2005) [28]	N	Y	N/A	Y	Y
Healy, E., et al. (2011) [34]	N	Y	N/A	N/A	P
Hjalte, F. (2009) [35]	N	Y	N/A	N/A	N
Hjelmgren, J. (2007) [36]	N	Y	N/A	N/A	N
Iskedjian, M. (2012) [17]	N	Y	N/A	N/A	N

	52	53	54	55	56
Iskedjian, M. (2010) [18]	N	Y	N/A	N/A	N
Iskedjian M. (2012) [19]	N	Y	N/A	N/A	N
Kiencke, P. (2013) [30]	N/A	Y	N/A	N/A	N
Lenoir-Wijnkoop, I. (2010) [37]	N	P	N/A	N/A	N
Mertens, J. (2012) [31]	N	Y	N/A	N/A	P
Norrlid, H. (2016) [39]	N	Y	N/A	N/A	Y
Pitt, M. (2006) [27]	N	Y	N/A	N/A	N
Su, J. (2012) [20]	N	Y	N/A	N/A	N
Tang, M. B. Y. (2015) [38]	N	Y	N/A	N/A	N
Xu, S. (2016) [40]	N/A	Y	N/A	N/A	N