BMJ TAG

Abrocitinib, tralokinumab and upadacitinib for treating moderate to severe atopic dermatitis

Protocol for Multiple Technology Appraisal

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DRAFT PROTOCOL

Date: 23 June 2021

1 TITLE OF THE PROJECT

Abrocitinib, tralokinumab and upadacitinib for treating moderate to severe atopic dermatitis

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3 PLAIN ENGLISH SUMMARY

Atopic dermatitis (AD), which is also known as eczema or atopic eczema, is a condition that affects the skin. AD is one of the most common skin disorders in children, with symptoms usually showing before the age of 5 years. But AD can also develop in adulthood. People with AD have dry, red (inflamed) skin that is also extremely itchy (pruritus). Oozing, weeping sores can occur in more

severe forms of AD. There is no cure for AD, and the aim of treatment at first is to provide symptom relief and then to control symptoms in the longer term. Mild cases of AD, which most people have, are treated by General Practitioners (GPs). Treatment starts with ointments that are applied to the skin, such as emollients (a cream or ointment that soothes the skin), and gels. Those with more severe AD are likely to need stronger therapies and are usually dealt with by doctors who specialise in treating skin disorders. Severe forms of AD might be treated with phototherapy (exposure to fluorescent light bulbs) or, more often, with systemic treatments, which are drugs that spread throughout the body to target the processes within the body that are causing the inflammation of the skin. Ciclosporin A (CsA) is often the first systemic therapy given. If AD does not get better with CsA, options available in the National Health Service (NHS) after CsA are dupilumab and baricitinib. New therapies that have been evaluated in clinical trials for AD but have not been assessed for use in the NHS are abrocitinib, tralokinumab and upadacitinib.

The aim of this project is to review abrocitinib, tralokinumab and upadacitinib for the treatment of moderate to severe AD in a multiple technology appraisal (MTA). The medical benefits and risks associated with the three treatments will be assessed and compared with each other and against the available standard treatments for AD. In addition, this project will assess whether abrocitinib, tralokinumab and upadacitinib are likely to be considered good value for money for the NHS.

4 DECISION PROBLEM

4.1 Purpose

Atopic dermatitis (AD), often referred to as atopic eczema, is a chronic relapsing inflammatory skin condition.[1] One of the most common skin disorders in children, AD typically manifests before the age of 5 years, but can develop at any age. AD is characterized by dry, inflamed skin accompanied by intense itchiness (pruritus). Oozing, weeping lesions can occur in more severe forms of the condition. Scratching constantly due to pruritus leads to sleep disturbance is considered an important factor in the transition of the classification of AD from acute to chronic disease. Bleeding and splitting of the skin, increased prevalence of skin infection are also hallmark features of AD in most people with xerosis (dry skin).[1] One in five children and one in ten adults in the UK are estimated to have AD,[2, 3] with about 18% of cases of childhood AD categorised as moderate and 2% as severe.[3] Of adults with AD, it has been reported that 5% of cases are severe.[4] Of the people who need treatment for AD, 7% are estimated to have moderate to severe disease, and, 27% of those receiving treatment will require systemic therapy to elicit sufficient symptom relief.[5, 6] Due to

repeated episodes of skin infections, extensive antibiotic prescriptions are common among AD patients. As well as physical symptoms, many children and adults experience sleeplessness, anxiety, depression and other mental health problems related to their AD.[2] Common co-morbidities are food allergies, allergic rhinitis and allergic asthma.

AD is currently uncurable, and the goal of treatment is to improve symptoms and achieve long-term disease control. Those with mild AD, who form the majority of cases, are predominantly managed in primary care.[7] Guidance for general practitioners (GPs) outlines a step-by-step approach to disease management for a person presenting with AD, starting with preparation of an individualised management plan.[7] Initial treatment focuses on topical therapy with emollients and moisturisers, which are the mainstay of therapy but their effectiveness is reliant on the patient applying the emollient as per the recommendations, which can be challenging. For those with mild AD, to effect relief of dry skin, regular use of moisturisers and/or emollients is usually effective in controlling symptoms. Additionally, advice is given on identifying and controlling specific triggers of flare (a worsening of symptoms), for example, overuse of irritants including shampoo and detergents. Cigarette smoke has also been discussed as a trigger factor. Children and adolescents typically receive the same treatments as adults.

For someone presenting to primary care with a flare, initial treatment is typically a topical corticosteroid (TCS) to suppress inflammation, if this is an acceptable treatment option to the patient. TCSs can be prescribed in different strengths, depending on the severity of disease and the areas of skin affected.[8] The topical immunomodulators tacrolimus and pimecrolimus, both of which are calcineurin inhibitors, are additional treatment options in primary care for those patients whose preference is not to use a TCS.[7] Topical immunomodulators are also an option for AD affecting areas for which TCSs are not recommended, for example, the eyelids and peri-orbital skin, and for when there are signs of skin atrophy.

Those with moderate to severe AD that only partially responds to treatment, and those presenting with severe disease, are referred to secondary care for more specialised therapy, where phototherapy is frequently the first treatment option. If phototherapy is unsuccessful, subsequent treatment typically on systemic therapies such as ciclosporin A (CsA), methotrexate, dupilumab and, more recently, baricitinib. The three treatments that are the focus of the project — abrocitinib, tralokinumab and upadacitinib — are systemic therapies that are potential additions to the treatments for AD currently available to the NHS. The purpose of the project outlined here is to

assess the clinical and cost-effectiveness of abrocitinib, tralokinumab and upadacitinib for treating moderate to severe AD compared with current treatments used in England. None of abrocitinib, tralokinumab and upadacitinib has a marketing authorisation in place for treatment of AD in the UK at the time of drafting of the protocol. Should the marketing authorisations become available during the timeframe of the project, the individual treatments will be incorporated into analyses within their respective marketing authorisation.

4.2 Interventions

Abrocitinib (CIBINQO®, Pfizer) is a once-daily, oral treatment for moderate to severe AD for those aged 12 years and older: abrocitinib has been evaluated in studies at a daily dose of 10 mg, 30 mg, 100 mg and of 200 mg. Abrocitinib is a selective Janus Kinase (JAK) 1 inhibitor. JAKs are enzymes that mediate the transduction of intracellular signals involved in the process of inflammatory disease. Abrocitinib has been studied in clinical trials as a monotherapy or in combination with TCS and compared with placebo or dupilumab in people with moderate to severe AD that is not adequately controlled with topical therapies or for whom topical treatments are not appropriate, or who are candidates for systemic therapy.[9-11]

Tralokinumab (Adtralza®, Leo Pharma UK) is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to circulating interleukin (IL)-13, which is thought to be one of the key cytokines involved in triggering the signs and symptoms of AD.[12] Administered subcutaneously, tralokinumab has been evaluated in studies:

- as a monotherapy compared with placebo in adults with moderate to severe AD;[13-15]
- in combination with topical therapies compared with placebo in adults with moderate to severe AD;[16, 17]
- in combination with topical therapies compared with placebo in adults with severe AD that is not adequately controlled with CsA or for whom CsA is contraindicated.[18]

In the studies evaluating tralokinumab, tralokinumab was given initially at a loading dose of 600 mg followed by tralokinumab 300 mg every 2 weeks (Q2W) for a period of 16 weeks, the induction phase. After the induction period, in some studies, those achieving a response, as defined in the study, could either remain on the Q2W regimen or move to tralokinumab 300 mg every 4 weeks (Q4W).

Upadacitinib (Rinvoq®, AbbVie) is a once-daily oral treatment for AD in those aged 12 years and older. The recommended daily dose of upadacitinib is 15 mg for adolescents and 15 mg or 30 mg for adults. Targeting JAKs, upadacitinib is a selective and reversible, second generation JAK inhibitor. Upadacitinib has been assessed in clinical trials:

- as a monotherapy compared with placebo in people aged 12 years and over with moderate to severe chronic AD;[19]
- as a monotherapy compared with dupilumab in adults with moderate to severe AD;[20]
- in combination with TCS compared with placebo in people aged 12 years and over with moderate to severe chronic AD.[21]

To evaluate the clinical and cost effectiveness of the three interventions fully, abrocitinib, tralokinumab and upadacitinib will be evaluated as both monotherapy and in combination with TCS.

4.3 Place of the interventions in the treatment pathway

Given that abrocitinib, tralokinumab and upadacitinib are systemic therapies, dependent on finalised marketing authorisations, the interventions could be introduced into the treatment pathway for AD at two steps:

- as first-line systemic therapy for those having inadequate response to topical treatments;

or

- as a subsequent systemic therapy on failure to respond to first-line systemic treatment, or for those who cannot tolerate or are contraindicated to other systemic therapies.

The final scope issued by the National Institute for Health and Care Excellence (NICE) for the project specifies the population to be those with moderate to severe AD, with no specification of previous treatment (publication in progress). However, a subgroup of interest is specified as people for whom systemic therapies have been inadequately effective, not tolerated or contraindicated. Thus, for the purposes of this project, and considering the proposed marketing authorisations, clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib will be evaluated as first-line systemic therapy in those who are eligible for systemic treatment on inadequate response to topical treatments and separately as second-line systemic therapy for those who achieve inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (often CsA,

azathioprine or methotrexate). Clinical effectiveness of abrocitinib, tralokinumab and upadacitinib will be evaluated when given as a monotherapy and when administered with concomitant TCS.

4.4 Relevant comparators

Comparators of interest listed in the final scope issued by NICE are:

- phototherapy including with ultraviolet (UVB) radiation or psoralen-ultraviolet A (PUVA);
- immunosuppressive therapies (azathioprine, CsA, methotrexate and mycophenolate mofetil);
- oral corticosteroids;
- alitretinoin (in people with atopic dermatitis affecting the hands);
- dupilumab;
- baricitinib;
- best supportive care (BSC; combination of emollients, low to mid potency topical corticosteroids, and rescue therapy including higher potency topical or oral corticosteroids or TCIs).

Of the listed comparators, systemic immunosuppressants with marketing authorisation in the UK for use in AD are:

- oral corticosteroids;
- CsA;
- dupilumab;
- baricitinib.

Systemic therapies used to manage AD and that are used outside of their marketing authorisation are:

- azathioprine;
- mycophenolate mofetil;
- methotrexate.

Based on advice from clinical experts, and considering the treatments, patient populations and options available in current clinical practice, the External Assessment Group (EAG) considers the comparators of interest to be:

- First-line systemic treatment:
  - CsA;
- Second-line after prior systemic therapy/immunosuppressant:
  - dupilumab with or without concomitant TCS;
  - baricitinib with or without concomitant TCS.

Estimates of clinical effectiveness will be reported for abrocitinib, tralokinumab and upadacitinib (as monotherapy or in combination with TCS) compared with treatments currently available in clinical practice as listed above. Where interventions are evaluated as a monotherapy, the intervention will be compared with relevant monotherapies and not in combination with TCS, and the same rationale will be applied to combination therapies.

The EAG's rationale for the choice of comparators is outlined in the subsequent text.

Clinical experts have advised that the immunosuppressant CsA is predominantly the first choice for systemic treatment. Given that CsA is widely used as initial systemic treatment, and that the other listed immunosuppressants are used outside of their marketing authorisation, the EAG considers azathioprine, mycophenolate mofetil and methotrexate not to be relevant comparators.

Additionally, clinical experts have advised that, although use of phototherapy can be considered at the same place in the treatment algorithm as systemic immunotherapies, phototherapy could potentially implemented earlier in the pathway depending on the circumstances of the individual and is unlikely to be preferred instead of a systemic treatment and is, thus, not a comparator of interest. Alitretinoin is specifically given to ease symptoms of AD on the hands. Abrocitinib, tralokinumab and upadacitinib are systemic treatments, and, based on published studies to date, the EAG notes that data are not available on clinical effectiveness in improving AD of the hands. For the purposes of the project, the EAG does not consider alitretinoin to be a relevant comparator. In line with NICE recommendations, dupilumab and baricitinib are treatment options on inadequate response to at least one other systemic therapy/immunosuppressant.[5, 6]

Choice of treatment is influenced by clinician and patient preference, and the order of systemic treatment is typically determined on a case-by-case basis. Non-response to systemic therapy could potentially indicate a more severe form of AD, which could influence prognosis and response to subsequent treatment. Treatment choice on non-response to second-line systemic therapy is influenced by location, with some sites able to offer an inpatient service during which a patient

would receive intense topical treatment. Where such services are not available, the patient may be treated with another systemic therapy, including CsA, or with BSC, the definition of which varies from practice to practice. For the lines of therapy considered in the project, the EAG considers BSC not to be a relevant comparator.

4.5 Population and relevant subgroups

As noted above, the population relevant to the project are those with moderate to severe AD, irrespective of previous treatment and of age, with a subgroup of interest being those for whom systemic therapies have been inadequately effective, not tolerated or contraindicated. Abrocitinib and upadacitinib have been evaluated in studies involving adolescents of age 12 years and above. The EAG considers the population outlined in the final scope to encompass adolescents aged 12 to 18 years, and, evidence permitting, will present data separately for this group. Other types of AD (e.g., contact dermatitis) are not covered in this project.

In clinical practice, assessment of the degree of severity of AD is based on clinical judgement of the appearance, location and extent of lesions, patient-reported symptoms and quality of life (QoL) outcomes.[22] Various clinical scales and patient reported outcomes are available to assess whether a prescribed treatment is improving symptoms (overview presented in Appendix 9.1). The scales vary considerably in the characteristics of AD evaluated to categorise severity of disease, which makes cross-comparison of the resulting categorisations applied in studies challenging. The Harmonising Outcomes for Eczema (HOME) initiative recommends the Eczema Area and Severity Index (EASI) to assess severity of clinical signs of AD.[23] In a clinical trial setting, additional tools used to assess severity of AD are the Investigator Global Assessment (IGA) and Scoring Atopic Dermatitis (SCORAD) index. Classification of disease as moderate or severe according to the various scales are:

- EASI: moderate AD, score of 6.0–22.9, severe AD score of 23.0–72;
- IGA: moderate AD, score of 3, severe AD score of 4;
- SCORAD: moderate AD, score of 25–50, severe AD, score of >50.

The criteria reported above will be followed by the EAG to identify studies involving those with moderate to severe AD.

If the evidence allows, the effectiveness of treatments in subgroups based on skin colour will be assessed. As outlined earlier, given that the interventions under assessment are systemic in nature,

the EAG considers the subgroup of those with AD affecting the hands not to be relevant to the decision problem.

4.6 Outcomes to be addressed

Outcomes of interest specified in the final scope issued by NICE are:

- measures of disease severity;
- measures of symptom control;
- disease free period/maintenance of remission;
- time to relapse/prevention of relapse;
- adverse effects of treatment;
- health-related quality of life.

As mentioned in the description of categorisation of severity of AD, the EASI is applied to determine initial disease severity and is subsequently used to evaluate the effectiveness of treatment, with a decrease in baseline EASI score by 75% the goal of therapy in clinical practice. To account for patient preference and experience, the patient-reported Dermatology Life Quality Index (DLQI) is also captured in clinical practice, with an improvement in score of at least 3 points generally considered to be clinically meaningful. The DLQI is not specific to AD but is tailored to evaluate QoL in skin diseases. An extensively validated generic QoL instrument is the EQ-5D, which, as a generic tool facilitates comparisons of QoL across patient groups and health conditions. EQ-5D is the tool preferred by NICE to inform the reference case in economic evaluations.[24] In line with preferences expressed by the NICE Committee when evaluating the Single Technology Appraisals for dupilumab and baracitinib,[5, 6] a composite outcome of reduction in EASI score of 50% and improvement in DLQI of at least four points (EASI 50 + ΔDLQI ≥4) is the primary clinical outcome for the project. Clinical experts fed back that EASI 50 + ΔDLQI ≥4 does inform their assessment of response to treatment, but they went on to caution that the subjective nature of the DLQI, as a patient-assessed tool that is open to recall bias, is also borne in mind and, consequently, their preference to assess clinical effectiveness is change in EASI by 75%. Additionally, data on the composite outcome of EASI 50 + ΔDLQI ≥4 may not be available for all interventions evaluated. To facilitate planned synthesis of the data to generate estimates of comparative clinical effectiveness, measures of symptom improvement, in addition to EASI 50 + ΔDLQI ≥4, will be captured during the project.

Clinical experts informed the EAG that disease free periods, maintenance of remission, time to relapse and prevention of relapse are not terms that are commonly used in clinical practice in AD and are not defined for AD. Endpoints that could inform the duration of treatment response include:

- number of days free from TCS during treatment;
- proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved.

For the purposes of the project, the EAG has focused on clinical outcomes that inform the economic evaluation. Data will be captured at the timepoints as reported in individual studies, together with longer term or maintenance of treatment effect. To summarise, the outcomes to be captured are:

- proportion of people achieving EASI 50 + ΔDLQI ≥4;
- proportion of people achieving EASI 75;
- change in EQ-5D score from baseline;
- proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study);
- proportion of people requiring use of rescue therapy during treatment;
- number of days free from TCS during treatment;
- proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved;
- serious adverse effects of treatment.

5 REPORT METHODS FOR SYNTHESIS OF EVIDENCE OF CLINICAL EFFECTIVENESS

A review of the evidence on the clinical effectiveness of abrocitinib, tralokinumab and upadacitinib in the treatment of moderate to severe AD will be undertaken systematically following the general principles recommended in the PRISMA statement (formerly the QUOROM statement).[25] A flow diagram illustrating the flow of information through the systematic review process will be presented according to the PRISMA reporting guidelines.[25]

5.1 Search strategy

During scoping, the EAG identified a systematic review reporting an NMA of systemic treatments for moderate to severe AD that searched records up to August 2019.[26] The EAG considers the review to

have been carried out systematically and following accepted systematic review methodology. The systematic review identified completed and ongoing studies evaluating all interventions and comparators of interest to the project outlined here. The EAG will re-evaluate the identified studies against the inclusion criteria presented in Table 1.

The identified review evaluated all systemic treatments used in the management of AD, and therefore implemented broad search terms relating to interventions.[26] For the purposes of the project outlined here, the EAG has designed the search strategies to incorporate terms specific to the interventions of interest. As the identified review retrieved studies on all interventions of interest to the project, the EAG's searches will be restricted to records published from 1 August 2019.[26] Multiple electronic databases will be searched, including MEDLINE, EMBASE, CENTRAL, and DARE. Bibliographies of retrieved studies (RCTs and systematic reviews) identified as relevant will be manually reviewed for potentially eligible studies. Ongoing clinical trials will be identified by searching clinical trial registries, including ClinicalTrials.gov and the EU Clinical Trials Register. In addition, clinical experts advising the EAG will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, submissions provided by companies will be assessed for unpublished data. Trial sponsors will be contacted with a request for data should relevant data not be available within the submissions. Should the randomised evidence base be insufficient to inform the decision problem that is the focus of this project, a search for non-randomised trials will be conducted. Any non-RCT evidence identified will be considered for suitability and recommended methods[27] used to minimise the introduction of bias.

No language restrictions will be applied to the search strategy. Full details of the terms to be used in the search are presented in Appendix 9.2. All searches will be updated when the draft report is under peer review, prior to submission of the final report.

5.2 Study selection criteria and procedures

Two reviewers will independently screen all titles and abstracts according to the inclusion criteria (see Table 1). It is anticipated that relevant companies will provide submissions that may include unpublished data that will be considered. Full paper manuscripts of any titles/abstracts that may be relevant will be obtained where possible and the relevance of each study assessed. Discrepancies will be resolved by consensus, with involvement of a third reviewer when necessary.

Table 1. Inclusion criteria

Factor	Inclusion criteria
Study design	Randomised controlled trials
Population	People with moderate to severe AD
Interventions	The interventions below will be considered as monotherapy or in combination with TCS: • Abrocitinib; • Baricitinib; • CsA; • Dupilumab; • Tralokinumab; • Upadacitinib.
Comparators	Specified interventions versus each other or BSC: where interventions are evaluated as a monotherapy, the intervention will be compared with other monotherapies and not in combination with TCS, and vice versa.

Abbreviation: AD, atopic dermatitis; BSC, best supportive care; CsA, ciclosporin A; TCS, topical corticosteroid.

5.3 Subgroups

The groups of interest to the project are:

- those with moderate to severe AD receiving first-line systemic treatment (adolescents and adults):
- those with moderate to severe AD receiving second-line systemic treatment after inadequate response to CsA (adolescents and adults), or where CsA cannot be tolerated or is contraindicated.

5.4 Outcomes

Data will be extracted on the following outcomes:

- proportion of people achieving EASI 50 + ΔDLQI ≥4;
- proportion of people achieving EASI 75;
- change in EQ-5D score from baseline;
- proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study);

- proportion of people requiring use of rescue therapy during treatment;
- number of days free from TCS during treatment;
- proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved;
- serious adverse effects of treatment.

5.5 Data extraction strategy

Full paper manuscripts of any included reference will be obtained where possible. Data will be extracted independently by two reviewers using a standardised data extraction form (see Appendix 9.3). Information extracted will include details of the study's design and methodology, baseline characteristics of participants and results including any adverse events reported. Where there is incomplete information the study authors will be contacted to gain further details. Authors will be asked to respond within 4 weeks of initial contact, after which time, unless the author has confirmed that they can supply the requested data, it will be assumed the data are not available. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

5.6 Quality assessment strategy

The quality of the clinical effectiveness studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and, if necessary, a third reviewer will be consulted. The study quality will be assessed according to the Cochrane Risk of Bias Tool, version 2, for randomised studies.[28]

5.7 Methods of analysis/synthesis

Extracted data and quality assessment for each study of clinical effectiveness will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Should sufficient comparable data be identified, network meta-analyses (NMA) will be performed to evaluate the comparative clinical effectiveness based on the intention to treat (ITT) population. Based on studies retrieved from scoping searches, the EAG noted variation in the definition of the population informing the primary analysis of clinical effectiveness. Some studies report censoring those who receive rescue medication during treatment as part of their ITT analysis, whereas others do not censor these patients. For the purposes of the research presented here, the EAG defines the ITT population to

include those who receive rescue medication during treatment because, based on advice from clinical experts, use of rescue medication more closely reflects what occurs in clinical practice in England. Treatment effects will be presented as odds ratios for dichotomous data, weighted mean differences for continuous data or as hazard ratios where appropriate. NMAs will be performed using a Bayesian Markov Chain Monte Carlo (MCMC) simulation using OpenBUGS.[29]

6 REPORT METHODS FOR SYNTHESISING EVIDENCE OF COST-EFFECTIVENESS

The purpose of this MTA will be to assess the cost-effectiveness of abrocitinib, tralokinumab and upadacitinib as monotherapies or in combination with TCS, within their marketing authorisation for treating moderate to severe AD in the UK. However, the EAG will take into consideration the expected position of use in clinical practice and any proposed positioning from the company. In the absence of any narrowing of positioning, the cost effectiveness of these treatments will be evaluated in first-line systemic therapy in patients who are eligible for systemic treatment on inadequate response to topical treatments; and separately as second-line for those who achieve inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy. As discussed in Section 4.4, abrocitinib, tralokinumab and upadacitinib will be compared against the following comparators currently used in clinical practice in England:

- In first-line systemic treatment:
  - CsA;
- In second line after prior systemic therapy/immunosuppressant:
  - dupilumab;
  - baricitinib.

The cost effectiveness of abrocitinib, tralokinumab and upadacitinib will be evaluated when given as monotherapies and when administered with concomitant TCS. Where interventions are evaluated as a combination regimen, the economic analysis will assume that all patients receive the intervention plus TCS and compare it to other combination regimes (for example, dupilumab with concomitant TCS).

Estimation of the cost effectiveness of the three interventions will be met through conducting a systematic review to identify and appraise published economic evaluations from the literature;

health-related quality of life (HRQoL) studies of AD including safety data; and UK specific resource use data. Non-UK sources will be considered if there is insufficient UK specific information.

Should the published or submitted economic evaluations prove insufficient to answer the review question; an independent *de novo* economic model will be developed.

6.1 Search strategy

The cost effectiveness search will aim to identify full economic evaluations and HRQoL studies through searches of multiple electronic databases. These databases will include MEDLINE, EMBASE, the International Network of Agencies for Health Technology Assessment (INAHTA) and the CEA Registry. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, identified systematic reviews and companies' submissions will be searched for additional references.

The Centre for Reviews and Dissemination (CRD) databases will not be searched as the CRD stopped adding records to the Health Technology Assessment (HTA) database in March of 2018 and the Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluations Database (NHS EED) in March of 2015. The EAG considers it unlikely that relevant studies will be missed from the CRD databases as the INAHTA has taken on the responsibility for the production of the HTA database. In addition, clinical experts have already advised that, they are unaware of any economic evaluations or HRQoL studies published prior to March of 2015 that will be of relevance to this review.

To identify cost and resource use evidence, the EAG will search the same sources identified for the economic evidence and treatment of AD, together with NHS reference costs,[30] the Unit Costs of Health and Social Care (Personal Social Services Research Unit [PSSRU]),[31] the Electronic Marketing Information Tool (eMIT)[32] and the British National Formulary (BNF).[33] If the latter do not provide sufficient data to populate the economic model, a separate targeted search on costs and resource use will be conducted.

As an example, the details of the MEDLINE search strategy are presented in full in Appendix 9.2. The search strategy will combine terms capturing the interventions or comparators of interest and the target condition (AD). Health economic and quality of life search terms will be applied to capture the study designs of interest. No language (to assess volume of foreign language studies available),

setting or country restrictions will be applied to the search strategy. A date limit of 2014 will be applied to the search strategy as clinical experts advised the EAG that clinical practice started to change following the publication of the first dupilumab RCT in 2014, with the most marked changes in UK's clinical practice taking place after NICE's approval of dupilumab in 2018. As such, a date limit of 2014 is considered to be inclusive.[34]

6.2 Inclusion and exclusion criteria

The titles and abstracts of papers identified through the searches outlined above will be independently assessed for inclusion by two reviewers using the following criteria:

Inclusion criteria:

- All economic evaluations (cost-effectiveness, cost-benefit, cost-consequence or cost minimisation);
- Any setting (to be as inclusive as possible);
- Intervention or comparators as defined at the beginning of Section 6 (as well as in Section 4.2 and Section 4.4);
- Study outcomes reported in terms of life-years gained (LYG) or quality adjusted life years (QALYs);
- Full publications in English (numbers of relevant non-English studies will be reported);
- Quality of life studies in AD.

Exclusion criteria:

- Abstracts with insufficient methodological details;
- Systematic reviews.

6.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction table and checked by a second reviewer for accuracy. Disagreement will be resolved by discussion; however, if no consensus is reached, a third reviewer will be consulted. In cases where there are missing data or unclear reporting in the published or submitted economic evidence or quality of life studies, attempts will be made to contact authors. A deadline for response to the initial contact of 4 weeks will be imposed. Additional time might be allowed should the author be able to supply the data requested.

Studies published in the UK will be reported in greater detail than non-UK studies as they are more likely to be relevant to the NHS. If sufficient EQ-5D data are found during the searches for utility data, the EAG will restrict the data extraction to EQ-5D data. **Table 1** and **Table 2** show the health economic evaluation and quality of life data that will be sought from each study. In addition, the reason for exclusion of each excluded study will be documented (**Table 3**).

Table 1. Health economic evaluation data extraction table

Author, year, country	Perspective, discounting & cost year	Model type	Patient population	Intervention/ comparator	Outcomes	Results ICER (per QALY gained) incl. uncertainty
Reviewer's comments:						
Abbreviations: QALY, quality adjusted life year.						

Table 2. Quality of life data extraction table

Author, year, country	Sample size	Patient population	Instrument (Valuation)	Utility results
Reviewer's comments:				
Abbreviations: .				

Table 3. Data exclusion table

Bibliographic reference	Reasons for exclusion
Abbreviations:	

6.4 Quality assessment strategy

All published economic evaluations in English identified within the review and any economic evaluations submitted by companies to NICE will be subject to critical appraisal. The methodological quality of each economic evaluation will be assessed against the Drummond checklist for economic evaluations[35] (see Appendix 9.4). Each economic evaluation will be assessed by one health

economist and the details of the assessment checked by a second health economist. Disagreement will be resolved by discussion; however, if no consensus is reached, a third health economist will be consulted

6.5 Methods of analysis

Published and submitted economic evaluations

A narrative summary and accompanying data extraction tables will be presented to summarise evidence from published or submitted economic evaluations.

Economic modelling

Should the economic evidence identified prove insufficient to answer the review question; a *de novo* economic model will be developed in Microsoft Excel®. The structure of the *de novo* model will be informed by economic evaluations identified in the published literature and company submissions; all structural assumptions will be documented and accompanying rationales provided. It is anticipated that the models used in the STAs for dupilumab and baricitinib will be the most informative sources in the development of any *de novo* economic evaluation.[5, 6] The EAG will also draw from any company submissions provided for tralokinumab; abrocitinib; and upadacitinib to inform the *de novo* modelling approach.

The clinical effectiveness parameters required for the economic model will be informed by the review of clinical effectiveness discussed in Section 5. In addition, parameters such as estimates of QoL (utility data) will be informed by the published literature, identified in the systematic review. In cases where parameters required to populate the model are not available from published studies or company submissions, expert clinical opinion will be considered.

Given the lack of clinical data on the effectiveness of sequences of AD treatments, the cost effectiveness analysis will, in an initial phase prior to the first Appraisal Committee Meeting (ACM), compare individual treatments against each other (as described at the beginning of Section 6). Once the EAG's conclusions on the ranking of cost effectiveness for all individual treatments has been discussed in the first ACM, the EAG can conduct further analysis of the cost effectiveness of treatment sequences if considered appropriate by the committee and provide these results for discussion at the second ACM.

The cost effectiveness of the interventions will be estimated in terms of an incremental cost per additional QALY gained, as well as the incremental cost per LYG. As appropriate, cost data will be obtained from NHS reference costs[30], Unit Costs of Health and Social Care,[31] eMit[32] and BNF,[33] published sources or company submissions. Costs will consist of direct medical costs (e.g. drug costs and cost of adverse events, monitoring and administering treatment) and direct non-medical costs (e.g. healthcare professional's costs). Resource use and costs will be valued from the NHS and Personal Social Services perspective. Both costs and outcomes will be discounted at 3.5% per annum after the first year in accordance with NICE methods guide.[24] The time horizon for the economic analysis will be long enough to reflect any differences in costs or outcomes between the technologies under comparison.

6.6 Methods for estimating quality of life

As discussed in Section 4, AD is currently uncurable, and the goal of treatment is to improve symptoms and achieve long-term disease control. Ideally, evidence of the impact of treatments included in this review on HRQoL will be available directly from identified trials. In the absence of such evidence, any *de novo* economic model may use indirect evidence on quality of life from alternative literature sources, such as related technology appraisals or clinical guidelines. In accordance with NICE methods guide, utility values will be taken from studies that have been based on the general population preferences elicited using a choice-based method. Preference will be given to EQ-5D values for measuring HRQoL in adults. Utility data will also be adjusted for age using data from the Health Survey of England.[36]

6.7 Analysis of uncertainty

As a standard, the model will be probabilistic; that is, all appropriate input parameters will be entered as probability distributions to reflect their imprecision and Monte Carlo simulation will be used to reflect this uncertainty in the model's results. In addition, uncertainty will also be explored through one-way sensitivity analysis. The outputs of probabilistic sensitivity analysis (PSA) will be presented in the cost-effectiveness plane and through the use of cost-effectiveness acceptability curves. One-way sensitivity analysis outputs will be presented in tables and tornado diagrams. Where possible, uncertainty pertaining to the structural assumptions used will be assessed in scenario analyses using alternative structural assumptions.

7 HANDLING THE COMPANY SUBMISSION(S)

All data submitted by the company/sponsors will be considered if received by the EAG on by September 2021. Data arriving after this date will not be considered. Data meeting the inclusion criteria for the review will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the EAG judges that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a *de-novo* model.

Any 'commercial in confidence' data taken from a manufacturer's submission, and specified as confidential in the supplied check list, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant manufacturer name, for example, in brackets). Any 'academic in confidence' data taken from a manufacturer's submission, and specified as confidential in the supplied check list, will be highlighted in yellow and underlined in the assessment report. Any 'depersonalised' data taken from a company submission, and specified as confidential in the check list, will be highlighted in pink and underlined in the assessment report (followed by an indication of the relevant company name, for example, in brackets).

8 COMPETING INTERESTS OF AUTHORS

None.

9 APPENDICES

9.1 Tools used to classify severity of atopic dermatitis

Overview of the key tools applied in the classification of severity of atopic dermatitis and the impact of the disease on patient quality of life[22]

Scale	Description
Disease severity	
EASI	The body is divided into four regions: • head and neck; • trunk;

	• upper limbs; • lower limbs. The extent of atopic dermatitis in each region is assessed and a score assigned based on the percentage of the region affected, scoring from 0 (no active eczema) to 6 (90%–100% of the region is involved). Severity of disease is assessed on a four-point scale, from none (0) to severe (3), where each region is evaluated for intensity of: • erythema; • oedema/papulation; • excoriation; • lichenification. The severity score is multiplied by the area score and a designated "multiplier" for the individual regions. The final EASI score is the total of the separate scores for the four regions, with a maximum EASI score of 72. Severity strata for EASI reported by Chopra et al:[37] • clear: 0; • mild:·1–5.9; • moderate: 6.0–22.9; • severe: 23.0–72. Response to treatment is the percentage reduction from baseline score.
SCORAD	Determines extent and severity of atopic dermatitis and includes a patient-reported assessment of itch and sleeplessness. The SCORAD score for an individual is calculated using the equation: A/5 + 7B/2 + C. A measures the extent of atopic dermatitis. The affected sites are shaded on a drawing of the body, with each part of the body assigned a different proportion: • head and neck 9%; • upper limbs 9% each; • lower limbs 18% each; • anterior trunk 18%; • back 18%; • genitals 1%. The score for A is the sum of the individual parts of the body, with a maximum score of 100%. B assess the intensity of disease. A representative area of atopic dermatitis is selected and, in that area, the intensity of the specific signs is assessed on a four-point scale (0=none through to 3= severe). Signs evaluated: • redness; • swelling;

	• oozing/crusting; • scratch marks; • skin thickening; • dryness. The score for B is the total of all intensity scores, with a maximum score of 18. C captures the symptoms of itch and sleep loss. The patient scores each symptom on a visual analogue scale from 0 (no symptom) to 10 (worst imaginable). The scores for each symptom are added together. The maximum SCORAD score is 103. Severity is defined as: • mild, score of <25 • moderate, score of 25–50 • severe, score of >50.
IGA	Assessment based on the overall appearance of lesions at a given point in time. Five-point score categorised as clear (0), almost clear (1), mild (2), moderate (3) and severe (4). Moderate is categorised as, "*Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present*". Severe is defined as, "*Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present*".
Quality of life	
DLQI	Most commonly used QoL tool in dermatology. A self-administered, dermatology-specific questionnaire comprising 10 items that focus on six dimensions: symptoms; daily activities; leisure; work; personal relationships; and treatment. Designed to gauge the patients' perception of the impact of their skin disease on QoL over the previous week. Each question is scored on a four-point scale from not at all (0) to very much (3). Maximum score of 30.
POEM	A self-administered disease-specific questionnaire, focusing on the illness as experienced by the patient. Involves seven questions about the frequency of eczema symptoms over the last week from no days (0), 1-2 days (1), 3-4 days (2), 5-6 days (3), to every day (4). Symptoms evaluated are: itch; sleep loss; bleeding; oozing/weeping; cracking of skin; flaking of skin; and skin feels dry/rough to the touch. POEM score is the total of scores reported for each question, with a maximum score of 28. Scores of 8–16, 17–24 and 25–28 represent moderate, severe and very severe atopic dermatitis, respectively.

Worst Pruritus NRS	WP-NRS is a single-item patient-reported outcome questionnaire designed to determine itch severity in the past 24 hours. Peak pruritis (worst itch) is evaluated using a rating scale from no itch (0) to worst imaginable itch (10). A change of 2–4-points in WP-NRS has been suggested as a clinically relevant, within-person response to treatment.[38]

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QoL, quality of life; SCORAD, SCORing Atopic Dermatitis.

Appendix 9.2. Draft search strategies

Clinical draft search strategy

Database: MEDLINE (OVID host)

- Search strategy is adapted from identified systematic review;[26]
- Animal-only studies to be excluded;
- No limits to be applied for language.

1. exp Eczema/ or eczema*.tw.

2. exp Dermatitis, Atopic/

3. exp Dermatitis/ or dermatitis.tw.

4. or/1-3

5. Cyclosporine/

6. (c?closporin* or 'Cy A' or CyA or Cy-A or 'Cs A' or CsA or Cs-A or csaneoral or neoral or sandimmun*).tw.

7. (dupilumab or dupixent or 'regn 668' or REGN-668 or regn668 or 'sar 231893' or sar-231893 or sar231893 or 420K487FSG or 1190264-60-8).tw.

8. (baricitinib or olumiant or 'ly 3009104' or ly3009104 or ly-3009104 or 'incb 028050' or incb-028050 or incb028050 or 'incb 28050' or incb-28050 or incb28050 or ISP4442I3Y or 1187594-09-7).tw.

9. (abrocitinib or 'pf 04965842' or pf04965842 or pf-04965842 or 'pf 4965842' or pf-4965842 or pf4965842 or 73SM5SF3OR or 1622902-68-4).tw.

10. (tralokinumab or 'cat 354' or cat354 or cat-354 or GK1LYB375A or 1044515-88-9).tw.

11. (upadacitinib* or rinvoq* or 'ABT 494' or ABT-494 or ABT494 or 4RA0KN46E0 or 1310726-60-3 or 1607431-21-9).tw.

12. Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/

13. ((humanized adj8 (monoclonal* or antibod* or MoAb* or mAb or mAbs or fab*1)) or rhuMAb*).tw.

14. (chim?eric adj3 (monoclonal* or antibod* or MoAb* or mAb or mAbs)).tw.

15. ((biological*1 or biologic*1) adj (treatment* or therap* or medicine* or drug* or agent* or product*)).tw.

16. (biologic* response modifier* or BRM*).tw.

17. targeted therap*.tw.

18. (systemic adj immunosuppressive treatment$).tw.

19. immuno-modulatory treatment$.tw.

20. anti inflammatory treatment$.tw.

21. Immunosuppressive Agents/

22. Anti-Inflammatory Agents/

23. Janus Kinase Inhibitors/

24. Interleukins/ or interleukin-4/ or interleukin-13/

25. or/5-24

26. randomized controlled trial.pt.

27. controlled clinical trial.pt.

28. randomized.ab.

29. placebo.ab.

30. clinical trials as topic.sh.

31. randomly.ab.

32. trial.ti.

33. or/26-32

34. exp animals/ not humans.sh.

35. 33 not 34

36. 4 and 25 and 35

37. limit 36 to ed=20190801-20210611

Draft search strategy for economic evaluations

1. exp Eczema/ or eczema*.tw.
2. exp Dermatitis, Atopic/

3. exp Dermatitis/ or dermatitis.tw.
4. or/1-3
5. Cyclosporine/
6. (c?closporin* or 'Cy A' or CyA or Cy-A or 'Cs A' or CsA or Cs-A or csaneoral or neoral or sandimmun*).tw.
7. (dupilumab or dupixent or 'regn 668' or REGN-668 or regn668 or 'sar 231893' or sar-231893 or sar231893 or 420K487FSG or 1190264-60-8).tw.
8. (baricitinib or olumiant or 'ly 3009104' or ly3009104 or ly-3009104 or 'incb 028050' or incb-028050 or incb028050 or 'incb 28050' or incb-28050 or incb28050 or ISP4442I3Y or 1187594-09-7).tw.
9. (abrocitinib or 'pf 04965842' or pf04965842 or pf-04965842 or 'pf 4965842' or pf-4965842 or pf4965842 or 73SM5SF3OR or 1622902-68-4).tw.
10. (tralokinumab or 'cat 354' or cat354 or cat-354 or GK1LYB375A or 1044515-88-9).tw.
11. (upadacitinib* or rinvoq* or 'ABT 494' or ABT-494 or ABT494 or 4RA0KN46E0 or 1310726-60-3 or 1607431-21-9).tw.
12. Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/
13. ((humanized adj8 (monoclonal* or antibod* or MoAb* or mAb or mAbs or fab*1)) or rhuMAb*).tw.
14. (chim?eric adj3 (monoclonal* or antibod* or MoAb* or mAb or mAbs)).tw.
15. ((biological*1 or biologic*1) adj (treatment* or therap* or medicine* or drug* or agent* or product*)).tw.
16. (biologic* response modifier* or BRM*).tw.
17. targeted therap*.tw.
18. (systemic adj immunosuppressive treatment$).tw.
19. immuno-modulatory treatment$.tw.
20. anti inflammatory treatment$.tw.
21. Immunosuppressive Agents/
22. Anti-Inflammatory Agents/
23. Janus Kinase Inhibitors/
24. Interleukins/ or interleukin-4/ or interleukin-13/
25. or/5-24
26. Economics/
27. exp "Costs and Cost Analysis"/

28. Economics, Nursing/
29. Economics, Medical/
30. Economics, Pharmaceutical/
31. exp Economics, Hospital/
32. Economics, Dental/
33. exp "Fees and Charges"/
34. exp Budgets/
35. budget*.ti,ab,kf.
36. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.
37. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
38. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.
39. (value adj2 (money or monetary)).ti,ab,kf.
40. exp models, economic/
41. economic model*.ab,kf.
42. markov chains/
43. markov.ti,ab,kf.
44. monte carlo method/
45. monte carlo.ti,ab,kf.
46. exp Decision Theory/
47. (decision* adj2 (tree* or analy* or model*)).ti,ab,kf.
48. or/26-47
49. 4 and 25 and 48
50. limit 49 to yr="2014 -Current"
51. exp animals/ not humans.sh.
52. 50 not 51

Draft search strategy for HRQoL studies

1. exp Eczema/ or eczema*.tw.

2. exp Dermatitis, Atopic/
3. exp Dermatitis/ or dermatitis.tw.
4. or/1-3
5. Quality-Adjusted Life Years/
6. Value of Life/
7. (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.
8. (quality adjusted or adjusted life year$).ti,ab,kf.
9. disability adjusted life.ti,ab,kf.
10. daly$1.ti,ab,kf.
11. ((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf.
12. (multiattribute$ or multi attribute$).ti,ab,kf.
13. (utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kf.
14. utility.ab. /freq=2
15. utilities.ti,ab,kf.
16. disutili$.ti,ab,kf.
17. (HSUV or HSUVs).ti,ab,kf.
18. health$1 year$1 equivalent$1.ti,ab,kf.
19. (hye or hyes).ti,ab,kf.
20. (hui or hui1 or hui2 or hui3).ti,ab,kf.
21. (illness state$1 or health state$1).ti,ab,kf.
22. (euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kf.
23. (eq-sdq or eqsdq).ti,ab,kf.
24. (short form$ or shortform$).ti,ab,kf.
25. (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.
26. (sf6 or sf 6 or sf6d or sf 6d or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).ti,ab,kf.
27. (sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf.
28. (sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf.
29. (sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf.

30. (15D or 15-D or 15 dimension).ti,ab,kf.
31. (standard gamble$ or sg).ti,ab,kf.
32. (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.
33. or/5-32
34. 4 and 33
35. limit 34 to yr="2014 -Current"
36. exp animals/ not humans.sh.
37. 35 not 36

Appendix 9.3. Data extraction forms

Data extraction form for characteristics of clinical effectiveness studies

Characteristic	Description
Study name	
Study references (insert citations from reference manager)	
Country(ies) where the clinical trial was conducted	
Multicentre trial (number, location)	
Trial sponsors	
Date the clinical trial was conducted	
Trial design (e.g. parallel, crossover, or cluster trial)	
Trial duration (treatment duration and follow-up)	
Inclusion criteria	
Exclusion criteria	
Concomitant medications	
Rescue therapy	
Outcomes	
Subgroups	
Criteria for determination of moderate to severe AD	

Abbreviation: AD, atopic dermatitis.

Data extraction form for baseline characteristics of populations enrolled in clinical effectiveness studies

Characteristic	Intervention (N=)	Comparator (N=)
Mean or median age, years		
Gender, n (%)		
Duration of AD		
Race		
• White, n (%)		
• Black or African American, n (%)		
• Asian, n (%)		
Mean or median EASI score		
Mean or median IGA score		
Mean or median DLQI score		
Mean or median SCORAD score		
Mean or median peak pruritus NRS score		
% BSA affected		
Prior treatment		
OCS		
Immunosuppressant		
TCS		
TCI		

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Data extraction form for information on interventions administered in clinical effectiveness studies

Characteristic	Intervention (N=)	Comparator (N=)
Study name		
Drug name		
Delivery		
Dose		
Number of cycles		
Length per cycle		
Notes		

Data extraction form for outcomes of interest in clinical effectiveness studies

	Intervention (N=)	Comparator (N=)
Study name		
Proportion of people achieving EASI 50 + ΔDLQI ≥4		
Proportion of people achieving EASI 75		
Change in EQ-5D score from baseline		
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study)		
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available)		
Number of days free from TCS during treatment		
Proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved		
Serious adverse effects of treatment		

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Data extraction form for quality assessment of clinical effectiveness studies

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
Study name				
Random sequence generation				
Allocation concealment				
Blinding (who [participants, personnel], and method)				
Blinding of outcome assessment				
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)				
Selective reporting				

Appendix 9.4. Drummond checklist

Item	Yes	No	Not clear	Not appropriate
Study design				
1. The research question is stated.	☐	☐	☐	☐
2. The economic importance of the research question is stated.	☐	☐	☐	☐
3. The viewpoint(s) of the analysis are clearly stated and justified.	☐	☐	☐	☐
4. The rationale for choosing alternative programmes or interventions compared is stated.	☐	☐	☐	☐
5. The alternatives being compared are clearly described.	☐	☐	☐	☐
6. The form of economic evaluation used is stated.	☐	☐	☐	☐
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	☐	☐	☐	☐
Data collection				
8. The source(s) of effectiveness estimates used are stated.	☐	☐	☐	☐

9. Details of the design and results of effectiveness study are given (if based on a single study).	☐	☐	☐	☐
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	☐	☐	☐	☐
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	☐	☐	☐	☐
12. Methods to value benefits are stated.	☐	☐	☐	☐
13. Details of the subjects from whom valuations were obtained were given.	☐	☐	☐	☐
14. Productivity changes (if included) are reported separately.	☐	☐	☐	☐
15. The relevance of productivity changes to the study question is discussed.	☐	☐	☐	☐
16. Quantities of resource use are reported separately from their unit costs.	☐	☐	☐	☐
17. Methods for the estimation of quantities and unit costs are described.	☐	☐	☐	☐
18. Currency and price data are recorded.	☐	☐	☐	☐
19. Details of currency of price adjustments for inflation or currency conversion are given.	☐	☐	☐	☐
20. Details of any model used are given.	☐	☐	☐	☐
21. The choice of model used and the key parameters on which it is based are justified.	☐	☐	☐	☐
Analysis and interpretation of results				
22. Time horizon of costs and benefits is stated.	☐	☐	☐	☐
23. The discount rate(s) is stated.	☐	☐	☐	☐
24. The choice of discount rate(s) is justified.	☐	☐	☐	☐
25. An explanation is given if costs and benefits are not discounted.	☐	☐	☐	☐
26. Details of statistical tests and confidence intervals are given for stochastic data.	☐	☐	☐	☐
27. The approach to sensitivity analysis is given.	☐	☐	☐	☐

28. The choice of variables for sensitivity analysis is justified.	☐	☐	☐	☐
29. The ranges over which the variables are varied are justified.	☐	☐	☐	☐
30. Relevant alternatives are compared.	☐	☐	☐	☐
31. Incremental analysis is reported.	☐	☐	☐	☐
32. Major outcomes are presented in a disaggregated as well as aggregated form.	☐	☐	☐	☐
33. The answer to the study question is given.	☐	☐	☐	☐
34. Conclusions follow from the data reported.	☐	☐	☐	☐
35. Conclusions are accompanied by the appropriate caveats.	☐	☐	☐	☐

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