Research Protocol
Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people
7th June 2016

Produced by CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York

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1 Plain English summary

Psoriasis is a chronic but non-contagious inflammatory disease of the skin and joints. The disease predominantly affects body parts like the scalp, elbows, knees and lower back that features a typical red, scaly and flaky skin also known as plaque psoriasis. The prevalence of psoriasis in the UK is estimated to be around 0.55% in children under 10 years and 1.4% between 10 to 19 year olds, with both genders equally affected.

Adult psoriasis is typically treated in three stages. As a first-line treatment, traditional topical therapies (such as corticosteroids, vitamin D and vitamin D analogues, dithranol and tar preparations) are administered. Second-line treatments can include phototherapies (broad- or narrow-band ultraviolet B light and psoralen plus UVA light) and systemic non-biological drugs such as ciclosporin and methotrexate. As a third-line treatment, systemic 'biological' therapies such as adalimumab, etanercept, infliximab, ustekinumab and secukinumab can be used.

The purpose of this project is to assess the benefits and adverse effects of three biological therapies (adalimumab, etanercept and ustekinumab) licensed for the treatment of plaque psoriasis in children and young people. This will be done by identifying and analysing data from relevant clinical trials. This study will also evaluate whether these three biological therapies are a cost-effective use of NHS resources for treating psoriasis in children and young people.

2 Decision problem

Objectives

The aim of the study is to determine the clinical effectiveness and cost-effectiveness of adalimumab, etanercept and ustekinumab within their respective licensed indications, for the treatment of plaque psoriasis in children and young people. If evidence allows, the clinical- and cost-effectiveness of sequential use of these treatments will also be evaluated.

Background

Psoriasis is a chronic but non-contagious inflammatory disease of the skin and joints.[1] The disease predominantly affects body parts like the scalp, elbows, knees and lower back that features a typical red, scaly and flaky skin also known as plaque psoriasis.[2] Plaque psoriasis is the most common type of psoriasis, although there are also other types of psoriasis such as *guttate* psoriasis (mostly in the trunk area), flexural psoriasis (affects the flexures), palmoplantar pustulosis psoriasis (affects the palms), and psoriatic nail diseases.[2] In children, plaques lesions appear most frequently on the scalp followed by the extensor surfaces of the extremities and the trunk.[3]

Psoriasis can appear at any age although it predominantly starts during adulthood.[1, 2, 4] The prevalence of psoriasis varies across the world ranging from 0-2.1% in children and 0.91-8.5% in adult population.[5] The prevalence of psoriasis in the UK is estimated to be around 0.4% and 2.2% for children (including adolescents) and adults, respectively, with both genders equally affected.[6]

The aetiology of psoriasis remains largely unknown; however, genetic predisposition and environmental factors are believed to be the key players.[7, 8] It is estimated that the heritability of psoriasis is 60-90%, however, a worldwide positive family history of psoriasis ranges between 4.5% to 88%.[9] Among environmental factors: alcohol consumption, infection, emotional stress, medications, obesity and smoking may be risk factors for psoriasis.[1, 9]

The natural history of psoriasis varies by clinical subtype, that is, it may present as chronic, stable plaques with intermittent remissions and exacerbations, or acutely with a rapid progression and widespread involvement.[1] For example, plaque psoriasis usually manifests as a chronic disease with intermittent remissions and in some cases joints and eyes can be involved.[1] In contrast to adults, plaque psoriasis in children is less scaly and the lesions are often smaller and thinner that can result in delayed diagnosis of the disease.[3] In children, plaques appear most frequently on the scalp and may lead to hair loss (psoriatic alopecia) if it reaches severe stage.[3]

According to NICE's guideline [CG153], in England, psoriasis patients are treated in three stages.[10] As a first-line therapy, traditional topical therapies (such as corticosteroids, vitamin D and vitamin D analogues, dithranol and tar preparations) are administered. Second-line therapy includes phototherapies narrow-band ultraviolet B light and psoralen plus UVA light [PUVA]) and systemic non-biological agents such as ciclosporin, methotrexate and acitretin are administered. As a third-line therapy, systemic biological therapies such as the tumour necrosis factor antagonists: adalimumab, etanercept and infliximab, and the monoclonal antibody ustekinumab that targets interleukin-12 (IL-12) and IL-23 can be provided.[10]

NICE technology appraisals encompass all systemic biological therapies with regulatory approval for the treatment of plaque psoriasis in adults. However, three biologics (adalimumab, etanercept and ustekinumab) have regulatory approval for the treatment of plaque psoriasis in children and young people, but as yet no NICE technology appraisal guidance is available for treating children and adolescents in the UK. Therefore, the aim of this project is to conduct an evaluation of the clinical and cost-effectiveness of these three biological therapies for the treatment of plaque psoriasis in children and young people.

Interventions

Adalimumab (Humira, AbbVie) is a fully human immunoglobulin G1 monoclonal antibody that inhibits the activity of tumour necrosis factor (TNF). It has a marketing authorisation in the UK for treating severe chronic plaque psoriasis in children and adolescents from 4 years of age who have an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Etanercept (Enbrel, Pfizer) is a recombinant human TNF receptor fusion protein that inhibits the activity of TNF. It has a marketing authorisation in the UK for treating chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Ustekinumab (Stelara, Janssen) is a fully human monoclonal antibody that acts as a cytokine inhibitor by targeting interleukin‑12 and interleukin‑23. It prevents the inflammation associated with psoriasis. It has a marketing authorisation for treating moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Table 1 Summary of drug properties and marketing authorisations

Treatment	Age range	Disease status	Mechanism of action	Dose / frequency	Treatment pathway
Adalimumab	4 years and older	Severe chronic plaque psoriasis	TNF-α inhibitor	0.8mg/kg up to a maximum of 40 mg at weeks 0 and 1, then every 2 weeks thereafter	Where topical therapy and phototherapies are inadequate or inappropriate
Etanercept	6 years and older	Severe chronic plaque psoriasis	TNF-α inhibitor	0.8mg/kg up to a maximum of 50 mg weekly for up to 24 weeks	Where systemic therapies or phototherapies are inadequate or not tolerated
Ustekinumab	12 years and older	Moderate to severe plaque psoriasis	IL-12/IL-23 inhibitor	0.75mg/kg for bodyweight <60kg; 45mg for bodyweight 60-100kg; 90mg for bodyweight >100kg at weeks 0 and 4 then every 12 weeks thereafter	Where systemic therapies or phototherapies are inadequate or not tolerated

Issues to be considered in this technology assessment

Based on the differences in the marketing authorisation, the evaluation will need to consider the clinical and cost-effectiveness of the interventions at a number of points in the treatment pathway: when patients are eligible for systemic therapy (conventional or biologic); after a conventional systemic therapy has been tried and failed; and after a biologic therapy. The potential impact of age (children versus young people) and disease severity will also be explored.

Other issues such as the potential response modifying effects of sex, age at diagnosis, time since diagnosis, body mass index, and co-morbid psoriatic arthritis may also be relevant. The relevance of adult data to the treatment of disease in children and young people will also be considered.

Previous NICE technology appraisals

NICE has published the following technology appraisal guidance for treating psoriasis in adults: TA103 (etanercept), TA134 (infiliximab), TA146 (adalimumab), TA180 (ustekinumab), TA350 (secukinumab) and TA368 (apremilast).[11-16] See **Error! Reference source not found.** for details.

Table 2 Summary of previous NICE appraisals for biologic drugs in adults

Technology appraisal	Biologic drug name	Summary of NICE recommendations
NICE TA103 [11]	Etanercept	Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met. • The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10. • The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments. Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these patients. An adequate response is defined as either: • a 75% reduction in the PASI score from when treatment started (PASI 75) **or** • a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from when treatment started.
NICE TA134 [13]	Infliximab	Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met. • The disease is very severe as defined by a total PASI of 20 or more and a DLQI of more than 18. • The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA, or the person is intolerant to or has a contraindication to these treatments. Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks
NICE TA146 [12]	Adalimumab	Adalimumab is recommended as a treatment option for adults with plaque psoriasis for whom anti-tumour necrosis factor (TNF) treatment is being considered and when the following criteria are both met. • The disease is severe as defined by a total PASI of 10 or more and a DLQI of more than 10. • The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant of, or has a contraindication to, these treatments. Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks.
NICE TA180 [14]	Ustekinumab	Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met. • The disease is severe, as defined by a total PASI score of 10 or more and a DLQI score of more than 10. • The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA, or the person is intolerant of or has a contraindication to these treatments. • The manufacturer provides the 90 mg dose (two 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial. Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment.
NICE TA350 [15]	Secukinumab	Secukinumab is recommended, within its marketing authorisation, as an option for treating adults with plaque psoriasis only when: • the disease is severe, as defined by a total PASI of 10 or more and a DLQI of

		more than 10 • the disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA, or these treatments are contraindicated or the person cannot tolerate them • the company provides secukinumab with the discount agreed in the patient access scheme. Secukinumab treatment should be stopped in people whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these people.
NICE TA368 [16]	Apremilast	Apremilast is **not recommended** within its marketing authorisation for treating psoriasis, that is, for treating adults with moderate to severe chronic plaque psoriasis that has not responded to systemic therapy, or systemic therapy is contraindicated or not tolerated.

Areas of uncertainty identified in the previous NICE technology appraisals for adults

In the previous NICE technology appraisals (TAs) for adults, a number of key areas of uncertainty and potential limitations of the evidence base were identified. These include, but are not limited to:

- The lack of consideration given to the sequential use of the interventions. With the exception of NICE technology appraisal TA368 (apremilast), only one treatment option was considered before best supportive care.
- Limitations with the network meta-analysis used to address the lack of direct head-to-head trial evidence evaluating the relative efficacy and safety of the interventions. Heterogeneity (particularly in relation to prior treatments received by patients in the trials) was a common concern that had not been adequately addressed in previous TAs.
- The lack of long-term data on disease progression and maintenance of PASI response.
- The rate of treatment withdrawal and the adverse effects associated with long-term use of the interventions.
- Uncertainty in the utility values used in the cost-effectiveness models. Most of the previous TAs used utility values based on an estimate of the relationship between PASI response rates and changes in DLQI score mapped onto EQ-5D utility values.
- The effectiveness and costs of best supportive care and the duration and costs associated with inpatient stay for individuals who do not respond adequately to treatment.
- Limited use of registry data as a source of information.
- The time horizon of 10 years used in previous TAs was considered too short.

For the clinical and cost-effectiveness of adalimumab, etanercept and ustekinumab for plaque psoriasis in children and adolescents, the assessment group will consider and attempt to address these limitations and areas of uncertainty using relevant evidence where available.

3 Report methods for synthesis of evidence of clinical effectiveness

A systematic review of the clinical effectiveness will be performed following the general principles recommended in CRD's guidance and the PRISMA statement. The protocol details will be submitted for registration on PROSPERO, an international database of prospectively registered systematic reviews in health and social care (http://www.crd.york.ac.uk/prospero/).

Search strategy

Initial searches of electronic databases will be conducted to identify relevant randomised controlled trials (RCTs) of adalimumab, etanercept and ustekinumab for children and young people with plaque psoriasis. Searches for studies will not be limited by date, language or study design. A draft search strategy developed in MEDLINE (Ovid) for the review of clinical efficacy is provided in appendix 1. This will be converted to run appropriately on other databases. Regulatory sources will be searched to identify biosimilars with marketing authorisation for psoriasis in children and/or young people. If any are identified, these will be added to the search strategy.

A separate search for RCTs of systemic non-biological (acitretin, methotrexate, ciclosporin) and biological therapies (infliximab, secukinumab) in children and/or young people with plaque psoriasis will be undertaken to inform network meta-analyses where appropriate.

The following resources will be searched: MEDLINE, MEDLINE In-Process, PubMed, Cumulative Index to Nursing & Allied Health (CINAHL), EMBASE, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, and Cochrane Central Register of Controlled Trials (CENTRAL).

In addition to utilising information and data from the company submissions, information on studies in progress, guidelines, unpublished research or research reported in the grey literature will also be sought by searching a range of relevant databases including: Conference Proceedings Citation Index-Science, PROSPERO, National Guideline Clearinghouse, NHS Evidence, NHS Clinical Knowledge Summaries, NICE evidence summaries: new medicines, ClinicalTrials.gov, WHO International Clinical Trials Registry portal and the EU Clinical Trials Register. At the time of receiving the company submission, update searches will be conducted to ensure the review remains up-to-date and covers all relevant evidence at the time of submission.

Information on adverse events will be identified from searching resources of the US and European drug regulatory agencies (i.e. FDA, EMEA). Where additional information is required, separate

searches will be conducted for studies reporting on the adverse events of drug unrestricted by date or study design.

Searches of electronic databases will be conducted as necessary to identify relevant sources of information on the natural history plaque psoriasis in children and young people and on the long-term effectiveness and sequential use of adalimumab, etanercept and ustekinumab.

Inclusion and exclusion criteria

Two reviewers will independently screen all titles and abstracts. Full manuscripts of any titles/abstracts that may be relevant will be obtained where possible and the relevance of each study assessed by two reviewers according to the criteria below. Any discrepancies will be resolved by consensus and, if necessary, a third reviewer will be consulted. Studies available only as abstracts will be included and attempts will be made to contact authors for further data.

Study design

For the review of clinical efficacy RCTs will be eligible (including any open-label extensions of RCTs).

Information on adverse events will also be sought from regulatory sources where appropriate. If further adverse events data are needed they will be sought from suitably large studies, including registries and observational studies.

To address the long-term effectiveness, adherence, and sequential use of therapies, published analyses based on large and long-term data sets (including studies of registry data) will also be considered.

Interventions

The relevant interventions are adalimumab, etanercept and ustekinumab.

Comparators

Relevant comparators are:

- Non-biological systemic therapy (including, but not limited to, ciclosporin and methotrexate)
- Topical therapy (for people in whom non-biological systemic therapy is not suitable), i.e. best supportive care
- Biological treatments used outside of their marketing authorisation (such as infliximab, adalimumab, etanercept or ustekinumab if used outside of the constraints of the relevant marketing authorisation in children and young people)
- Biosimilars of etanercept, adalimumab, or ustekinumab

- When appropriate, adalimumab, etanercept and ustekinumab will be compared with each other

Participants

Studies of children and/or young people who have moderate to severe plaque psoriasis will be included. Studies of guttate, erythrodermic, and pustular psoriasis will be excluded, as will studies of psoriatic arthritis.

Studies in children or young people with psoriasis in whom topical, systemic or phototherapies are inadequate, inappropriate or not tolerated will be eligible for inclusion. Participants aged below 12 years will be considered children, with those aged 12-17 years considered young people.

Outcomes

Data on the effectiveness, adverse effects, patient-centred outcome measures, costs to the health service, and cost-effectiveness will be extracted. The eligible outcomes will be:

- Severity of psoriasis such as body surface area (BSA), Physician's Global Assessment (PGA) score
- Response and remission rates (such as PASI 50/75/90 response)
- Relapse rate
- Rates of treatment discontinuation and withdrawal
- Short and long-term adverse effects of treatment (such as injection site and allergic reactions, serious infections, re-activation of infections including tuberculosis, malignancy)
- Health-related quality of life (such as Children's Dermatology Quality of Life Index (CDLQI), EQ-5D)

Data extraction strategy

Data relating to both study design and quality will be extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements will be resolved through consensus, and if necessary, a third reviewer will be consulted. If time constraints allow, attempts will be made where possible to contact authors for missing data. Data from studies with multiple publications will be extracted and reported as a single study.

Quality assessment strategy

The quality of RCTs will be assessed using the Cochrane risk of bias tool, with additional assessments made for baseline imbalance of important prognostic indicators.[17, 18] The relevant prognostic and treatment response indicators will be identified from both published research and clinical advice. The

risk of bias assessments will be performed by one reviewer, and independently checked by a second. Disagreements will be resolved through consensus, and if necessary, a third reviewer will be consulted.

The quality of non-randomised studies will be assessed using a checklist based on CRD Guidance [19] and used in other technology assessments for NICE. [20] This assesses study eligibility criteria and recruitment methods, baseline similarity of comparison groups, blinding of allocation, completeness of follow-up, and outcome reporting.

Methods of analysis/synthesis

The analysis and synthesis of clinical data in this review will be conducted in distinct sections. In the first instance the results of the data extraction in terms of study characteristics and quality assessment will be presented in a series of structured tables and summarised narratively. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques. Clinical, methodological and statistical heterogeneity will be investigated. If necessary, sensitivity analyses will be undertaken when possible. Evidence relating to the potential short- and long-term benefits of the biologic treatments will be investigated and synthesised using accepted methods. Subgroup analyses will be conducted where relevant data are available, including: sex, disease duration, psoriasis severity, weight/BMI, and presence of psoriatic arthritis. The serious adverse effects of these treatments will also be explored.

It is anticipated that trials conducting head-to-head comparisons of systemic biological therapies will not be available. Therefore, if feasible and appropriate, indirect and/or mixed treatment comparisons will be conducted using Bayesian statistical methods to provide information on the benefits of the active treatments relative to the appropriate comparators and each other.[21] Meta-analysis using mixed treatment comparisons enables the estimation of different parameters from several studies with similar comparisons to be combined when direct evidence on comparisons of interest is absent or sparse.[22] For example, should active treatments being evaluated have a common comparator of placebo, this would allow a network to be established between them, providing information on the benefits of these treatments relative to placebo and to each other.

4 Report methods for synthesising evidence of cost-effectiveness

Searches will be used to identify studies of the cost-effectiveness of adalimumab, etanercept and ustekinumab (including biosimilars) for the treatment of plaque psoriasis in children and young people. The searches will be undertaken in NHS Economic Evaluation Database (NHS EED).

Additional searches will be undertaken as necessary in the databases listed in Section 3. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) for the treatment of plaque psoriasis in children and young people will be included in the review of economic literature. Additional hand-searching of related NICE technology appraisals for the treatment of plaque psoriasis in adults (TA 103, 134, 146, 180, 350, 368) will also be undertaken.

The quality of the cost-effectiveness studies in children and young people will be assessed according to a checklist updated from that developed by Drummond *et* al. [23] This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Health and Care Excellence (NICE). [24] This information will be tabulated and summarised within the text of the report. In particular information will be extracted on the comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).

The review will examine existing decision-analytic models (including those in the previous TAs in adults) in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will assist in the conceptualisation of a new de-nova model for children and adolescents. We will also consult with clinical advisors at this conceptualisation stage.

It is anticipated that a separate search will be undertaken to identify published studies reporting utility estimates in children and adolescents which i) directly estimate EQ-5D utility values; and ii) establish the relationship between generic measures of utility (in particular, the EQ-5D) and quality of life measures (such as the Dermatology Quality of Life Index (DLQI) and CDLQI) and PASI response score (including mapping studies).

The other areas of uncertainty identified in the previous NICE technology appraisals for adults (see section 2) and the presence of any additional data gaps identified during the development of the model may require additional searches. We will also work with our clinical advisors at the start of the project to identify relevant UK data sources (e.g. British Association of Dermatologists Biologic

Interventions Register (BADBIR)) and will make contact with the relevant investigators with a view to securing access to this data should this be required.

- **Development of a new decision-analytic model**

A new decision-analytic model will be developed to estimate the cost-effectiveness of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people. Where data permits, the comparators included will be consistent with the final NICE scope. The model will be developed in accordance with the NICE reference case. The model will have a time horizon sufficiently long to reflect differences in costs and outcomes between the interventions being compared. All costs will be considered from the perspective of the National Health Services and Personal Social Services. Both costs and quality-adjusted life years (QALYs) will be discounted at 3.5% per annum.

Where sufficient data permits an analysis, the cost-effectiveness assessment will also explore the sequential use of adalimumab, etanercept and ustekinumab as this has been identified as an important area of uncertainty in the previous appraisals in adults. However, it is envisaged that, due to limitations in existing data, such analyses are likely to be exploratory in nature. Furthermore, we do not envisage that these analyses will specifically address the optimal sequence for adalimumab, etanercept and ustekinumab and the potential comparators, but it will show how the cost-effectiveness of these interventions might be affected under different scenarios, e.g. in patients who have not had an adequate response, or who are intolerant to, one of the therapies or who have received prior biological therapies.

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise patients' care and subsequent disease progression and the impacts of alternative therapies on psoriasis, in a way that is clinically acceptable.
- To populate this model using the most appropriate data. This is likely to be identified systematically from published literature, routine data sources and potentially using data elicited from relevant clinical experts.
- To relate initial and intermediate outcomes (such as PASI response rate) to final health outcomes, expressed in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units which permit comparison with other uses of health service resources.

- To estimate the mean cost-effectiveness of each of the therapies based on an assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival.
- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this *parameter uncertainty*, is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, *decision uncertainty*. This is presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.
- To use scenario analysis to explore the sensitivity of the cost-effectiveness results to changes in the structural assumptions of the model and the time horizon over which the treatments are assessed.

The specific details of the data to be used to populate the model will have to await the development of the structure, the systematic searches of the literature and the company submissions. In terms of the structure, we anticipate developing a similar 2-part model commonly used in the previous NICE technology appraisals for adults: comprising a decision-tree to capture the initial response period (which will vary depending on the biological therapy) and a longer-term Markov model to inform longer term response rates and assumptions. Estimates of short-term response are likely to be derived from the clinical effectiveness review and associated syntheses. Estimates of the longer term prognosis for patients who continue or withdraw from treatment may use observational evidence relevant to clinical practice in England, identified by the reviews of clinical and cost-effectiveness. It is anticipated that the model will be developed in either Microsoft Excel or the statistical programming language of R; the choice of software will have to await the conceptualisation of the model.

Depending upon the limitations of the available data, it may be necessary to consider expert elicitation with a sample of UK experts who have experience of using biologics for the treatment of psoriasis in children and young people. If this is necessary, an interactive elicitation exercise will be designed to generate estimates of the relevant unknown parameters with uncertainty. [25]

5 Handling the company submissions

All data submitted by companies and other consultees will be considered if received by the review team no later than 31st August 2016. Data arriving after this date will only be considered if time constraints allow.

If efficacy and/or adverse effects data meet the inclusion criteria for the review then they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission will be assessed. This will include a detailed analysis of the appropriateness of the parametric and structural assumptions involved in any models in the submission and an assessment of how robust the models are to changes in key assumptions. Clarification on specific aspects of the model may be sought from the relevant company. An assessment of any differences between the published evidence, those submitted by the companies and any economic evaluation developed by us will be reported.

Any 'commercial in confidence' and 'academic in confidence' data taken from a company submission will be clearly marked in the NICE report (CIC or AIC) and removed by NICE from the subsequent submission to the HTA.

6 Competing interests of authors

None

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8 Appendices

8.1 Appendix 1: Draft search strategy for clinical effectiveness searches

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1946 to Present

29th April 2016

1 Psoriasis/ (28932)

2 (psorias$ or psoriat$).ti,ab. (35994)

3 parapsoriasis.ti,ab. (523)

4 (pustul$ adj2 palm$).ti,ab. (772)

5 1 or 2 or 3 or 4 (41820)

6 Adalimumab/ (3299)

7 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (4993)

8 Etanercept/ (4613)

9 (etanercept or enbrel or 185243-69-0).af. (6442)

10 Ustekinumab/ (401)

11 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (735)

12 6 or 7 or 8 or 9 or 10 or 11 (9809)

13 5 and 12 (2551)

14 exp Child/ (1659204)

15 exp Infant/ (1003645)

16 Adolescent/ (1723024)

17 (adolescen$ or baby or babies or child or children or boy or boys or girl or girls or infant$ or infanc$ or juvenile$ or paediatric or pediatric or preschooler$ or schoolboy$ or schoolgirl$ or schoolchild$ or teens or teenager$ or toddler$ or youth or youths or young people or young person$).ti,ab. (1633258)

18 14 or 15 or 16 or 17 (3441984)

19 13 and 18 (324)