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Assessment Group's Report
Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people

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Rider on responsibility for report

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Contributions of authors

Ana Duarte contributed to the protocol, the development of the economic model, the review of economic analyses, the interpretation of the results and the writing of the report.

Teumzghi Mebrahtu contributed to the protocol, study selection, data extraction, validity assessments and synthesis of the included studies. He also contributed to the interpretation of the results and the writing of the report.

Pedro Saramago Goncalves contributed to the protocol and conducted the network meta-analyses. He also contributed to the interpretation of the results and the writing of the report.

Melissa Harden developed the search strategies, conducted a range of searches to locate studies, and wrote the sections of the report relating to the literature searches.

Ruth Murphy provided expert clinical advice, contributed to the protocol, interpretation of the results and commented on drafts of the report.

Stephen Palmer contributed to the protocol, advised on the economic analysis, the interpretation of the results and commented on drafts of the report.

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Claire Rothery had overall responsibility for the cost-effectiveness sections. She contributed to the development of the protocol, the network meta-analyses, the economic model, and the economic analyses. She also contributed to the interpretation of the results and the writing of the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

Keywords

Psoraisis; children; young people; adalimumab; etanercept; ustekinumab; clinical effectiveness; cost-effectiveness

Abstract

Background

Psoriasis is a chronic inflammatory disease that predominately affects the skin. Adalimumab, etanercept and ustekinumab are the three biologics currently licensed for psoriasis in children.

Objective

To determine the clinical and cost-effectiveness of adalimumab, etanercept and ustekinumab within their respective licensed indications, for the treatment of plaque psoriasis in children and young people.

Design

Systematic review and economic model

Data sources

Searches of the literature and regulatory sources, contact with European psoriasis registries, company submissions and clinical study reports from manufacturers, previous NICE Technology Appraisals' documentation.

Methods

Included studies were summarised and subjected to detailed critical appraisal. A network meta-analysis incorporating adult data was developed to connect the effectiveness data in children and young people and populate a *de novo* decision analytic model.

The model estimated the cost-effectiveness of adalimumab, etanercept and ustekinumab to each other and to either methotrexate or best supportive care (BSC) depending on the position of the intervention in the management pathway.

Results

Nine studies (three RCTs and six observational studies) were included in the review of clinical effectiveness and safety.

Etanercept and ustekinumab lead to significantly greater improvements in psoriasis symptoms than placebo at 12 weeks' follow-up. The magnitude and persistence of effects beyond 12 weeks is less certain. Adalimumab lead to significantly greater improvements in psoriasis symptoms than methotrexate for some, but not all measures at 16 weeks. Observed quality of life benefits were inconsistent across different measures.

There was limited evidence of excess short-term adverse events. However, the relatively small number of observations and limited length of follow-up mean the possibility of rare events cannot be excluded.

Based on the economic assessment, the majority of incremental cost-effectiveness ratios for the use of biologics in children and young people exceeded NICE's usual range of cost-effectiveness and were reduced significantly only when combined assumptions that align with those for the management of psoriasis in adults were adopted.

Conclusions

The paucity of clinical and economic evidence to inform the cost-effectiveness of biological treatments in children and young people imposed a number of strong assumptions and uncertainties. Health-related quality of life (HRQoL) gains associated with treatment and the number of hospitalisations in children and young people are areas of considerable uncertainty. Findings suggest that biological treatments may not be cost-effective for the management of psoriasis in children and young people at £30,000 per QALY, unless a number of strong assumptions on HRQoL and costs of BSC are combined.

Future work recommendations

Adequately powered randomised trials are needed to inform the effectiveness of biological treatments in biologic-experienced populations of children and young people, particularly in younger children. Such trials should establish the impact of biological therapies on HRQoL in this population, ideally by collecting direct estimates of EQ-5D-Y.

Biologic registry data would help determine safety, patterns of treatment switching, and long-term withdrawal rates. Resource use and costs associated with BSC is another area requiring further research.

Study registration

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Plain English Summary

Psoriasis is an inflammatory disease that predominately affects the skin. It can greatly reduce a person's quality of life. A range of treatments are used in psoriasis, including the relatively new 'biologic' therapies. NICE currently recommends a number of biologic therapies for treating severe psoriasis in adults. The purpose of this project was to assess the benefits, harms and the cost-effectiveness of three biologic therapies that can be used in children – adalimumab, etanercept, and ustekinumab.

We identified and analysed all the data from relevant clinical trials. The results showed that adalimumab, etanercept and ustekinumab all improve the symptoms of psoriasis but the small amount of evidence from children mean that the longer-term effects are not so clear. The only way to estimate which treatment was best was to include extra evidence about the effects of these drugs when used in adults.

The economic assessment found that the use of biologics in children and young people would probably only be good value for NHS money if various circumstances and consequences of biologic treatment in children are considered to be the same as those in adults.

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List of abbreviations

ADA	Adalimumab
AEs	Adverse Events
AG	Assessment Group
APRE	Apremilast
AWMSG	All Wales Medicines Strategy Group
BAD	British Association of Dermatologist
BADBIR	British Association of Dermatologists Biologic Interventions Register
BIW	Bi-weekly
BNF	British National Formulary
BSA	Body Surface Area
BSC	Best Supportive Care
CDLQI	Children Dermatology Life Quality Index
CEA	Cost-effectiveness Analysis
CEACs	Cost-effectiveness acceptability curves
CG	Clinical Guideline
CI	Confidence Interval
CLAD	Censored Least Absolute Deviations
CRD	Centre for Reviews and Dissemination
CS	Cyclosporine
CSR	Clinical Study Report
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing & Allied Health
DARE	Database of Abstracts of Reviews of Effects
GDG	Guideline Development Group
DIC	Deviance Information Criterion
DLQI	Dermatology Life Quality Index
DMARDs	Disease-modifying anti-rheumatic drugs
EFA	Efalizumab
EMEA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions questionnaire
EQ-5D-Y	European Quality of Life-5 Dimensions questionnaire for Youth
ERG	Evidence Review Group
ETA	Etanercept

FDA	Food and Drugs Agency
FE	Fixed Effect
FUM-A	Fumaric Acid
GLiMs	Generalised Linear Models
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
HRQoL	Health Related Quality of life
ICER	Incremental Cost-effectiveness Ratio
IL	Inter-leucine
IPD	Individual level Patient Data
INF	Infliximab
IVR	Interactive Voice Response
IWR	Interactive Web Response
ITT	Intent-to-treat
LOCF	Last Observation Carried Forward
LOS	Length of Stay
MCID	Minimally Clinical Important Difference
MCMC	Markov Chain Monte Carlo
MIMS	Monthly Index of Medical Specialities
MTA	Multiple Technology Appraisal
MTX	Methotrexate
NHS	National Health Services
NMA	Network Meta-Analysis
NICE	National Institute for Care and Excellence
NRI	Non-responder Imputation
OLS	Ordinary Least Squares
ONS	Office of National Statistics
PASI	Psoriasis Area and Severity Index
PedsQL	Paediatrics Quality of Life
PGA	Physician Global Assessment
PLB	Placebo
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted Life Year

RCT	Randomised Controlled Trials
RE	Random Effects
RR	Relative Risk
SAEs	Serious Adverse Events
SD	Standard deviation
SEC	Secukinumab
SF-6D	Short Form–6 Dimension
sPGA	Physician Static Global Assessment
SPC	Summary of Product Characteristics
STA	Single Technology Appraisals
TA	Technology Appraisal
T-QoL	Teenager's Quality of Life Index
TNF-α	Alpha Tumour Necrosis Factor
UST	Ustekinumab
WHO	World Health Organisation

Glossary

Adverse effect: An abnormal or harmful effect caused by and attributable to exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism, or increases the susceptibility of the organism to other chemical or biological stress.

Between-study variance: Between-study variance is a measure of statistical heterogeneity that depends on the scale of the outcome measured. It represents the variation in reported study effects over and above the variation expected given the within-study variation.

Biological therapies (biologic): Any pharmaceutical product derived from biological sources. In PsA treatment these are generally monoclonal antibodies which bind to and inactivate immune cell signalling molecules (e.g. tumour necrosis factor and interleukins) thereby dampening the inflammatory response.

Biosimilar: An imitation biological medical product (such as an anti-TNF) usually marketed by a different manufacturer to the original biological product, once a patent has expired. The biosimilar should be similar to the original licensed product in terms of safety and efficacy.

Cyclosporin: A medication originally developed to prevent the immune system from rejecting transplanted organs, but which has also proved helpful in treating psoriasis.

Confidence Interval (CI): The typical ('classical' or 'frequentist') definition is the range within which the 'true' value (e.g. size of effect of an intervention) would be expected to lie if sampling could be repeated a large number of times (e.g. 95% or 99%).

Cost-benefit analysis: An economic analysis that converts the effects or consequences of interventions into the same monetary terms as the costs and compares them using a measure of net benefit or a cost–benefit ratio.

Cost-effectiveness analysis: An economic analysis that expresses the effects or consequences of interventions on a single dimension. This would normally be expressed in 'natural' units (e.g. cases cured, life-years gained). The difference between interventions in terms of costs and effects is typically expressed as an incremental cost-effectiveness ratio (ICER) (e.g. the incremental cost per life-year gained).

Cost–utility analysis: The same as a cost-effectiveness analysis, but the effects or consequences of interventions are expressed in generic units of health gain, usually quality-adjusted life-years (QALYs).

Credible interval: In Bayesian statistics, a credible interval is a posterior probability interval estimation that incorporates problem-specific contextual information from the prior distribution. Credible intervals are used for the purposes similar to those of confidence intervals in frequentist statistics.

Crohn's disease: An inflammatory condition of the digestive tract; rheumatic diseases are often associated with it and ulcerative colitis is related to it.

Deviance Information Criterion (DIC): A model fit statistics and used for Bayesian model comparison. The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed.

Disease-modifying anti-rheumatic drugs (DMARDs): DMARDs are drugs capable of modifying the progression of rheumatic disease. The term is, however, applied to what are now considered to be traditional (or conventional, cDMARDS) disease modifying drugs, in particular sulphasalazine, methotrexate and ciclosporin, as well as azathioprine, cyclophosphamide, antimalarials, penicillamine and gold. The newer agent leflunomide is also a DMARD. Biologics are not generally referred to as DMARDs, though occasionally bDMARD may be used.

European Quality of Life-5 Dimensions questionnaire (EQ-5D): A standardised instrument for measuring generic health-related quality of life, used in computation of the QALY.

Fixed-effect model: A statistical model that stipulates that the units under analysis (e.g. people in a trial or study in a meta-analysis) are the ones of interest, and thus constitute the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed effect model.

Health Assessment Questionnaire (HAQ): HAQ is a self-administered questionnaire measuring an individual's physical disability and pain. HAQ scores ability to perform various activities between 0 (without any difficulty) and 3 (unable to do), it is reported as an average of all activity scores.

Heterogeneity: In systematic reviews heterogeneity refers to variability or differences between studies in the estimates of effects. A distinction is sometimes made between "statistical heterogeneity"

(differences in the reported effects), "methodological heterogeneity" (differences in study design) and "clinical heterogeneity" (differences between studies in key characteristics of the participants, interventions or outcome measures).

Intention-to-treat (ITT): An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not.

Methotrexate (MTX): One of the oldest chemotherapy drugs used in treatment of cancer and autoimmune diseases such as rheumatoid and psoriatic arthritis.

Network meta-analysis (NMA) (synonym: mixed treatment comparison - MTC, indirect treatment comparison - ITC): Used when there is insufficient direct evidence linking two interventions, a meta-analysis comparing three or more different treatments using both direct comparison within RCTs and indirect comparison between trials based on a common comparator (such as placebo).

Placebo: An inactive substance or procedure administered to a patient, usually to compare its effects with those of a real drug or other intervention, but sometimes for the psychological benefit to the patient through a belief that s/he is receiving treatment.

Plaque psoriasis: The most common form of psoriasis, also known as psoriasis vulgaris, recognised by red, raised lesions covered by silvery scales. About 80% of patients with psoriasis have this type.

Psoriasis: A chronic skin disease characterised by inflammation and scaling. Scaling occurs when cells in the outer layer of skin are produced faster than normal and build up on the skin's surface. It is thought to be caused by a disorder of the immune system.

Psoriasis Area and Severity Index (PASI) score: A number representing extent of skin coverage, redness, scaliness and thickness of a person's psoriasis. PASI response is presented as PASI 50, PASI 75, PASI 90. This represents the reduction of the individual's PASI score from baseline as a percentage.

Psoriatic arthritis (PsA): A disease characterised by stiffness, pain, and swelling in the joints, especially of the hands and feet. It affects about 30% of people with psoriasis. Early diagnosis and treatment can help inhibit the progression of joint deterioration.

Quality Adjusted Life Year (QALY): An index of health gain where survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Quality of Life: A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity as well as other factors which might affect their physical, mental and social well-being.

Random effects model: A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

Randomised controlled trial (RCT) (synonym: randomised clinical trial): An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared.

Relative risk (RR) (synonym: risk ratio): The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability, or rate) is the ratio of people with an event in a group to the total number in the group. A RR of one indicates no difference between comparison groups. For undesirable outcomes, an RR of <1 indicates that the intervention was effective in reducing the risk of that outcome.

Residual deviance: An analysis used for model comparison and goodness-of-fit. The residual deviance is equal to the deviance for a given model minus the deviance for a saturated model. A saturated model is one where all of the predictions from the model are equal to the observed data values. Total residual deviance should approximate the number of data points for a good fit.

Rheumatoid arthritis (RA): A chronic autoimmune disease characterised by pain, stiffness, inflammation, swelling, and, sometimes, destruction of joints.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Statistical significance: An estimate of the probability of an association (effect) as large as or larger than what is observed in a study occurring by chance, usually expressed as a p-value.

Tumour necrosis factor alpha (TNF, TNFα): A cell signalling molecule (cytokine) involved in the inflammatory response pathway, known to be fundamental to the pathological processes causing psoriasis and psoriatic arthritis. It plays a key role in onset and persistence of joint and skin inflammation.

1 Scientific Summary

1.1 Background

Psoriasis is a chronic inflammatory disease of the skin and joints and typically features red, scaly and flaky skin also known as plaque psoriasis.

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.

The impact of psoriasis encompasses functional, psychological, and social dimensions. Factors that contribute to this include skin symptoms, psoriatic arthritis, treatment related problems, and the effect of living with a highly visible, disfiguring skin disease.

Existing psoriasis guidance for all age groups (NICE guideline CG153 in England), states that traditional topical therapies can be prescribed as a first-line therapy. Second-line therapies include phototherapy and non-biological systemic agents such as ciclosporin, methotrexate and acitretin. Third-line therapy includes systemic biological therapies. While there is currently no childhood-specific treatment pathway, CG153 highlights special considerations for children (e.g. referral to a specialist at presentation; avoidance of very potent corticosteroids, PUVA, and acitretin).

Adalimumab (Humira, AbbVie) etanercept (Enbrel, Pfizer) and ustekinumab (Stelara, Janssen) are the three biologics currently licensed in children, though the exact populations and ages for these licenses vary.

1.2 Objectives

The aim of the study was 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.

1.3 Methods

1.3.1 Methods of clinical review and network meta-analysis

Studies were identified through searches of the literature and regulatory sources and requests for clinical study reports from the relevant manufacturers. Registry data were identified though literature searches and direct contact with European psoriasis registries.

Studies of children and/or young people with moderate to severe plaque psoriasis, in whom topical, systemic or phototherapies were inadequate, inappropriate or not tolerated were eligible for inclusion.

Relevant interventions were adalimumab, etanercept and ustekinumab, and relevant comparators included: alternative biologic therapies with relevant marketing authorisation (adalimumab, etanercept or ustekinumab); non-biological systemic therapy; topical therapy; biologic treatments used outside of their marketing authorisation (including adalimumab, etanercept or ustekinumab if used outside of the constraints of the relevant marketing authorisation in children and young people); and biosimilars of etanercept, adalimumab, or ustekinumab.

Data on the effectiveness, adverse effects, patient-centred outcome measures, costs to the health service, and cost-effectiveness were eligible for inclusion.

RCTs were eligible for the review of clinical efficacy. To address longer-term measures of efficacy and drug survival, published analyses based on large and long-term data sets were also considered. Two reviewers independently selected studies for inclusion, with all extraction and quality assessment undertaken by one reviewer and checked by a second.

The results of included studies were presented in a series of structured tables, summarised narratively and subjected to detailed critical appraisal. A naive indirect treatment comparison of adalimumab and etanercept was initially conducted based solely on the available placebo-controlled RCT data in children with psoriasis. In order to populate the economic model, a network meta-analysis (NMA) framework incorporating adult data was developed to allow connecting the effectiveness data in children and young people.

1.3.2 Methods of cost-effectiveness review

A systematic review was undertaken to identify published evidence on the cost-effectiveness of adalimumab, etanercept and ustekinumab, and relevant comparators, for psoriasis in children and young people. This included the company submissions from Janssen (ustekinumab) and AbbVie (adalimumab); Pfizer (etanercept) did not submit. Additional hand-searching of published documents associated with previous NICE Technology Appraisals of psoriasis in adults was carried out. The aim was to examine existing decision-analytic models, to identify important structural assumptions, highlight key areas of uncertainty and outline the potential issues associated with generalising evidence from the adult population to a population of children and young people.

1.3.3 Methods of economic modelling

A de novo decision analytic model was developed to estimate the cost-effectiveness of adalimumab, etanercept and ustekinumab to each other and to either, methotrexate or best supportive care (BSC) depending on the position of the intervention in the management pathway. Before systemic therapy, methotrexate was considered the relevant comparator (as the current standard of care), whereas after systemic therapy BSC was considered the most relevant comparator. The cost-effectiveness model takes the form of a cohort Markov model and the time horizon extends until individuals reach 18 years old, when separate NICE recommendations for the use of the interventions in adults apply. Outcomes are expressed using quality-adjusted life years (QALYs) and costs take the perspective of the NHS and Personal Social Services.

In order to reflect differences in marketing authorisation by age and positioning of treatment in the pathway, the cost-effectiveness analysis considers three separate populations:

1. Children and young people **aged 4-17 years** with **adalimumab** as the only licensed intervention for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **topical therapy and phototherapies, i.e. as an alternative to systemic therapies.**
2. Children and young people **aged 6-11 years** with **adalimumab** and **etanercept** for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **systemic therapies or phototherapies.**
3. Children and young people **aged 12-17 years** with **adalimumab, etanercept** and **ustekinumab** for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **systemic therapies or phototherapies.**

1.4 Results of clinical effectiveness review

A total of nine studies (three RCTs and six observational studies) were included.

1.4.1 Efficacy data from pivotal RCTs

Three randomised clinical trials (RCTs) were retrieved – one for each of the three biologics of interest. The etanercept and ustekinumab trials had 12 weeks of follow-up and used placebo as a comparator, whilst the adalimumab trial was of 16 weeks' duration and included methotrexate as the comparator. Risk of bias was low for most domains in each study.

While only older children and adolescents (12-17 years of age) were included in the ustekinumab trial, the median age of children did not differ greatly across the three trials as relatively few younger children were included in the adalimumab and etanercept trials. Across the three RCTs, just four children aged under 6 years received biologic treatment (etanercept in all cases).

All three trials used a composite measure of disease severity incorporating baseline PASI, PGA and BSA measurements. Average PASI scores ranged from 18.3 to 21.2, with 93-100% of participants having a PGA score exceeding 3 ("mild/moderate disease"). Though adalimumab and etanercept are licenced for "severe chronic plaque psoriasis" and ustekinumab for "moderate-to-severe plaque psoriasis", on average, measures of disease duration and the component measures of severity did not appear to differ markedly between the three trials.

29.8% of participants in the adalimumab trial had received prior systemic therapy, compared with 42.7% of participants in the ustekinumab trial. 56.8% of participants in the etanercept trial had received either prior systemic therapy or phototherapy.

A similar proportion of participants in the adalimumab and ustekinumab trials had received some form of biologic treatment prior to enrolment (9.6% and 10.8% respectively). No participants recruited to the etanercept trial had previously been treated with a biologic.

1.4.1.1 Adalimumab

One multicentre RCT (M04-717) found that adalimumab at the licenced dose of 0.8mg/kg (up to 40mg) lead to significantly greater responses than methotrexate for the outcomes of PASI 50 and PASI 75, but not PASI 90 at 16 weeks. PGA 0/1 response rates were non-significantly higher for adalimumab 0.8mg/kg than methotrexate. The benefits of half-dose adalimumab were not statistically greater than those for methotrexate. Evidence on quality of life was inconsistent across different measures, possibly due to baseline imbalance on PedsQL. In children and young people, adalimumab did not appear to be associated with an increase in adverse effects relative to methotrexate over 16 weeks, though the possibility of rare adverse events cannot be entirely excluded. The trial did not provide evidence for children aged 4 to 6 years of age.

[redacted]

1.4.1.2 Etanercept

One multicentre RCT (20030211) found etanercept to be significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50, 75 and 90, and PGA 0/1 response rates at 12 weeks. Improvements in health-related quality of life were larger for etanercept than placebo, but only reached statistical significance when measured by CDLQI.

Adverse events rates were mostly similar in etanercept and placebo groups at 12 weeks with no serious adverse events observed for either treatment. However, a higher observed rate of infections among participants receiving etanercept was of borderline statistical significance. Relatively few young children (9% aged under 8 years; 4.3% aged under 6 years) were included in study.

Up to six years open-label follow-up (20050111) found that the proportion of PASI and PGA responders were stable over time, though only 36% of participants were available at the latest follow-up point. The proportion of participant withdrawing due to lack of efficacy is unknown. Through 264 weeks of follow-up, withdrawals due to adverse events were infrequent, and no deaths or malignancies were observed.

1.4.1.3 Ustekinumab

One multicentre trial (CADMUS) in children 12 to 17 years of age found both the standard dosage and half dosage of ustekinumab were significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50, 75 and 90 and PGA 0/1 responses at 12 weeks. Both ustekinumab dosages also lead to significantly greater improvements in health-related quality of life (CDLQI and PedsQL).

Among participants originally allocated to ustekinumab, PASI and PGA effects observed at 12 weeks appeared to be largely sustained at 52 weeks, with few withdrawals due to lack of efficacy.

There were no notable adverse effects associated with ustekinumab, though the number of observations was small and longest the follow-up time was just 60 weeks. Few participants withdrew due to adverse effects.

1.4.2 Efficacy data from network meta-analyses

The treatment effects for the interventions were assumed to be exchangeable across age since no statistically significant differences were identified in PASI response outcomes by age within the trials.

The wider network including evidence from adult trials facilitated an indirect comparison of adalimumab, etanercept and ustekinumab. The network meta-analysis results – adjusted for differences in population and placebo response rates – demonstrated that ustekinumab is the most effective intervention, followed by adalimumab, etanercept and methotrexate.

1.5 Results of cost-effectiveness evaluation

1.5.1 Cost-effectiveness reported in existing published studies and manufacturer submissions

No previously published cost-effectiveness studies of adalimumab, etanercept or ustekinumab for psoriasis in children and young people were identified. One economic model of psoriasis in this population was discussed as part of the All Wales Medicines Strategy Group (AWMSG) advice No.138 for the use of etanercept within NHS Wales.

None of the companies participating in this appraisal submitted an economic model.

1.5.2 Cost effectiveness results from de novo modelling

The *de novo* model generated incremental cost-effectiveness ratios (ICERs) for the three populations above according to age and position of the intervention in the pathway of treatment. Results were generated for a base case and for separate scenarios. The base case ICERs were:

1. For the evaluation of adalimumab as an alternative to systemic therapy, the ICER for adalimumab compared to methotrexate is £308,329 per QALY gained.
2. For the evaluation of adalimumab and etanercept after failed systemic therapy in ages 6-11 years, adalimumab is the more effective but also more costly treatment compared to etanercept and BSC. Based on a fully incremental analysis, the ICER for etanercept compared to BSC is £71,903 per QALY, while the ICER for adalimumab compared to etanercept is £174,519 per QALY. The individual pairwise ICER for adalimumab compared to BSC is £115,825 per QALY.
3. For the evaluation of ustekinumab, adalimumab and etanercept after failed systemic therapy in ages 12-17 years, ustekinumab is the most effective and most costly treatment, followed by adalimumab, etanercept and BSC. Based on a fully incremental analysis, etanercept is extendedly dominated by adalimumab (i.e. etanercept produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy of adalimumab), the ICER of adalimumab compared to BSC is £110,430 per QALY, and the ICER of ustekinumab compared to adalimumab is £201,507 per QALY. The individual

pairwise ICERs for etanercept, adalimumab and ustekinumab compared to BSC are £137,059, £110,430 and £116,568 per QALY, respectively.

The model was also used to explore a number of uncertainties through scenario analyses. The scenarios which had the most impact on the cost-effectiveness results were: (i) the utility estimates based on an adult population; (ii) the health benefits associated with BSC; and (iii) the average number of hospitalisations per annum for BSC. Using utility values from an adult population brings the ICER of etanercept compared to BSC under a threshold of £30,000 per QALY in children and young people aged 6-11 years. The ICERs for ustekinumab and adalimumab are reduced significantly but remain above £30,000 per QALY threshold. Under the assumption of no health benefits for BSC, the ICERs are reduced substantially but remain quite high with the lowest ICER of £56,430 per QALY gained for etanercept compared to BSC. If the average number of hospitalisations per annum is increased from 0 days to 6.49 days based on a study inadults, the ICERs for the interventions reduce significantly; however, the only ICER which falls below £30,000 is for the use of etanercept compared to BSC in children and young people aged 6-11 years. If the average number of hospitalisations per annum is increased significantly to 26.6 days per annum based on a very high need adult population, the biological treatments compared to BSC are all considered cost-effective in individuals who have failed systemic therapy.

1.6 Discussion

While the total number of included participants and average length of follow-up was limited, this systematic review included the best available evidence on the efficacy and short- to medium-term safety of adalimumab, etanercept and ustekinumab directly relevant to the decision problem.

Very little evidence of efficacy or safety was available for young children. The ustekinumab trial (CADMUS) restricted inclusion to participants aged over 12 years, and the adalimumab and etanercept studies included few children aged under 8 years. Just nine 4 to 5 year-olds were included across all RCTs of biologics for psoriasis.

The review of cost-effectiveness evidence in this population, and the absence of economic models from the companies, highlights the challenges involved in evaluating the cost-effectiveness of biological interventions in children and young people with plaque psoriasis. The fundamental challenge is the limited clinical evidence base for short- and long-term outcomes. A key strength of this evaluation was that it went beyond the scope of the appraisal by bringing together evidence from

the adult population in order to support an economic evaluation in children and young people. However, inevitably the results aresubject to a number of uncertainties.

1.7 Conclusions

The paucity of clinical and economic evidence to inform the cost-effectiveness of biological treatments in children and young people has imposed a number of strong assumptions and uncertainties. Health-related quality of life gains associated with treatment and number of hospitalisations in children and young people are areas of considerable uncertainty.

Based on the economic assessment, the majority of ICERs for the use of biologics in children and young people are in excess of NICE's usual range of cost-effectiveness and are reduced significantly only when combined assumptions that align with those for the management of psoriasis in adults are adopted.

1.8 Suggested research priorities

- Adequately powered randomised trials are needed to inform the effectiveness of biological treatments in biologic-experienced populations of children and young people, i.e. treatment response rates conditional on prior treatment are required. Evidence for the clinical effectiveness and safety of adalimumab and etanercept in younger children in particular is currently lacking.
- Further research is needed to establish the impact of biological therapies on improving the health-related quality of life of children and young people. Future trials should consider collecting direct estimates of EQ-5D-Y.
- With the introduction of biological treatments in the population of children and young people continued collection of data through biologic registries for individuals younger than 18 years is warranted in order to investigate safety, patterns of treatment switching, and long-term withdrawal rates.
- Resource use and costs associated with best supportive care is an area of further research.

1.9 Study Registration

PROSPERO: CRD42016039494

1.10 Funding

Health Technology Assessment programme of the National Institute for Health Research

2 Background

2.1 Description of the health problem

2.1.1 Epidemiology

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, plaque 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]

2.1.2 Aetiology, pathology and prognosis

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] 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; this can result in delayed diagnosis of the disease.[3] Also in children, plaques appear most frequently on the scalp and may lead to hair loss (psoriatic alopecia) if severe.[3]

2.1.3 Significance in terms of ill health

The impact of psoriasis encompasses functional, psychological, and social dimensions. [10] Factors that contribute to this include symptoms specifically related to the skin (for example, chronic itch, bleeding, scaling and nail involvement), problems related to treatments (mess, odour, inconvenience

and time), psoriatic arthritis, and the effect of living with a highly visible, disfiguring skin disease (difficulties with relationships, difficulties with securing employment and poor self-esteem). Even people with minimal involvement (less than the equivalent of three palm areas) state that psoriasis has a major effect on their life. The combined costs of long-term therapy and social costs of the disease have a major impact on healthcare systems and on society in general.[11]

Mortality primarily due to psoriasis is not common; however the chronic and incurable nature of psoriasis means that associated morbidity is significant.[11] Studies show that a significant proportion of childhood psoriasis cases (12-37%) don't grow out of it,[12] which implies that childhood psoriasis has a substantial long-term social and economic impact on individuals and the community.[13]

Some reports also suggest that adult psoriasis patients who were diagnosed during childhood have worse lifetime quality of life than those diagnosed during adulthood,[14, 15] although this claim is not supported by others.[16]

2.1.4 Assessment and management of psoriasis in children

Currently, there is no treatment pathway specific to psoriasis in children in the UK. Treatment depends to some extent on the extent and severity of an individual's disease, local custom and practice. Existing psoriasis guidance for all age groups (NICE guideline CG153 in England) states that traditional topical therapies (such as corticosteroids, vitamin D and analogues, dithranol and tar preparations) can be prescribed as a first-line therapy. Second-line therapies can include, phototherapy, broad- or narrow-band ultraviolet [UV] B light, with or without supervised application of complex topical therapies such as dithranol in Lassar's paste or crude coal tar and photochemotherapy, psoralen plus UVA light [PUVA], and non-biological systemic agents such as cyclosporine, methotrexate and acitretin. Third-line therapy includes systemic biological therapies that use molecules designed to block specific molecular steps important in the development of psoriasis such as the TNF antagonists, and anti-IL12-23 monoclonal antibodies. However, this guideline highlights special considerations for children (e.g. avoidance of very potent corticosteroids, PUVA, and acitretin) and recommends that children and young people with any type of psoriasis should be referred to a specialist at presentation.

2.1.5 Assessment of treatment response and quality of life

In children, there are a variety of clinical scales used to assess treatment response in psoriasis, including the Physician Global Assessment (PGA), Psoriasis Area and Severity Index (PASI), Children's Dermatology Life Quality Index (CDLQI) and Paediatrics Quality of Life (PedsQL)[17, 18]

2.1.5.1 The Physician global assessment (PGA)

The PGA is an instrument that provides a subjective overall evaluation of plaque psoriasis severity using a scale of seven categories ('clear', 'almost clear', 'mild', 'mild to moderate', 'moderate', 'moderate to severe', 'severe'.[19] There are two primary forms: a static form (physician static global assessment (sPGA)), which measures the physician's impression of the disease at a single point, and a dynamic form (physician dynamic global assessment (dPGA) in which the physician assesses the global improvement from baseline.[17]

The sPGA assumes seven scaled scores based on the severity of the disease, that is, 0='clear', 1='almost clear', 2='mild', 3='mild to moderate', 4='moderate', 5='moderate to severe', 6='severe'.[17, 20] The dPGA, on the other hand, uses six scaled scores to describe either improvement or deterioration of disease. For an improvement, the scores would be: +1= mild;+2=moderate; +3=moderate to large; +4=large; and, +5=very large improvement. For a disease deterioration: -1=mild; -2=moderate; -3=moderate to large; -4=large; and, -5=very large deterioration. A score of zero indicates no or minimal change.

The sPGA scoring system is simpler to use than dPGA; since physicians have to record the severity of psoriasis at baseline in order to evaluate the change in disease status after a follow-up period when they use dPGA, the sPGA has become widely used treatment response assessment tool in practice.[17] However, the sPGA does not discriminate small changes and the range scores are not robust.[17]

2.1.5.2 Psoriasis Area and Severity Index (PASI)

In clinical trials of patients with psoriasis, assessment of the response to treatment is usually based on the Psoriasis Area and Severity Index (PASI). Although it is widely used, the PASI measure also has a number of deficiencies: its constituent parameters have never been properly defined; it is insensitive to change in mild-to-moderate psoriasis; estimation of disease extent is notoriously inaccurate; and the complexity of the formula required to calculate the final score further increases the risk of errors. It combines an extent and a severity score for each of the four body areas (head, trunk, upper extremities and lower extremities). The extent score of 0–6 is allocated according to the percentage of skin involvement (e.g. 0 and 6 represent no psoriasis and 90%–100% involvement, respectively). The severity score of 0–12 is derived by adding scores of 0–4 for each of the qualities of erythema (redness), induration and desquamation representative of the psoriasis within the affected area. It is probable, but usually not specified in trial reports, that most investigators take induration to mean plaque thickness without adherent scale and desquamation to mean thickness of scale rather than severity of scale shedding. The severity score for each area is multiplied by the extent score and the

resultant body area scores, weighted according to the percentage of total BSA that the body area represents (10% for head, 30% for trunk, 20% for upper extremities and 40% for lower extremities), are added together to give the PASI score. Although PASI can theoretically reach 72, scores in the upper half of the range (>36) are not common even in severe psoriasis. Furthermore, it fails to capture the disability that commonly arises from involvement of functionally or psychosocially important areas (hands, feet, face, scalp and genitalia), which together represent only a small proportion of total BSA. However, PASI-based measures have discriminatory capability and are generally accepted for the assessment of treatment effects. However, clinical expert opinion is that PASI is not widely used in clinical practice.

Despite the fact that it has not been validated in children, PASI has been chosen as the primary outcome variable of psoriasis in the economic evaluation because it is used in the majority of randomised controlled trials (RCTs). Typically this is reported as a dichotomous measure indicating a 50%, 75%, or 90% reduction in PASI score from baseline (PASI 50, PASI 75, and PASI 90 respectively).

2.1.5.3 Childhood Dermatology Quality of Life Index (CDLQI)

The CDLQI is a 10 item questionnaire that aims to measure the quality of life of children (4-16 years of age) based on how much they have been affected by a skin problem over the week preceding the date of questioning.[21] The 10 items cover six areas of daily activities, including: symptoms and feelings, leisure, school or holidays, personal relationships, sleep and treatment.[22, 23] Usually children alone, or with the help of their parents, choose one of the four possible replies (scored 0-3) for a maximum overall score of 30, with a high score corresponding to low quality of life and vice versa.[23]

CDLQI scores can be divided into scoring bands: band 0 (score = 0-1), band 1 (score = 2-6), band 2 (score= 7-12), band 3 (score=13-18) and band 4 (score=19=30) that respectively correspond to no, small, moderate, very large or extremely large effects on the child's quality of life.[23]. However, the CDLQI is not considered appropriate for use as health-related quality of life assessment tool beyond the age of 16 years.

2.1.5.4 Pediatric Quality of Life (PedsQL)

The PedsQL is a modular instrument for measuring of health-related quality of life in children and adolescents (2 to 18 years of age). It has 23 items in four domains: a) physical functioning (8 items); b) emotional functioning (5 items); c) social functioning (5 items); and, d) school functioning (5 items). Each item receives a score 0-4 (0 = never a problem; 1 = almost never a problem; 2 =

sometimes a problem; 3 = often a problem; 4 = almost always a problem) and are reverse-scored and linearly transformed to a 0 to 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better HRQOL.[24] Paediatric self-report is measured in children and adolescents ages 5-18 years, and parent proxy-report of child HRQOL is measured for children and adolescents ages 2-18 years.

2.1.5.5 Teenager's Quality of Life Index (T-QoL)

Built on qualitative data from patients, the T-QoL is a validated tool to quantify the impact of skin disease on adolescents' quality of life. The index contains 18 items categorised into three domains: 'Self-image', 'Physical wellbeing and the future', and 'Psychological impact and relationships'. The authors have proposed the T-QoL as an outcome measure in both clinical practice and in clinical research.[25]

2.1.5.6 General issues with quality of life measurement in childhood psoriasis

Quality of life measurements may not be particularly meaningful in younger children who are less good at articulating how much the disease is bothering them. In the case of younger children, proxy measurements may more accurately reflect parental perception or concern. There is only moderate correlation between PASI/PGA response measures and CDLQI;[26]some children with relatively mild disease can have very poor HRQoL scores, while others with more severe disease can have acceptable HRQoL. As well as disease symptoms and consequences, frequency of injections can be an important quality of life consideration in children.

2.2 Description of technology under assessment

"Biological therapies" or "biologics" are agents extracted or semi-synthesised from biological sources, used for treating specific medical conditions, including auto-immune diseases. They are frequently produced using recombinant DNA technology and designed to act on specific parts of human immune system. For example, biologics such as certolizumab, etanercept, adalimumab, infliximab and golimumab block Tumour Necrosis Factor (TNF) alpha; and, ustekinumab and secukinumab inhibit interleukin 12/23 and interleukin 17-A, respectively. Such biologics are indicated for a range of conditions, including psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease.

Three biologics (adalimumab, etanercept and ustekinumab) have regulatory approval for the treatment of plaque psoriasis in children and young people.

Adalimumab (Humira, AbbVie) is a fully human immunoglobulin G1 monoclonal antibody that inhibits the activity of tumour necrosis factor alpha (TNFα). 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 TNFα receptor fusion protein that inhibits the activity of TNFα. 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 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

More recently, versions of biologic drugs have become available that are manufactured after the expiry of an original innovator agent's patent. These "biosimilars" are developed to be highly similar to the existing biologic agent physicochemical and biological terms and are typically cheaper than the original agent. Biosimilar medicines are usually licensed for all indications specified in the licence of the originator biological medicine, but this requires appropriate scientific justification on the basis of demonstrated or extrapolated equivalence. Benepali, a biosimilar of etanercept, has been approved in Europe for use in adults with moderate to severe rheumatoid arthritis, psoriatic arthritis, severe ankylosing spondylitis, severe non-radiographic axial spondyloarthritis, and moderate-to-severe plaque psoriasis. Currently, three biosimilars of infliximab (Inflectra, Remsima, Flixabi) are approved for use in ankylosing spondylitis, Crohn's disease, psoriatic arthritis, psoriasis, rheumatoid arthritis, and ulcerative colitis.

3 Definition of decision problem

According to NICE guideline CG153 in England, psoriasis patients are treated in three stages.[11] First-line therapy includes traditional topical therapies (such as corticosteroids, vitamin D and vitamin D analogues, dithranol and tar preparations). Second-line therapy includes phototherapies narrow-band ultraviolet B light and psoralen plus UVA light [PUVA]) and systemic non-biological agents such as cyclosporine, methotrexate and acitretin are administered. 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 as third-line therapy.[11]

The three biologics (adalimumab, etanercept and ustekinumab) that have regulatory approval for the treatment of plaque psoriasis in children and young people have not yet been appraised by NICE and no NICE technology appraisal guidance is available for treating children and adolescents in the UK for these treatments in this indication

3.1 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.

4 Assessment of clinical effectiveness

4.1 Methods for synthesis of evidence of clinical effectiveness

A systematic review of the clinical effectiveness was performed following the general principles recommended in CRD's guidance and the PRISMA statement while a protocol was registered with PROSPERO.[27]

4.1.1 Literature searching – adalimumab, etanercept and ustekinumab

The literature search for the clinical effectiveness review aimed to systematically identify relevant randomised controlled trials (RCTs) of adalimumab, etanercept and ustekinumab for children and young people with plaque psoriasis.

The search strategy was developed in MEDLINE (Ovid) and included search terms for:

- psoriasis
- adalimumab, etanercept, ustekinumab or biosimilars
- children or young people

The 3 sets of terms were combined using the Boolean operator AND. Search terms were developed through discussion with the review team, use of database thesauri and online drug information resources. No language, date, geographical or study design limits were applied. The MEDLINE strategy was adapted for use in the other resources searched.

The searches were carried out on 24th/25th May 2016 and updated during September 2016. The following databases were searched: MEDLINE (including: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Cumulative Index to Nursing & Allied Health (CINAHL Plus), Database of Abstracts of Reviews of Effects (DARE), EMBASE, Health Technology Assessment (HTA) database, PubMed, and the Science Citation Index.

In addition, the following resources were searched for on-going, unpublished or grey literature: ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, PROSPERO and the WHO International Clinical Trials Registry Platform portal.

A search for guidelines on psoriasis in children or young people was carried out via the following guideline websites: National Guideline Clearinghouse, NICE Clinical Knowledge Summaries (CKS), NHS Evidence, NICE Evidence summaries: new medicines, and the NICE website.

In addition to utilising other published and unpublished data resources, requests for clinical study reports (CSRs) relating to adalimumab, etanercept and ustekinumab were made to Abbvie, Pfizer and Janssen respectively.

The search results were imported into EndNote x7 (Thomson Reuters, CA, USA) and deduplicated. Full search strategies can be found in appendix 12.1.

4.1.2 Literature searching – network meta-analysis

4.1.2.1 Alternative treatments in children and young people

A search was undertaken to identify relevant RCTs of systemic non-biological (acitretin, methotrexate, and cyclosporine) and other biological therapies (infliximab, secukinumab) in children and young people with plaque psoriasis to inform the network meta-analysis. No language, date, geographical or study design limits were applied to the search.

This search was carried out on 31st May 2016 on the following databases: MEDLINE (including: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Cumulative Index to Nursing & Allied Health (CINAHL Plus), Database of Abstracts of Reviews of Effects (DARE), EMBASE, Health Technology Assessment (HTA) database, PubMed, and the Science Citation Index.

In addition, the following resources were searched for on-going, unpublished or grey literature: ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, PROSPERO and the WHO International Clinical Trials Registry Platform portal.

The search results were imported into EndNote x7 (Thomson Reuters, CA, USA) and de-duplicated. The search was updated in September 2016 to capture more recent studies.

4.1.2.2 Registry data

In order to identify longer-term follow-up evidence, a literature search was conducted within the MEDLINE database for the search terms “psoriasis AND regist*”. The results of this search were screened for publications from psoriasis registries, secondary analyses of registry data, and systematic

reviews of broader dermatological and psoriasis registries. The list of registries generated through these searches was compared against three relevant systematic reviews[28-30] to verify those studies included and to identify any which had been overlooked. Twenty patient registries for psoriasis treatment were identified in this way, 14 of which were located in European countries, three were international in scope, and two were based in the USA and one in Malaysia. Each registry name was then separately used as a search term in MEDLINE, and any publications referencing these which had not been found in the initial searches were retrieved.

In addition, representatives of the 14 psoriasis registries from European countries (Austria, Australia, Czech Republic, Denmark, France, Germany, Italy, Netherlands, Portugal, Slovenia, Spain, Sweden, Switzerland and UK) were contacted and asked to provide any relevant information on psoriasis treatment for three biologics (adalimumab, etanercept and ustekinumab) in children and young people.

4.1.3 Inclusion and exclusion criteria

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

4.1.3.1 Study design

RCTs (including any open-label extensions of RCTs) were eligible for the review of clinical efficacy.

Information on adverse events was also sought from regulatory sources where appropriate. Registries and observational studies were included where relevant outcome data were available.

To address longer-term measures of efficacy and drug survival, published analyses based on large and long-term data sets (including studies of registry data) were also considered.

4.1.3.2 Participants

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

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

4.1.3.3 Interventions

The relevant interventions were adalimumab, etanercept and ustekinumab.

4.1.3.4 Comparators

Relevant comparators are:

- Alternative biologic therapies with relevant marketing authorisation (adalimumab, etanercept or ustekinumab)
- Non-biological systemic therapy (including, but not limited to, cyclosporine 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

4.1.3.5 Outcomes

Data on the effectiveness, adverse effects, patient-centred outcome measures, costs to the health service, and cost-effectiveness were eligible for inclusion, including the following outcomes:

- 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 CDLQI, PedsQL, EQ-5D)

4.1.4 Data extraction

Data relating to both study design and quality were extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus, and if necessary, a third reviewer was consulted. Data from studies with multiple publications were extracted and reported as a single study.

4.1.5 Quality assessment

The quality of RCTs was assessed using the Cochrane risk of bias tool, with additional assessments made for baseline imbalance of important prognostic indicators.[31, 32] Relevant prognostic and treatment response indicators were identified from both published research and clinical advice. Risk of bias assessment was performed by one reviewer, and independently checked by a second. Disagreements were resolved through consensus, and if necessary, a third reviewer was consulted.

The quality of non-randomised studies was assessed using a checklist based on CRD Guidance[27] and used in previous technology assessments for NICE.[33] This assesses study eligibility criteria and recruitment methods, baseline similarity of comparison groups, blinding of allocation, completeness of follow-up, and outcome reporting.

4.1.6 Methods of data synthesis

The analysis and synthesis of clinical data in this review were conducted in distinct sections. In the absence of sufficient trials to conduct pairwise meta-analysis, the results of included studies are presented in a series of structured tables and summarised narratively and subjected to detailed critical appraisal.

In order to assess the relative clinical effectiveness of the three biologics (i.e. adalimumab, etanercept and ustekinumab) syntheses of both pairwise (head-to-head) and indirect comparative data were planned. Where possible, treatment response (PASI) outcomes were to be synthesized using Bayesian network meta-analysis methods. Bayesian statistical methods provide information on the benefits of the active treatments relative to the appropriate comparators and each other.[34] 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.[35] 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.

However, the available trials conducted in children precluded the construction of the necessary network. To inform the economic evaluation, trials conducted in adults were included in a network meta-analysis. Full details of the methods and results are presented in Section 5.

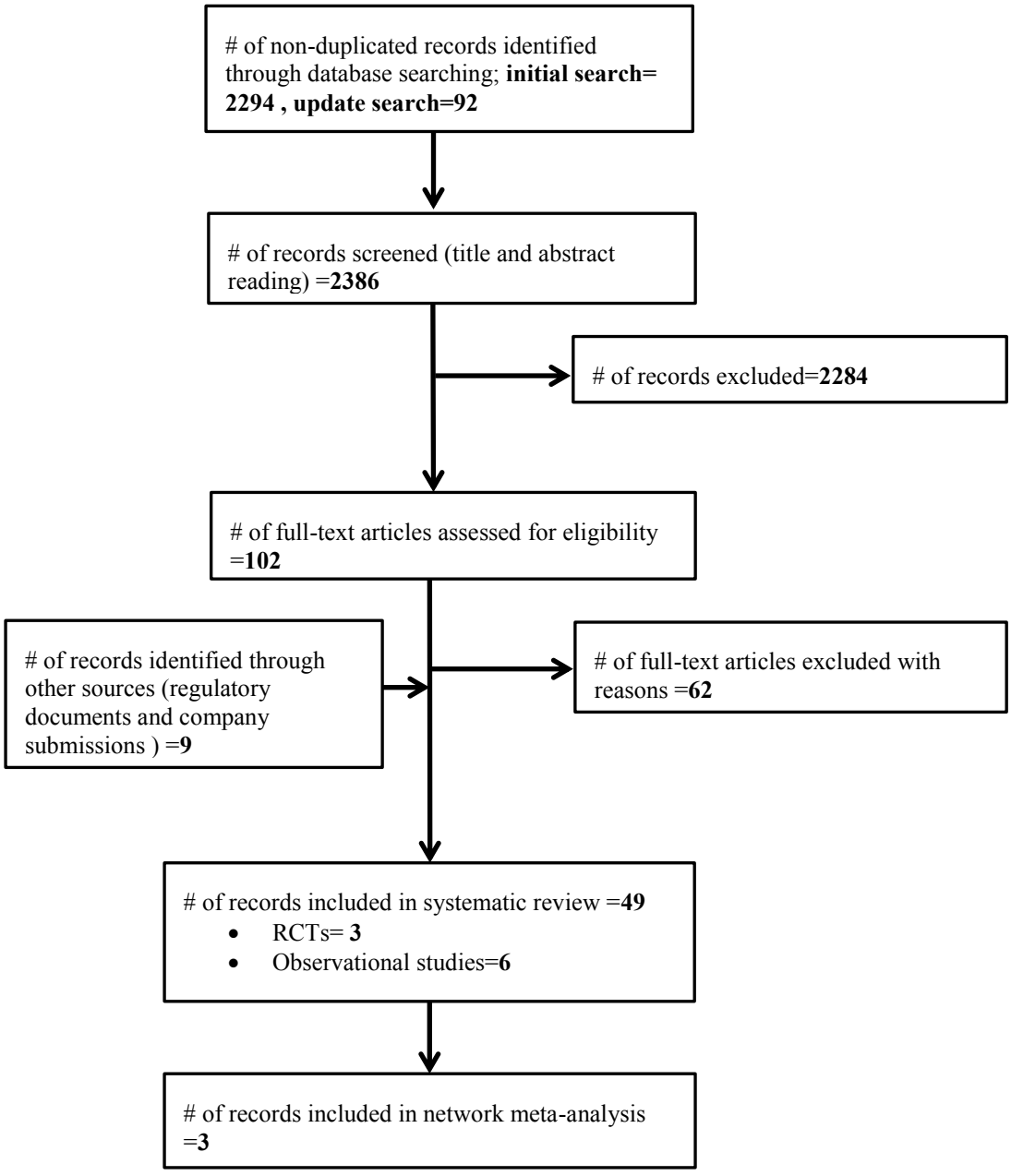
4.2 Results

4.2.1 Quantity of identified evidence

A total of 2386 non-duplicate records were identified from the clinical effectiveness database searches. Of these, 2284 records were excluded after title or abstract screening. In addition, eight relevant regulatory documents were retrieved. Thus, a total of 111 records were read in full, resulting in 62 records being excluded and a total of 48 records being included in the review. A total of nine studies (3 RCTs and 6 open-label or observational follow-up of RCTs) were included in the review of clinical effectiveness, see **Figure 1**. The included records are summarised in appendix 12.2. Appendix 12.3 also lists the excluded studies and reasons of exclusion.

Searches for relevant registry data identified 685 publications. Three publications from two registries were found to include children with psoriasis who were treated with biologics. Of the 14 national psoriasis registry representatives contacted, seven responded but no relevant additional data were available.

Figure 1 PRISMA flow diagram of studies in children and young people



4.2.2 Characteristics of studies included

Three randomised clinical trials (RCTs) were retrieved – one for each of the three biologics of interest (i.e. adalimumab, etanercept and ustekinumab). The RCTs investigated short term clinical efficacy and adverse events. The etanercept and ustekinumab trials had 12 weeks of follow-up and used placebo as a comparator, whilst the adalimuimab trial was of 16 weeks' duration and included methotrexate as the comparator. Each RCT also incorporated an open-label phase (**Table 3**). These open-label or observational periods investigated longer-term efficacy and adverse events, incorporating withdrawal and/or re-treatment phases. The adalimumab, etanercept and ustekinumab trials had 52, 312, and 60 weeks of follow-up data available, respectively.

4.2.2.1 Patients' baseline characteristics

The baseline characteristics are presented in **Table 4**. While only older children and adolescents (12-17 years of age) were included in the ustekinumab trial, the median age of children across the three trials did not differ greatly; since it appears relatively few younger children were included in the adalimumab and etanercept trials.

All three trials used a composite measure of disease severity incorporating baseline PASI, PGA and BSA measurements. When used in isolation, a PASI score between 10 and 20 is considered to indicate moderate to severe psoriasis, while severe psoriasis has a score above 20. Across the included studies, average PASI scores ranged from 18.3 to 21.2, with 93-100% of participants having a PGA score exceeding 3 ("mild/moderate disease"). Though adalimumab and etanercept are licenced for "severe chronic plaque psoriasis" and ustekinumab for "moderate-to-severe plaque psoriasis", on average, measures of disease duration and the component measures of severity did not appear to differ markedly between the three trials. The degree of psoriasis affecting high-impact and difficult to treat sites (e.g. face, scalp, palms, soles, flexures and genitals) across the three studies was less clear.

A key difference in the licences between the three agents is the availability of adalimumab for patients for whom topical and phototherapy are inadequate or inappropriate. Unlike the licences for etanercept and ustekinumab, there is no mention of prior non-biologic systemic treatment. However, the baseline characteristics of the included studies indicate that a substantial minority of participants in the adalimumab trial (29.8%) had received prior systemic therapy, compared with 42.7% of participants in the ustekinumab trial. 56.8% of participants in the etanercept trial had received either prior systemic therapy or phototherapy (separate data were not reported).

A similar proportion of participants in the adalimumab and ustekinumab trials had received some form of biologic treatment prior to enrolment (9.6% and 10.8% respectively). As etanercept was the first

TNF-α inhibitor to be approved for psoriasis, none of the participants recruited to the etanercept trial had previously been treated with a biologic.

While there were noticeable differences in participant characteristics between trials, these were not as clear as the respective licences of the three treatments might suggest. Notwithstanding methodological differences, there appears to be sufficient overlap in populations to discuss these three trials together.

4.2.2.2 Length of follow-up and early escape

The initial randomised treatment period was 12 weeks in the etanercept and ustekinumab trials and 16 weeks in the adalimumab trial. Twelve week outcome data were not available for the adalimumab trial, though clinical advice suggested that the difference in length of follow-up between treatments was acceptable.

All three trials allowed participants to "escape" from the randomised treatment period before 12/16 week follow-up. The criteria and statistical handling of early escape data are discussed separately for each trial in sections 4.3 to 4.5.

Post randomised treatment periods are briefly summarised in **Table 3**.

4.2.2.3 Outcomes

The adalimumab and etanercept trials considered PASI 75 response to be the primary outcome measures, whereas the ustekiniumab trial used a primary measure of PGA score of 0 or 1 ("clear" or "almost clear"). However, all three trials reported PASI, PGA and some measure of HRQoL (CDLQI and/or PedsQL), all of which are presented in the following sections.

Table 2 Inclusion and exclusion criteria for included RCTs

Adalimumab (Trial M04-717)	Etanercept (Trial 20030211)	Ustekinumab (CADMUS Trial)

Inclusion Criteria:
• Subject is ≥ 4 years and < 18 years of age;
• Participant weighs ≥ 13 kg;
• Participant must have failed to respond to topical therapy;
• Participant must need systemic treatment to control his/her disease and meet one of the following:
  • Physician's Global Assessment (PGA) ≥ 4
  • Body surface area (BSA) involved > 20%
  • Very thick lesions with BSA > 10% - Psoriasis Area and Severity Index (PASI) > 20
  • PASI > 10 and at least one of the following:
  • Active psoriatic arthritis unresponsive to non-steroid anti-inflammatory drugs (NSAIDs)
  • Clinically relevant facial involvement
  • Clinically relevant genital involvement
  • Clinically relevant hand and/or foot involvement
  • Children's Dermatology Life Quality Index (CDLQI) > 10
• If participant is < 12 years of age and resides in a geographic region where heliotherapy is practical, participant must have failed to respond, be intolerant, or have a contraindication to heliotherapy, or is not a suitable candidate for heliotherapy;
• If ≥12 years of age, participant must have failed to respond, be intolerant, or have a contraindication to phototherapy, or is not a suitable candidate for phototherapy;
	Inclusion criteria:
	• age 4 to 17 years;
	• stable, moderate-to-severe plaque psoriasis at screening, defined as a psoriasis area-and-severity index (PASI) score of at least 12 (PASI scores range from 0 to 72, with higher scores indicating worse condition;
	• A static physician's global assessment of at least 3 (where 0 indicates clear and 5 severe psoriasis), and psoriasis involvement of at least 10% of the body-surface area;
	• A history of psoriasis for at least 6 months; and,
	• Previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids) or psoriasis considered by the investigator as poorly controlled with topical therapy.
	Exclusion criteria:
	• Pregnancy or lactation (sexually active patients were required to use contraception);
	• Guttate, erythrodermic, or pustular psoriasis;
	• Skin conditions that would interfere with study evaluations;
	• Previous treatment with anti-TNF agents;
		Inclusion Criteria:
		• Age 12 to 17 years, (inclusive),
		• Had a diagnosis of moderate-to-severe plaque psoriasis (ie, baseline Psoriasis Area and Severity Index [PASI] ≥12, a Physician's Global Assessment [PGA] ≥3; and ≥10% body surface area involved with psoriasis) for ≥6 months,
		• Candidates for phototherapy or systemic treatment, or had psoriasis that was poorly controlled with topical therapy
		• Have a diagnosis of plaque-type psoriasis with or without psoriatic arthritis (PsA) for at least 6 months
		Exclusion Criteria:
		• Currently have nonplaque forms of psoriasis (e.g. erythrodermic, guttate, or pustular) or drug-induced psoriasis (e.g. a new onset of psoriasis or an

• Participant must have a clinical diagnosis of psoriasis for at least 6 months as determined by the participant's medical history and confirmation of diagnosis through physical examination by the Investigator; 8. Participant must have stable plaque psoriasis for at least 2 months prior to Baseline **Exclusion Criteria:** • Prior biologic use other than prior treatment with etanercept; • Treatment with etanercept therapy within 4 weeks prior to the Baseline visit; • Methotrexate (MTX) use within the past year or prior MTX use at any time where the participant did not respond, or did not tolerate MTX; • Contraindication for treatment with MTX during the study; • Erythrodermic Ps, generalized or localized pustular Ps, medication-induced or medication exacerbated Ps or new onset guttate Ps; • Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit; • Treatment of Ps with topical therapies such as corticosteroids, vitamin D analogs, or retinoids within 7 days prior to the Baseline visit; • Treatment of Ps with UVB phototherapy, excessive sun exposure, or the use of tanning beds within 7 days prior to the Baseline visit; • Treatment of Ps with PUVA phototherapy, non-biologic systemic therapies for the treatment of Ps, or systemic therapies known to improve Ps within 14 days prior to the Baseline visit;	• Major concurrent medical conditions; • Treatment with psoralen and ultraviolet A (PUVA), ultraviolet A, ultraviolet B, systemic psoriasis medications, oral or parenteral corticosteroids, topical corticosteroids, topical vitamin A or D analogue preparations, anthralin, or calcineurin inhibitor within a 14-day washout period before the study; and, • Treatment with biologic agents within a 30-day washout period before the study. Patients could use low-to-moderate-potency topical steroids on the scalp, axillae, or groin	exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) • Have used any therapeutic agent targeted at reducing interleukin-12 (IL-12) or interleukin-23 (IL-23), including but not limited to ustekinumab and briakinumab • Received conventional systemic therapies or phototherapy within the last 4 weeks • Received biologic therapies within the last 3 months

Table 3 Trial durations (including open-label extensions) and dosing regimens

Study reference	Relevant dosing and regimens used	Duration of randomised and blinded phase	Post-randomised period design details	Latest time point with available result data	Anticipated time to response: information from Summary of Product Characteristics (SPC)
M04-717 Adalimumab	Adalimumab standard dose (initial 0.8mg/kg up to a maximum to 40mg, followed by 0.8mg/kg weekly) or half-dose.	16 weeks	• After the primary treatment phase (Period A-Blinded period), responders from period A were withdrawn from active treatment for up to 36 weeks and monitored for loss of disease control —Withdrawal Phase or Period B. • Participants from period B who had experienced loss of disease control were treated with adalimumab for up to 16 weeks—Re-treatment phase or Period C. • Participants from periods A, B, and C who met entry criteria to long-term follow-up phase or Period D received adalimumab or were observed off-treatment (if disease remained under control during Period B)	52 weeks	Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.
20030211 Etanercept	Etancercept at a dose of 0.8mg per kilogram of body weight up to a maximum of	12 weeks	A 24-week, open-label treatment period (weeks 13 to 36) to assess the efficacy of etanercept therapy in all patients; and a 12-week, randomized, double-blind, withdrawal–retreatment period (weeks 37 to	312 weeks	The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with

	intended dose of 50 mg		48) to examine the effects of withdrawal of study drug and subsequent retreatment		Enbrel is indicated, the above guidance on treatment duration should be followed.
CNTO1275 PSO3006 CADMUS Ustekinumab	Ustekinumab standard dose (0.75mg/kg up to 60kg; fixed 45mg for 60-100kg; fixed 90mg >100kg) or half-dose at 0, 4 and every 12 weeks subsequently	12 weeks	After the double blinded period (12 weeks), the placebo group were allowed to cross over to receive either standard or half-dose ustekinumab at weeks 12 and 16 and then every 12 weeks. Participants were followed for efficacy and safety through weeks 52 and 60, respectively.	60 weeks	Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Table 4 Baseline patients' characteristics of RCTs

	M04-717-Adalimumab			20030211- Etanercept		CNTO1275PSO3006 CADMUS-Ustekinumab		
	ADA 0.8mg/kg	**ADA 0.4mg/kg**	**MTX**	**ETA 0.8mg/kg**	**PLB**	**UST 0.75mg/kg**	**UST 0.375mg/kg**	**PLB**
Study duration	16 weeks	16 weeks	16 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
Number of patients	38	39	37	106	105	36	37	37
Median age (range) in years	[redacted]	[redacted]	[redacted]	14 (4-17)	13 (4-17)	15.0 (12-17)	15.0 (12-17)	16 (12-17)
Mean (SD) age in years	13.0 (3.3)	12.6 (4.4)	13.4 (3.5)	-	-	14.8 (1.7)	15.1 (1.7)	15.6 (1.5)
Male %	44.7	53.8	29.7	52	50	44.4	48.6	54.1
Mean (SD) duration of psoriasis (yrs)	5.0 (3.8)	4.8 (3.3)	5.1 (3.8)	-	-	5.6 (3.8)	5.9 (4.0)	6.2 (5.0)
Median (range) duration of psoriasis (yrs)	[redacted]	[redacted]	[redacted]	6.8 (0.3-17.9)	5.8 (0.3-15.8)	[redacted]	[redacted]	[redacted]
Mean (SD) weight (kg)	-	-	-	-	-	62 (17.1)	68.2 (24.5)	64.7 (14.7)

	M04-717-Adalimumab			**20030211- Etanercept**		**CNTO1275PSO3006 CADMUS-Ustekinumab**		
	ADA 0.8mg/kg	**ADA 0.4mg/kg**	**MTX**	**ETA 0.8mg/kg**	**PLB**	**UST 0.75mg/kg**	**UST 0.375mg/kg**	**PLB**
Median (range) weight (kg)	48.5 (17-95)	53 (15-108)	52 (20-87)	59.6 (17.7-168.3)	59.8 (17.2-131.5)	[redacted]	[redacted]	[redacted]
Mean (SD) height (cm)	-	-	-	-	-	163.9 (9.2)	168 (11.0)	169.7 (11.3)
Median (range) height (cm)	156.5 (104-185)	157 (121-182)	157 (121-182)	159 (104-188)	158 (104-191)	[redacted]	[redacted]	[redacted]
Mean (SD) BSA% affected	27.7 (20.4)	26.0 (16.2)	30.3 (21.2)	-	-	31.9 (23.2)	33.6 (21.4)	27.4 (16.4)
Median (range) BSA% affected	[redacted]	[redacted]	[redacted]	21 (10 - 90)	20 (10 - 95)	-	-	-
Median (range) PASI score	15.3 (10.2-50.4)	15.6 (6.1-29.4)	17.5 (5-51.4)	16.7 (12.0 - 51.6)	16.4 (12.0 - 56.7)	16.8	19.5	19.6
Mean (SD) PASI score	18.9 (10)	16.9 (5.8)	19.2 (10)	18.5 (6.7)	18.6 (6.8)	21.7 (10.4)	21.0 (8.5)	20.8 (8.0)
PGA of at least 3 (%)	92	90	97	99	99	[redacted]	[redacted]	[redacted]

	M04-717-Adalimumab			20030211- Etanercept		CNTO1275PSO3006 CADMUS-Ustekinumab		
	ADA 0.8mg/kg	**ADA 0.4mg/kg**	**MTX**	**ETA 0.8mg/kg**	**PLB**	**UST 0.75mg/kg**	**UST 0.375mg/kg**	**PLB**
PsA (%)	0	2.6	0	5	13	[redacted]	[redacted]	[redacted]
Previous use of topical therapy (%)	100	100	100	-	-	91.7	83.8	91.9
Previous use of phototherapy (%)	44.7	59	51.4	-	-	38.9	48.6	29.7
Previous use of systemic therapy (%)	36.8	28.2	24.3	55 *	59 *	47.2	37.8	43.2
Previous use of biologic therapy (%)	10.5	10.3	8.1	0	0	8.3	10.8	13.5
Mean (SD) CDLQI	10.9 (6.6)	11.6 (7.9)	11.4 (5.6)	8.7 (6.0)	10 (6.4)	10.3 (6.6)	9.4 (6.5)	9.1 (6.4)
Median (range) CDLQI	10 (1-23)	10.5 (0-27)	12 (1-23)	7.0 (0-26)	9.5 (0-29)	9.0 (1.0-26.0)	10.5 (0.0-24.0)	10.0 (1.0-26.0)
Mean (SD) PedsQL	70.4 (14.2)	70.4 (21.3)	78.8 (14.9)	74.8 (17.8)	76.1 (16.9)	[redacted]	[redacted]	[redacted]

	M04-717-Adalimumab			**20030211- Etanercept**		**CNTO1275PSO3006 CADMUS-Ustekinumab**		
	ADA 0.8mg/kg	**ADA 0.4mg/kg**	**MTX**	**ETA 0.8mg/kg**	**PLB**	**UST 0.75mg/kg**	**UST 0.375mg/kg**	**PLB**
Median (range) PedsQL	72.3 (41.3-93.5)	75 (5.4-100)	84.8 (38.98.9)	77.2 (5.4-100)	79.9 (79.9-100)	[redacted]	[redacted]	[redacted]

Note: ADA= Adalimumab, ETA=etanercept, PLB=Placebo, UST=Ustekinumab, *= phototherapy or systemic therapy

4.3 Efficacy and safety of adalimumab

One multicentre RCT (M04-717), comparing two doses of adalimumab against methotrexate, met the selection criteria. While this has not been published in a peer-reviewed journal, data were available from regulatory documentation, conference proceedings, and a clinical study report (CSR) provided by the manufacturer. [36-42, 43, 2015, 44, 45]

The M04-717 study was separated into four periods:

- Period A: Double blind randomised controlled trial of initial treatment (16 weeks)
- Period B: Observational study of treatment withdrawal (up to 36 weeks)
- Period C: Double-blind re-treatment study based on original randomisation in Period A (16 weeks)
- Period D: Long-term follow-up (up to 52 weeks)

The double-blind RCT ('Period A') recruited paediatric patients (ages 4 to 17 years, weighing at least 13kg) with severe chronic psoriasis from 42 centres across 13 countries. Severe chronic psoriasis was defined as failure to respond to topical therapy, requiring systemic treatment to control disease and one of the following: (a) sPGA≥4, (b) BSA>20%, (c) very thick lesions with BSA>10%, (d) PASI>20, or (e) PASI>10, plus one of the following (i) active PsA unresponsive to nonsteroidal anti-inflammatory drugs; (ii) Clinically relevant facial involvement; (iii) Clinically relevant genital involvement; (iv) Clinically relevant hand and/or foot involvement or (v) Children's Dermatology Life Quality Index (CDLQI) >10.

A total of 114 participants were randomised: 38 to standard dose adalimumab (subcutaneous; initial 0.8mg/kg up to a maximum to 40mg, followed by 0.8mg/kg eow); 39 to low dose adalimumab (subcutaneous; initial 0.4mg/kg up to a maximum to 20mg, followed by 0.4mg/kg eow); and 37 to methotrexate (oral; initial 0.1mg/kg up to a maximum to 7.5mg, followed by weekly dose of up to 0.4mg/kg, up to a maximum dose of 25mg/week). To maintain blinding, participants allocated to adalimumab received placebo tablets and participants allocated to methotrexate received placebo injection following the adalimumab schedule. As methotrexate is a folic acid antagonist, all participants received folic acid (0.8 to 1.0mg/day) as a dietary supplement (to maintain study blinding).

Previous therapy received by trial participants included topical therapy (100%), phototherapy (52%), non-biologic systemic therapy (30%), and biologic therapy (10%; all etanercept).

4.3.1 Risk of bias assessment

The risk of bias for the trial was low for most domains, with appropriate methods used for allocation of participants, blinding, handling of missing data, and reporting of outcomes (on the basis of information reported in the CSR; see **Table 5.** Baseline characteristics were mostly balanced across treatment groups, with the exception of male sex, which appeared to be lower in the methotrexate arm. It should be noted that only six of the 114 children randomised were aged less than seven years at recruitment, all of whom were randomised to the low dose adalimumab group. This means that, despite adalimumab having marketing authorisation in children aged 4 years and older, this particular trial does not provide any efficacy data on the licenced standard dose of adalimumab in children aged 4-6 years.

16 of the 114 participants received the wrong medication. Regulatory documents indicate that the incidence of the error ”wrong medication” occurred at single time points and were unlikely to have affected the results of the study.

Table 5 Risk of bias assessment using Cochrane tool of bias for M04-717 RCT (“Period A”)

Assessment criterion	Risk of bias judgement	Support for judgement
Sequence generation	Low	“Participants were randomized by interactive voice/web response system to receive adalimumab 0.8 mg/kg, adalimumab 0.4 mg/kg, or MTX in a 1:1:1 ratio, respectively. Randomization was stratified by prior treatment with etanercept.”
Allocation concealment	Low	Participants were randomized by interactive voice/web response (IVR/IWR) system
Baseline comparability	Moderate	Higher proportion of female participants in MTX group than adalimumab groups. Only six children aged <7 years included in the trial, all of whom were in the 0.4mg/kg adalimumab group. Higher baseline PedsQL score in MTX group.
Blinding of participants, personnel, and outcome assessors	Low	“All AbbVie personnel with direct oversight of the conduct and management of the trial, (with the exception of the AbbVie Drug Supply Management Team), the PI, study site personnel, and the participant were to remain blinded to each participant's treatment throughout the blinded period of the study. The IVR/IWR system was to provide access to blinded participant treatment information in the case of medical emergency.” There was 1 participant for whom the blind was broken due to an SAE of

		proctocolitis that occurred on Day 195 of Period B and was thus nontreatment-emergent.
Incomplete outcome data	Low	Eight participants "early escaped" by week 8 of Period A: Five initially randomised to MTX, two randomised to low dose adalimumab, one randomised to standard dose adalimumab. [redacted]
Selective reporting	Low	All outcomes from clinicaltrials.gov protocol NCT01251614 reported in CSR

Primary efficacy endpoints for the randomised controlled period were ≥PASI 75 response at week 16 and sPGA rating of "cleared" or "minimal" (0 or 1) at week 16. Secondary outcomes included PASI 50, 90 and 100 responses, PGA score or 0, CDLQI and PedsQL scores.

Participants were evaluated at all visits for worsening of psoriasis. Up to and including the Week 8 visit, participants were eligible for "early escape" if they met the following criteria: (1) PASI scores increased by 50% relative to baseline at Week 4; or (2) PASI scores increased by 25% relative to baseline and by at least 4 points at each of two consecutive study visits (prior to or at Week 8). After Week 8, participants were to continue in the trial until the Week 16 visit.

Participants entering "early escape" were permitted to enter a longer-term observational study period (Period D; see below) in which they would receive open-label adalimumab at a dose of 0.8 mg/kg every other week (up to a maximum of 40 mg).

Primary efficacy analyses were conducted in the intent-to-treat (ITT) population (i.e. all randomised participants). Participants with missing or incomplete data at week 16 (including those entering "early escape") were imputed to be non-responders for categorical variables (non-responder imputation method; NRI), and had last observation carried forward (LOCF) for continuous variables. Analyses using per-protocol and "as observed" data were also reported in the CSR. The safety analysis was conducted in the safety population (i.e. all participants who received at least one dose of study medication).

4.3.2 Efficacy of adalimumab at 16 weeks

The absolute and relative results for PASI, sPGA, CDLQI and PedsQL outcomes at week 16 are shown in **Table 6** and **Error! Reference source not found.**)

Table 6 Results of key outcomes of adalimumab (Trial M04-717) at 16 weeks

Treatment	Dichotomous outcomes (ITT; NRI)				Continuous outcomes (ITT; LOCF)	
	PASI 50	PASI 75	PASI 90	sPGA 0 or 1	CDLQI mean change (SD)	PedsQL mean change (SD)
ADA 0.8mg/kg	[redacted]	22/38 (57.9%)	11/38 (28.9%)	23/38 (60.5%)	[redacted]	[redacted]
ADA 0.4mg/kg	[redacted]	17/39 (43.6%)	12/39 (30.7%)	16/39 (41.0%)	[redacted]	[redacted]
MTX 0.1mg/kg	[redacted]	12/37 (32.4%)	8/37 (21.6%)	15/37 (40.5%)	[redacted]	[redacted]

ADA=Adalimumab; CDLQI= Childhood Dermatology Quality of Life Index; ITT= Intention to Treat; LOCF=Last observation carried forward; NRI=non responder imputation; PASI=Psoriasis Area and Severity Index; PedsQL=Pediatric Quality of Life; sPGA=Physician static Global Assessment.

Table 7 Relative risks of key outcomes of adalimumab (Trial M04-717) at 16 weeks

Treatment	Relative risk and 95% CI				Mean Difference (MD) and 95% CI	
	PASI 50	PASI 75	PASI 90	sPGA 0 or 1	CLDQI	PedsQL

ADA 0.8mg/kg	[redacted]	1.79 (1.04 to 3.06)	1.34 (0.61 to 2.95)	1.49 (0.94 to 2.38)	1.6 (-1.44 to 4.64)	8.9 (2.94 to 14.86)
ADA 0.4mg/kg	[redacted]	1.34 (0.75 to 2.42	1.42 (0.65 to 3.08)	0.81 (0.46 to 1.41)	-0.1 (-3.14 to 2.94)	7.6 (2.42 to 12.78)
MTX 0.1mg/kg (reference)	[redacted]	1.00	1.00	1.00	0.00	0.00

4.3.2.1 PASI response

[redacted]PASI 75 response rates at 16 weeks were significantly greater for standard dose adalimumab (0.8mg/kg) than for methotrexate [redacted] 58% vs 32% [redacted]. Low dose adalimumab (0.4mg/kg) did not show a statistically significant improvement over methotrexate on these outcomes ([redacted]44% vs 32%). PASI 90 response rates did not differ significantly between the three treatment arms.

[redacted]

4.3.2.2 Physicians Global Assessment (PGA)

The proportion of participants achieving a sPGA score of 0 or 1 ('clear' or 'minimal') at 16 weeks was greater for standard dose adalimumab than low dose adalimumab or methotrexate (61% vs 41% vs 41%), though this difference was not statistically significant.

[redacted]

4.3.2.3 Quality of life

Two health related quality of life measures, CDLQI and PedsQL, were reported at 16 weeks. All three treatment groups showed improvements from baseline in the dermatology-specific quality of life measure (CDLQI), exceeding the published minimally clinical important difference (MCID) of a 2.5 point change from baseline. [46] However, these improvements were similar across the three treatment groups, with no significant difference between either dose of adalimumab or methotrexate ([redacted]).

Unlike CDLQI, improvements on the generic health related quality of life measure (PedsQL) significantly favoured both doses of adalimumab over methotrexate (mean changes of [redacted] and [redacted] for standard and low dose adalimumab respectively vs [redacted] for methotrexate). The mean changes in the adalimumab groups both exceed the published MCID of 4.4 for PedsQL.[24]

It is unclear why PedsQL scores would increase in the absence of dermatology-related QoL benefits as measured by CDLQI. However, both mean and median PedsQL scores at baseline were noticeably higher at baseline for methotrexate than adalimumab treatment arms (see **Table 4Error! Reference source not found.**), so the observed PedsQL change scores in the adalimumab arms may be overestimates due to regression to the mean.[47]

Table 8 PASI and sPGA response by age subgroups at 16 weeks

Subgroup	Treatment	PASI 50	PASI 75	PASI 90	sPGA 0 or 1
4 to 6 years of age	ADA 0.8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 0.4 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	MTX	[redacted]	[redacted]	[redacted]	[redacted]
>6 to 9 years of age	ADA 0.8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 0.4 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	MTX	[redacted]	[redacted]	[redacted]	[redacted]
>9 to 12 years of age	ADA 0.8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 0.4 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	MTX	[redacted]	[redacted]	[redacted]	[redacted]

>12 to 15 years of age	ADA 0.8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 0.4 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	MTX	[redacted]	[redacted]	[redacted]	[redacted]
>15 years of age	ADA 0.8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 0.4 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	MTX	[redacted]	[redacted]	[redacted]	[redacted]

4.3.3 Longer term efficacy of adalimumab

4.3.3.1 Period B: Withdrawal

[redacted]

4.3.3.2 Period C: Retreatment

[redacted]

[redacted]

[redacted]

[redacted]

Table 9 Reported PASI responses during retreatment phase (week 16 of period C)

	PASI 50	PASI 75	PASI 90	sPGA 0/1
Participants from Period B who had experienced loss of disease control, retreated with originally randomised dose of adalimumab 0.8mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
Participants from Period B who had experienced loss of disease control, retreated with originally randomised dose of adalimumab 0.4mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
Participants from Period B who had experienced loss of disease control, who were initially randomised to methotrexate, retreated with adalimumab 0.8mg/kg	[redacted]	[redacted]	[redacted]	[redacted]

4.3.3.3 Period D: Long-term follow-up

[redacted]

[redacted]

Table 10 Reported PASI responses during long-term follow-up phase (week 52 of period D)

	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.3.4 Safety of adalimumab

4.3.4.1 Adverse events at 16 weeks

Adverse event rates were comparable among the three treatment groups (**Error! Reference source ot found.**). Three serious adverse events considered unrelated to treatment (hand fracture, gastrointestinal infection due to food poisoning, and agitation due to alcohol overtake) were reported, all of which occurred in participants receiving adalimumab 0.4 mg/kg. One participant in the same treatment arm withdrew due to an adverse event (moderate psoriasis flare).

Table 11 Reported safety outcomes of Adalimumab (Trial M04-717) at week 16

Treatment	Participants with safety reports (%)						
	AE	SAEs	Infections	Serious infections	Injection site reactions	Malignancies	Withdrawals due to adverse events
ADA 0.8mg/kg	26/38 (68.4)	0/38 (0.0)	18/38 (47.4)	0/38 (0.0)	4/38 (10.5)	0/38 (0.0)	0/36 (0.0)
ADA 0.4mg/kg	30/39(76.9)	3/39 (7.7)*	22/39 (56.4)	1/39 (2.6)	3/39 (7.7)	0/39 (0.0)	1/39 (2.6) [+]
MTX	28/37 (75.7)	0/37 (0.0)	20/37 (54.1)	0/37 (0.0)	3/37 (8.1)	0/37 (0.0)	0/37 (0.0)

AE= Adverse Events; SAE=Serious Adverse events. *=1 hand fracture, 1 gastrointestinal infection, 1 agitation; [+]=due to moderate psoriasis flare

4.3.4.2 Longer-term safety of adalimumab

Table 12 shows the overall numbers of adverse events during patient follow-up across all four study periods to be similar across treatment arms. A total of nine SAEs were reported in eight participants. In terms of episodes per 100 patient years (E/100 PYs), the total rate of SAEs was 5.9 E/100 PYs for all participants ever treated with adalimumab 0.8 mg/kg from the first dose of adalimumab 0.8 mg/kg and 7.4 E/100 PYs for all participants treated with adalimumab (0.4 mg/kg and 0.8 mg/kg) from the first dose of adalimumab 0.8 mg/kg.

One SAE of hemorrhagic ovarian cyst occurred in Period B in a participant who had been initially randomized to adalimumab 0.8 mg/kg.

Five SAEs occurred during Period D, including one death due to an accidental fall, one tendon injury in a participant receiving adalimumab 0.4 mg/kg, one rash maculopapular in a participant receiving adalimumab 0.8 mg/kg, one chest pain in a participant randomized to MTX but receiving adalimumab 0.8 mg/kg, and one eye nevus in a participant receiving adalimumab 0.8 mg/kg (Table 12). All SAEs were considered by investigators to be unrelated or probably unrelated to study drug with the exception of eye nevus, which was assessed as possibly related.

In addition to the participant who discontinued treatment due to a moderate event of psoriasis flare in Period A, one participant initially randomized to MTX but receiving adalimumab 0.8 mg/kg during Period D discontinued due to an event of severe urticaria.

The rate of all infections reported by participants receiving adalimumab 0.8 mg/kg was 170.4 E/100 PY. Only two events of tuberculosis occurred, both during period D.

Table 12 Reported safety outcomes of adalimumab (Trial M04-717) for the follow-up periods

		Participants with safety reports							
		AE	**SAEs**	**Infections**	**Serious infections**	**Injection site reactions**	**Malignancies**	**Tuberculosis**	**Withdrawals due to adverse events**
Period B	ADA 0.8mg/kg (n=23)	[redacted]	[redacted]	[redacted]	0	0	0	0	0
	ADA 0.4mg/kgmg/kg (n=18)	[redacted]	[redacted]	[redacted]	0	0	0	0	0
	MTX (n=13)	[redacted]	[redacted]	[redacted]	0	0	0	0	0
Period C	ADA 0.8mg/kg (n=19)	[redacted]	[redacted]	[redacted]	0	0	2	0	0
	ADA 0.4mg/kgmg/kg (n=11)	[redacted]	[redacted]	[redacted]	0	0	0	0	0
	MTX (n=8)	[redacted]	[redacted]	[redacted]	0	0	0	0	1
Period D	ADA 0.8mg/kg (n=36)	[redacted]	3	25	0	2	0	1	0
	ADA 0.4mg/kgmg/kg (n=36)	[redacted]	1	15	0	1	0	1	0
	MTX (n=36)	[redacted]	1	22	0	1	0	0	1*

*= Severe urticaria in patient initially randomised to MTX but receiving adalimumab 0.8mg/kg

4.3.5 Summary of the efficacy and safety of adalimumab

- There is evidence from one 16-week randomised controlled trial comparing adalimumab to methotrexate in children and young people with severe chronic psoriasis.
- The trial does not provide evidence for children aged 4 to 6 years of age.
- Adalimumab at the licenced dose of 0.8mg/kg (up to 40mg) leads to significantly greater responses than methotrexate for the outcomes of PASI 50, PASI 75, but not PASI 90.
- PGA 0/1 response rates were higher for adalimumab 0.8mg/kg than methotrexate, though the difference was not statistically significant.

- The benefits of half-dose adalimumab were not statistically greater than those observed for methotrexate.
- Evidence on quality of life was inconsistent across different measures, possibly due to baseline imbalance on PedsQL.
- [redacted]
- [redacted]
- In children and young people adalimumab does not appear to be associated with an increase in adverse effects relative to methotrexate over 16 weeks, [redacted]
- However, due to the small numbers of observed participants, the possibility of rare adverse events cannot be entirely excluded.

4.4 Efficacy and safety of etanercept

One multicentre RCT (20030211) comparing etanercept with placebo met the selection criteria. Data on short-term safety and efficacy (blinded period) were available from published peer-reviewed journal papers,[46, 48-52] conference proceedings [53-59]and regulatory documentations [60-70].

The double-blind RCT recruited children between 4 to 17 years of age from 42 sites in the United States and Canada who had stable, moderate-to-severe plaque psoriasis at screening. Moderate-to-severe plaque psoriasis was defined as a psoriasis area-and-severity index (PASI) score of at least 12 (PASI scores range from 0 to 72, with higher scores indicating worse condition); a static physician's global assessment of at least 3 (where 0 indicates clear and 5 severe psoriasis), and psoriasis involvement of at least 10% of the body-surface area; a history of psoriasis for at least 6 months; and previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids) or psoriasis considered by the investigator as poorly controlled with topical therapy.

Within each age stratum, participants were randomized to either etanercept 0.8 mg/kg once weekly up to maximum dose of 50 mg once weekly or placebo in a 1:1 ratio. A total of 106 and 105 participants were randomized to etanercept and placebo arms, respectively.

The primary outcomes measures used in the RCT was PASI 75 response, defined as a 75% or greater decrease in PASI score (i.e., improvement) from baseline at week 12. The secondary outcome measures were: PASI 50 response, PASI 90 response, clear or almost clear status of sPGA (Static Physician Global Assessment of psoriasis), and percentage improvement from baseline in CDLQI (Children's Dermatology Life Quality Index) at week 12.

A total of 264 participants were screened and 211 children were randomised to etanercept or placebo. At baseline, both groups were similar in terms of age and gender composition, BSA, PASI and PGA scores , though the placebo group had a slightly higher proportion of patients with psoriatic arthritis (13% vs. 5%). There was no previous use of biologic therapy in either group (see Table 4). It should be noted that just 19 (9%) of children included in study were under the age of 8 years, and only 9 (4.3%) were under 6 years old.

At or after Week 4, participants with >50% increase or an absolute increase of at least 4 points in PASI score from baseline were allowed to enter an “escape” arm to receive open-label etanercept every week through Week 12. During this initial 12-week comparative period, a higher number of participants from the placebo group (27 out of 105) than the etanercept group (5 out of 106) entered early escape. Participants who entered the escape arm were recorded as non-responder at the time they entered the escape arm. Data for those participants from before they entered the escape arm were not changed. For participants who had missing data, their missing data were imputed as non-responder but their existing data were included as observed.

4.4.1 Risk of bias assessment

The trial had a low overall risk of bias for most domains, with appropriate methods used for randomisation, handling of missing data, and reporting of outcomes (see Table 13). The study was described as ‘double-blinded’, though the methods used to achieve blinding were not described.

Table 13 Risk of bias assessment using Cochrane tool of bias for 20030211 RCT

Assessment criterion	Risk of bias judgement	Support for judgement

Sequence generation	Low	Interactive voice or web response system was used
Allocation concealment	Low	Interactive voice or web response system was used during randomisation
Baseline comparability	Low	No obvious baseline imbalance, though slightly higher PsA rate (13% vs 5%) in placebo group.
Blinding of participants and personnel	Unclear	Although double blinded initially, patients could enter to escape group and receive open-label etanercept. 27/105 placebo-allocated patients entered escape group vs. 5/106 etanercept-allocated patients. For binary endpoints, efficacy measures taken after entering the escape group were imputed as non-responses. Blinding methods not described.
Blinding of outcome assessment	Unclear	Participants, caregiver, investigator and outcomes assessor were blinded, though method of blinding was not described.
Incomplete outcome data	Low	For binary measures, missing post-baseline data were imputed as non-responses. Continuous measures were imputed to have baseline values.
Selective reporting	Low	The reported treatment response and health quality outcomes match those described in the study protocol.

4.4.2 Efficacy of etanercept at week 12

Data on the outcomes of treatment response for the 20030211 RCT were available from publications and regulatory documents. PASI and PGA scores are reported in Table 14 and Table 15.

4.4.2.1 PASI response

PASI 50, 75 and 90 for the etanercept group were 74.5%, 56.6% and 27.4%, respectively. Response rates for the placebo group were 22.9%, 11.4% and 6.7%. When translated into relative risk values, the etanecept group had significantly higher probability of achieving PASI 50, 75 and 90, with respective RRs of 3.26 (95% CI 2.26 to 4.71), 4.95 (95% CI 2.84 to 8.65) and 4.10 (95% CI 1.88 to 8.95).

Table 14 Reported treatment response and health quality of life outcomes of Etanercept (Trial 20030211) at week 12

Treatment	Dichotomous outcomes				Continuous outcomes	
	PASI 50	**PASI 75**	**PASI 90**	**sPGA 0 or 1**	**CDLQI (SD)***	**PedsQL (SD)***
ETA 0.8mg/kg	79/106 (74.5%)	60/106 (56.6%)	29/106 (27.4%)	56/106 (52.8%)	5.4 (5.6)	6.8 (17.6)
PLB	24/105 (22.9%)	12/105 (11.4%)	7/105 (6.7%)	14/105 (13.3%)	3.1 (5.1)	3.8 (10.1)

Note: *= mean change from baseline

Table 15 Relative effects of reported outcomes of Etanercept (Trial 20030211) at week 12

Treatment arms	Relative risk and 95% CI				Mean difference (95% CI)	
	PASI 50	**PASI 75**	**PASI 90**	**sPGA 0 or 1**	**CDLQI**	**PedsQL**
ETA 0.8mg/kg	3.26 (2.26 to 4.71)	4.95 (2.84 to 8.65)	4.10 (1.88 to 8.95)	3.96 (2.36 to 6.66)	2.3 (0.85 to 3.74)	3.0 (-0.87 to 6.87)
PLB (reference)	1.00	1.00	1.00	1.00	0.00	0.00

4.4.2.2 Physicians Global Assessment (PGA)

The proportion of participants achieving a PGA score of 0 or 1 ('clear' or 'minimal') at 12 weeks was significantly greater for etanercept than placebo (52.8% vs 13.3%), equating to a relative risk of 3.96 (95% CI 2.36 to 6.66).

4.4.2.3 Quality of life

Data for two health related quality of life measures, CDLQI and PedsQL, were available at 12 weeks (**Table 14**). Both etanercept and placebo treatment groups showed improvements from baseline in CDLQI scores, exceeding the published minimally clinical important difference (MCID) of a 2.5

point change from baseline,[46]PedsQL though the improvement in the etanercept group was statistically significantly greater than in the placebo group (mean difference: 2.3, 95% CI:0.85 to 3.74).

Both treatment groups also showed improvements in the PedsQL, though for the placebo group this fell below the published MCID of 4.4. The mean change in PedsQL from baseline, while favouring etanercept, was not statistically significantly different between the treatment groups (mean difference: 3.0, 95% CI: -0.87 to 6.87).

4.4.2.4 Sub-group outcomes

Age-based subgroup analysis results of PASI responses for the Trial 20030211 were available (see **Table 16**). A higher proportion of the etanercept treatment group achieved PASI 50, 75 and 90 responses than the placebo group in all age categories. Imputation of treatment failure for participants entering early escape reduced the magnitude of the difference between treatments, though these differences remained formally statistically significant for all comparisons, with the exception of PASI 90, which was of borderline statistical significance (p=0.054).

Table 16 Sub-group PASI responses at week 12 (published results)[49]

		PASI 50	PASI 75	PASI 90
Age				
≥ 8 years	Etanercept	70/95* (73.7%)	52/95* (54.7%)	26/95* (27.4%)
	Placebo	23/97* (23.7%)	11/97* (11.3%)	6/97* (6.2%)
4-11 years	Etanercept	29/38 (76.3%)	22/38 (57.9%)	N/A
		30/38 (78.9%)†	22/38 (57.9%)†	12/38 (31.6%)†
	Placebo	8/38 (21.1%)	4/38 (10.5%)	N/A
		16/38 (42.1%)†	10/38 (26.3%)†	5/38 (13.2%)†
12-17 years	Etanercept	50/68 (73.5%)	38/68 (55.9%)	N/A
		51/68 (75.0%)†	38/68 (55.9%)†	17/68 (25.0%)†
	Placebo	16/67 (23.9%)	8/67 (11.9%)	N/A
		21/67 (31.3%)†	11/67 (16.4%)†	4/67(5.6%)†

*back-calculated from reported percentages, so integers may not be entirely accurate; N/A= not available; †ITT with treatment failure imputation extracted from EMEA document[62]

4.4.3 Longer-term efficacy of etanercept

4.4.3.1 Weeks 12-36: Open-label etanercept treatment

At the end of the 12-week double-blind period, a total of 208 participants (105 and 103 from the original etanercept and placebo groups respectively) entered to an open-label treatment phase (i.e. all were treated with etanercept) and followed-up until week 36.

Patients who did not achieve PASI 50 at week 24 were given the option to discontinue the study or to enter the incomplete-responder arm. Participants in the incomplete-responder arm had the option to receive topical psoriasis therapy according to the standard of care in addition to receiving open-label etanercept (see Figure 2).

By weeks 24 and 36 (i.e. 12 and 24 weeks of open-label etanercept), participants who were originally randomised to the placebo during the double-blind period achieved a similar PASI and PGA responses as participants receiving etanercept throughout (see Table 17).

Table 17 Results of key outcomes of Etanercept (Trial 20030211) between 12 and 36 weeks

		PASI 50	PASI 75	PASI 90
Week 24	ETA/ETA	92/105 (88%)	72/105 (68%)	39/105 (37 %)
	PLB/ETA	80/103 (78%)	64/103 (62%)	37/103 (37%)
Week 36	ETA/ETA	91/105 (87%)	71/105 (68%)	43/105 (41%)
	PLB/ETA	89/103 (86%)	67/103 (65%)	39/103 (38%)

ETA/ETA= participants randomised to etanercept and received etanercept after double-blind period (12 weeks); PLB/ETA=participants randomised to placebo but received etanercept after double-blind period.

4.4.3.2 Weeks 36-48: Re-randomised 'withdrawal-retreatment' period

At week 36, 138 patients who had achieved PASI 50 at week 24 or PASI 75 at week 36 were randomised 1:1 to receive either etanercept or placebo in a double-blinded fashion and followed-up for further 12 weeks until week 48.

During the follow-up, 42 participants from the ITT population (29/69 and 13/69 from the placebo and etanercept arms respectively) lost PASI 75 response and so were allocated to receive etanercept in open-label fashion until week 48.

Overall, 52 out of 65 (80%) participants who received etanercept throughout the withdrawal-retreatment period maintained PASI 75. 85% of those re-randomised to placebo and did not lose PASI 75 during follow-up retained response at week 48. Only 36% of those who were retreated with open-label etanercept after losing PASI75 response on placebo had regained response by week 48 (Table 18). The use of PASI75 as both a retreatment rule and as an outcome makes these results difficult to interpret; however, a relatively high rate of late cross-over from placebo to etanercept could partly explain a lack of response among these participants on PASI and PGA measures.

Table 18 Results of key outcomes of Etanercept (Trial 20030211) at week 48 (observed data)

	PASI 75	sPGA 0 or 1
Re-randomised to etanercept and received blinded etanercept (no loss of PASI 75 response) or open-label etanercept (after loss of PASI 75 response)	52/65 (80%)	38/65 (58%)
Re-randomised to placebo and stayed on blinded placebo until week 48 (no loss of PASI 75 response)	34/40 (85%)	27/40 (68%)
Re-randomised to placebo but received open label etanercept after loss of PASI 75 response	10/28 (36%)	8/28 (29%)

4.4.3.3 Weeks 48-312 (Study 20050111)

194 participants completed 48 weeks of follow-up in the 20030211 trial (57 participants who received etanercept and topical therapy starting from the open-label treatment phase, 95 participants who were randomised to etanercept and placebo arms and continued to receive blinded drug, and 42 participants who were randomised to either etanercept or placebo but did not achieve PASI 75 and were re-treated with etanercept until the end of the study).

Of the 194 participants who completed the 20030211 trial, 182 were enrolled in an open-label extension study (20050111) to establish long-term safety of etanercept. Participants received etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) subcutaneously once weekly for a further 264 weeks. 63 participants (34.6%) completed 264 weeks of follow-up.

During the 264 weeks of further follow-up, the probability of achieving of PASI 50, 75 and 90 was similar across all the outcome recoding points. However, it should be noted that by week 264, 63.6% of the participants (115/181) withdrew from the study (Table 19) and reasons for withdrawal were unavailable.

Table 19 Reported efficacy outcomes during long-term follow-up period (study 20050111)

Week	≥PASI 50 (%)	≥PASI 75 (%)	≥PASI 90 (%)	sPGA 0 (%)	sPGA 0 or 1 (%)
12	162/181(89.5)	122/181 (67.4)	64/181 (35.4)	12/181 (13.3)	97/181 (53.6)
48	150/168 (89.3)	113/168 (67.3)	55/168 (32.7)	18/168 (10.7)	82/168 (48.8)
96	123/138 (89.1)	84/138 (60.9)	41/138 (29.7)	16/139 (11.5)	66/139 (47.5)
144	101/114 (88.6)	71/114 (62.3)	32/114 (28.1)	9/114 (7.9)	52/114 (45.6)
192	80/92 (87)	64/92 (69.6)	3392 (35.9)	19/92 (20.7)	44/92 (47.8)
240	68/74 (91.9)	48/74 (64.9)	27/74 (36.5)	13/74 (17.6)	37/74 (50)
264	58/66 (87.9)	42/66 (63.6)	19/66 (28.8)	8/66 (12.1)	25/66 (37.9)

4.4.4 Safety of Etanercept

4.4.4.1 Adverse events at 12 weeks

The number of adverse events reported during the 12 week period was similar for etanercept and placebo (68 vs. 62). There were 50 infections and seven injection site reactions in the etanercept group, compared with 33 infections and 5 injection site reactions in the placebo group. While difference in rate of infections fell short of formal statistical significance, there were noticeably more infections in the etanercept treatment arm (47.2% vs 31.4%; p=0.0683). One participant in the etanercept group withdrew due to an adverse effect (no further details available). No serious adverse events were observed during the 12-week randomised phase.

Table 20 Reported safety outcomes of Etanercept (Trial 20030211) at week 12

Treatment	Participants with safety reports(%)						
	AE	SAEs	Infections	Serious infections	Injection site reactions	malignancies	Withdrawals due to adverse events

ETA	68/106 (64.2)	NR	50/106 (47.2)	0/106 (0.0)	7/106 (6.6)	NR	1/106 (0.9)
PLB	62/105 (59.0)	NR	33/105 (31.4)	0/105 (0.0)	5/105 (4.8)	NR	0/105 (0.0)

NR=Not reported

4.4.4.2 Adverse events weeks 12-36

Through week 36, 282 infections were reported during treatment with etanercept (238.18 events per 100 person-years). The most common infections were upper respiratory tract infection, nasopharyngitis, influenza, pharyngitis, streptococcal pharyngitis, and viral upper respiratory infection (59.97, 33.79, 16.05, 15.20, 8.45, and 8.45 events per 100 participant-years, respectively). During the same period, a single serious non-infectious adverse event (due to benign ovarian mass) and one serious infection of gastroenteritis with dehydration were observed.

Through week 36, a total of 2.4% (5/208) withdrew due to adverse events: three participants were withdrawn because of non-infectious adverse events (psoriasis, atopic dermatitis and muscle cramps) and two participants because of infections (pneumonia and skin infection), see Table 21.

Table 21 Reported safety outcomes of Etanercept (Trial 20030211) through week 36

Participants with safety reports (%)							
AE	**SAEs**	**Infections**	**Serious infections**	**Injection site reactions**	**Malign-ancies**	**Withdrawals due to adverse events**	**Deaths**
584.48 events per 100 person-years	1/208 (0.4)	238.18 events per 100 person-years	1/208 (0.4)	26/208 (12.5)	0	5/208 (2.4)*	0/208 (0.0)

*= psoriasis, atopic dermatis, muscle cramps, pnuemonia and skin infection

4.4.4.3 Adverse events weeks 48 to 312

A total of 161 participants (89.0%) reported at least one adverse event during the study through week 264 of follow-up study 20050111. Seven participants (3.9%) reported serious adverse events with each participant reporting a single event: anxiety, cellulitis, infectious mononucleosis, post-operative intestinal obstruction, osteonecrosis, and thyroid cyst; a seventh participant underwent an elective

abortion (Table 22) However, of the seven serious adverse events, only the cellulitis infection was considered by the investigator to be related to etanercept treatment.

Six participants (3.3%) withdrew from the study due to either an infectious or non-infectious adverse event: Two participants withdrew due to Crohn's disease, and one participant each withdrew due to glomerulonephritis (secondary to infection), psoriasis, sinusitis, and nerve paralysis. Glomerulonephritis and one of the cases of Crohn's disease were considered to be related to treatment.

No serious adverse event led to study withdrawal. No opportunistic infections or deaths occurred during the study and no malignancies were reported.

Table 22 Reported safety outcomes of Etanercept (Trial 20030211) through week 264

Treatment	Participants with safety reports (%)						
	AE	SAEs	Infections	Serious infections	Injection site reactions	Malignancies	Withdrawals due to adverse events
ETA	161/181 (89.0)	7/181 (2.8)	140/181 (77.3)	2/181(1.1)	16/181 (8.8)	NR	6/181 (3.3)*

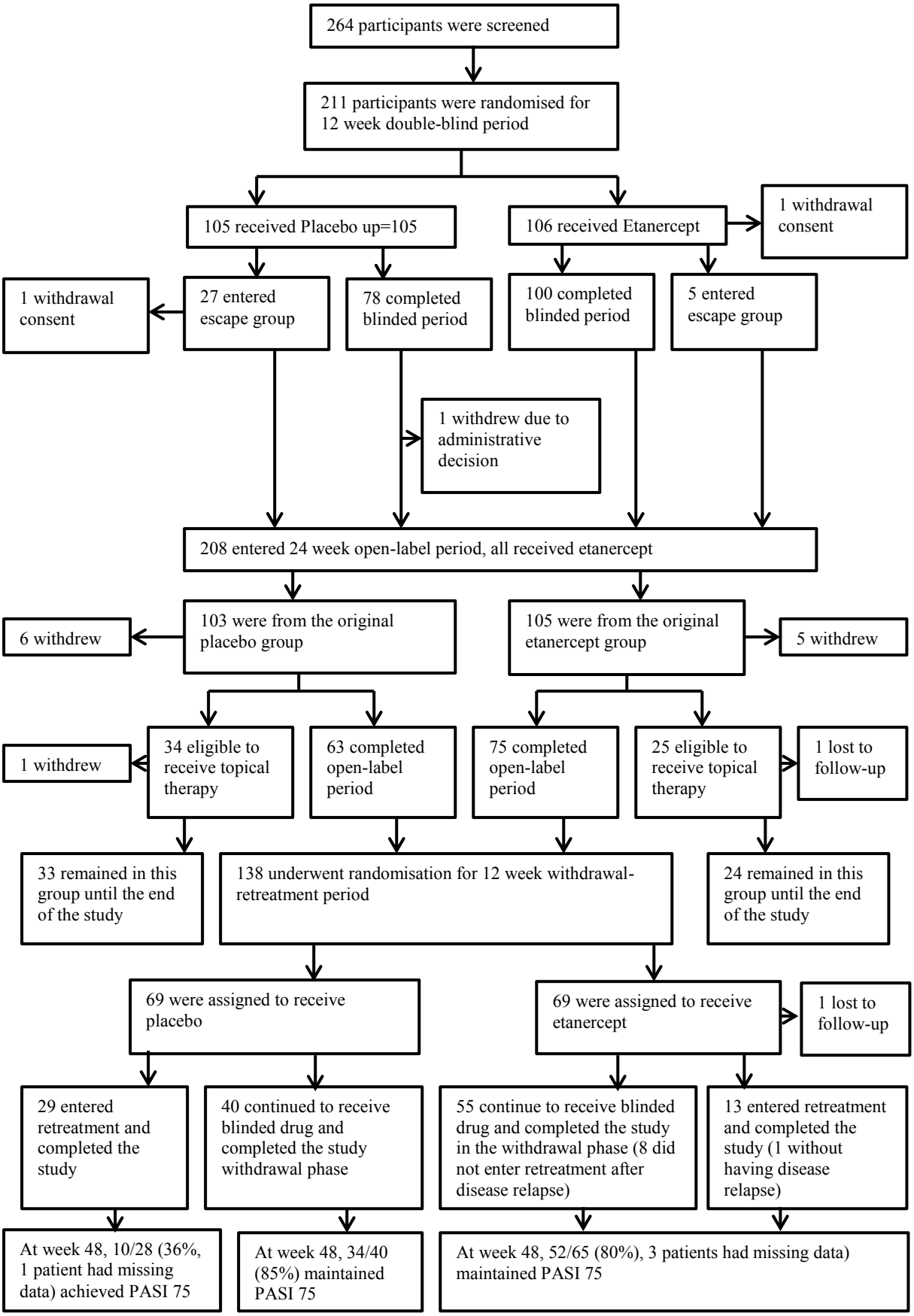
NR=Not reported; * = 2 Crohn's disease, 1 glomerulonephritis, 1 psoriasis, sinusitis, and 1 nerve paralysis

4.4.5 Summary of the efficacy and safety of etanercept

- One multicentre RCT (20030211) compared etanercept versus placebo in children aged 4 to 17 years of age with moderate-to-severe plaque psoriasis.
- Relatively few young children (9% aged under 8 years; 4.3% aged under 6 years) were included in study
- At 12 weeks, etanercept was significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50, 75 and 90, and PGA cleared or minimal scores.
- Improvements in health-related quality of life were larger for etanercept than placebo, but only reached statistical significance for CDLQI.
- Adverse events rates were similar between etanercept and placebo groups at 12 weeks with no serious adverse events observed for either treatment. However, observed higher rate of infections among participants receiving etanercept was of borderline statistical significance.

- A subsequent open-label extension study followed-up participants for up to six years from entry into the original RCT. The proportion of PASI and PGA responders were stable over time, though only 36% of participants were available at the latest follow-up point. The proportion of participant withdrawing due to lack of efficacy is unknown. These longer-term uncontrolled observational response data may therefore overestimate the efficacy of etanercept.
- Through 264 weeks of additional follow-up, withdrawals due to adverse events were infrequent, and no deaths or malignancies were observed.

Figure 2 Short-term and long-term participant follow-up flow chart of etanercept trial



4.5 Efficacy and safety of ustekinumab

One multicentre RCT (1275PSO3006; CADMUS) comparing standard and half dosages of ustekinumab (0.75mg/kg and 0.375mg/kg, respectively) with placebo met the selection criteria. Data on safety and efficacy (blinded period) were available from one peer-reviewed journal paper,[71] conference proceedings,[72] regulatory documentation,[73, 74] and a clinical study report provided by the manufacturer.

The CADMUS RCT was a double-blind, placebo-controlled study in adolescent participants (≥12 to <18 years of age) ,who had a diagnosis of moderate-to-severe plaque psoriasis for at least 6 months, conducted at multiple sites in Europe (Belgium, France , Germany , Hungary , Portugal , Russia, Sweden , Ukraine and United Kingdom) and Canada. Moderate-to-severe disease was defined as Psoriatic Area and Severity Index (PASI) ≥12, Physician's Global Assessment (PGA) ≥3, and body surface area (BSA) involvement ≥10%.

A total of 157 participants were screened. One hundred ten participants were eligible and randomized (37 participants to placebo, 37 participants to ustekinumab half-standard dosage and 36 participants to ustekinumab standard dosage). The standard dosage of ustekinumab was 0.75 mg/kg for participants ≤60 kg of weight, 45mg for participants weighing 60kg to 100 kg, and 90mg for participants weighing >100 kg. The half-standard dosage ustekinumab was 0.375 mg/kg weighing 60kg to 100 kg, and 45mg for participants weighing >100 kg. Randomization was stratified by investigational site and baseline weight (≤60 kg or >60 kg).

The study had three periods:

- Controlled period (0-12weeks): participants received either ustekinumab (full or half doses) or placebo. In the ustekinumab groups, participants were allowed to early escape at week 8 to have moderate-to-high potency topical steroid preparations through Week 12 if their PASI scores increased by ≥50% from baseline. However no participants entered the escape route during this period.
- Placebo crossover and active treatment period (12-52 weeks): participants randomised to placebo during the controlled period were allowed to crossover to the full or half-dose of ustekinumab at week 12.
- Follow-up period (52-60 weeks): participants continued to be followed for safety analysis.

To preserve blinding, participants in the half-standard dosage and standard dosage groups received ustekinumab at Week 0 and Week 4 followed by doses every 12 weeks until Week 40. Participants in

the placebo group also received placebo at Week 0 and Week 4, crossed over to receive either half-standard dosage or standard dosage ustekinumab at Week 12 and Week 16, followed by 12 weekly doses of either a half-standard dosage or standard dosage ustekinumab, with the last dose at Week 40. All participants were followed for efficacy through Week 52 and for safety through Week 60.

The primary outcome measure was the proportion of participants who achieved sPGA score of 'cleared' or 'minimal' at Week 12. Data from all randomized participants were analysed according to their assigned treatment group. Participants who met treatment failure criteria prior to Week 12 or who entered early escape were considered non-responders at Week 12. In addition, participants who had a missing PGA score at Week 12 were considered as not achieving the primary endpoint at Week 12.

The secondary outcome measures were the PASI 50, 75 and 90 at Week 12 based on all randomized participants, and changes from baseline in CDLQI at Week 12 based on efficacy evaluable participants.

4.5.1 Risk of bias assessment

Based on the Cochrane risk of bias assessment tool, the CADMUS RCT double-blind period had a low risk of bias: appropriate randomisation and blinding techniques were implemented, no obvious difference of baseline characteristics between treatment arms was apparent, missing data were handled appropriately and that all protocol-stated outcome measures were reported (see Table 23).

Table 23 Risk of bias assessment using Cochrane tool of bias for Ustekinumab RCT (CADMUS)

Assessment criterion	Risk of bias judgement	Support for judgement
Sequence generation	Low	"Dynamic central randomization was implemented in conducting this study. Participants were randomly assigned to 1 of 4 treatment groups based on an algorithm implemented in the Interactive Voice/Web Response System (IVRS or IWRS) before the study"
Allocation concealment	Low	Based on the algorithm, the IVRS/IWRS assigned a unique treatment code, which dictated the treatment assignment.
Baseline comparability	Low	No obvious difference in baseline characteristics
Blinding of participants, personnel and outcome assessors	Low	"The Sponsor, investigative study sites, and participants remained blinded to treatment assignment until the last participant enrolled completed the Week 60 evaluations and the database was locked"
Incomplete outcome data	Low	"Participants who discontinued study treatment due to lack of efficacy, an adverse event (AE) of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could affect their psoriasis were considered as treatment failures. A participant who met 1 or more treatment failure criteria was considered as a treatment failure from that point onward. The baseline values were used for all directly measured endpoints regardless of the actual measurements. Zeros were assigned to improvements and percent improvements, and nonresponder status was assigned to binary response variables. " "Participants who used a moderate to high potency topical steroid as a result of being eligible to early escape were considered as nonresponders at Week 12 for binary endpoints and their continuous outcomes at Week 12 were imputed by the last value at or prior to Week 8. The analysis at Week 16 was the observed data without imputation. After Week 16, if participants continued to use a moderate to high potency topical steroid, treatment failure rules were applied to those participants.
Selective reporting	Low	Primary and secondary outcomes reported match the study protocol

4.5.2 Efficacy of ustekinumab

4.5.2.1 Efficacy at week 12

Data on treatment response (PASI and PGAs) and health quality of life (CDLQI and PedsQL) outcomes for CADMUS RCT are presented in Table 24 and Table 25 below.

Table 24 Results of key outcomes of Ustekinumab (Trial CNTO1275PSO3006 CADMUS) at week 12

Treatment	Number of participant who achieved the outcomes (%)					Mean change (SD)	
	PASI 50	PASI 75	PASI 90	sPGA 0 or 1	sPGA 0	CDLQI	PedsQL
UST 0.75mg/kg	32/36 (88.9)	29/36 (80.6)	22/36 (61.1)	25/36 (69.4)	17/36 (47.2)	-6.7 (5.6) n=32	8.03 (10.4) n=32
UST 0.375mg/kg	30/37 (81.2)	29/37 (78.4)	20/37 (54.1)	25/37 (67.6)	12/37 (32.4)	-5.6 (6.4) n=35	10.81 (12.9) n=35
PLB	11/37 (29.7)	4/37 (10.8)	2/37 (5.4)	2/37 (5.4)	1/37 (2.7)	-1.5 (3.2) n=32	3.35 (10.0) n=32

Table 25 Relative effects of Ustekinumab (Trial CNTO1275PSO3006 CADMUS) at week 12

Treatment	Relative risks and 95% CI					Mean Difference (MD) and 95% CI	
	PASI 50	PASI 75	PASI 90	sPGA 0/1	sPGA 0	CDLQI	PedsQL
UST 0.75mg/kg	2.99 (1.79 to 4.97)	7.5 (2.9 to 19.1)	11.0 (2.8 to 43.5)	12.9 (3.3 to 50.3)	17.5 (2.5 to 124.5)	5.2 (2.96 to 7.44)	8.9 (2.46 to 15.34)
UST 0.375mg/kg	2.72 (1.62 to 4.48)	7.3 (2.8 to 18.6)	10.0 (2.5 to 39.8)	12.5 (3.2 to 49)	12.0 (1.6 to 87.7)	4.1 (1.7 to 6.5)	7.6 (2.16 to 13.04)
PLB	1.00	1.00	1.00	1.00	1.00	0.00	0.00

Physicians Global Assessment (PGA)

Significantly greater proportions of participants in the standard dosage and the half-standard dosage groups (69.4% and 67.6%, respectively) achieved PGA scores of cleared (0) or minimal (1) at Week 12 compared with the placebo group (5.4%). The proportions of participants who achieved PGA scores of cleared (0) were also higher in the standard dosage and half-standard dosage groups (47.2% and 32.4%, respectively) than the placebo groups (2.7%). The relative risks for these outcomes are shown in Table 25

PASI response

Higher proportions of participants in the standard dosage and the half-standard dosage groups achieved PASI 50, 75 and 90 than the placebo group. For example, whilst 80.6% and 78.4% of the standard dosage and half-standard dosage groups, respectively, achieved a PASI 75 response at week 12, only 10.8% the placebo group achieved the same PASI response (see Table 24). The relative risk values also show that both ustekinumab dosage groups had significantly higher probabilities of achieving the PSAI 50, 75 and 90 responses than the placebo group (Table 25)

Health-related quality of life

Changes from baseline in CDLQI were significantly greater in both the standard dosage and half-standard dosage groups (mean of -6.7 and -5.6, respectively) compared with the placebo group (-1.5). Whilst both ustekinumab treatment groups showed improvements from baseline in the CDLQI that exceed the published minimally clinical important difference (MCID) of a 2.5 point change from baseline, this was not the case for the placebo group. The mean difference values indicate that CDLQI changes were significantly greater for both ustekinumab dosage groups than the placebo group (mean difference: 5.2, 95% CI: 2.96 to 7.44 and mean difference: 4.1, 95% CI: 1.7 to 6.5, respectively; see **Table 25**).

Participants in both the standard dosage and half-standard dosage groups (mean of 8.03 and 10.81, respectively) showed significantly larger improvements in the PedsQL total scale scores than participants in the placebo group (3.35). The mean changes for the half dosage and standard dosage were above the published MCID of 4.4 while changes for the placebo group was below the MCID figure. Mean differences at 12 weeks indicate that standard dosage and half dosage groups had significantly higher improvement in PedsQL than the placebo group (mean difference: 8.9, 95% CI: 2.46 to 15.34 and mean difference: 7.6, 95% CI: 2.16 to 13.04, respectively).

Sub-group efficacy outcomes

Sub-group efficacy results of PASI 75 and PGA 0 or 1 were available from the CSR (Table 26) [redacted]

Table 26 Sub-group efficacy outcomes of Ustekinumab (Trial CNTO1275PSO3006 CADMUS) at week 12

		PASI 75*	sPGA 0 or 1*
Age <=15			
	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]

	Placebo	[redacted]	[redacted]
Age >15 years			
	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
Sex			
Male	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
Female	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
Weight			
≤60kg	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
>60-≤100kg	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
>100kg	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]

*back-calculated from reported percentages, so values may not be entirely accurate.

4.5.3 Longer term efficacy of ustekinumab

4.5.3.1 PASI response

Among participants continuing ustekinumab treatment, PASI responses observed in week 12 appeared to be sustained at week 52, with few participants lost to follow-up (one participant was lost from the standard dose arm and two from the half-dose arm).

Participants who were randomised to placebo and crossed over to standard ustekinumab dosage (0.75mg/kg) achieved better PASI responses than those who crossed over to half-standard dosage (0.375mg/kg), see Table 27.

4.5.3.2 PGA response

A similar pattern of responses as can be seen for PGA response data, with similar response rates at week 52 as at week 12 among participants continuing ustekinumab treatment, and a large improvement between weeks 12 and 52 for participants crossing over to active treatment from placebo (Table 27).

Table 27 Reported PASI and PGA response outcomes at week 52

	PASI 50	PASI 75	PASI 90	sPGA 0	sPGA 0 or 1
UST 0.75mg/kg	[redacted]	[redacted]	23/35 (65.7%)	18/36 (50%)	26/36 (72%)
UST 0.375mg/kg	[redacted]	[redacted]	17/34 (50%)	13/37 (35%)	23/37 (62%)
PLB→ UST 0.75mg/kg	[redacted]	[redacted]	16/17 (94.1%))	11/17 (65%)	16/17 (94%)
PLB→ UST 0.375mg/kg	[redacted]	[redacted]	9/17 (52.9%))	9/19 (47%)	13/19 (68%)

4.5.4 Safety of ustekinumab

4.5.4.1 Adverse events at week 12

Total reported adverse events did not significantly differ between the ustekinumab treatment (44.4% standard and 51.4% half-dose) and placebo groups (56.8%; Table 28) There were no serious adverse events reported in the standard ustekinumab dosage or placebo groups, while one participant in the ustekinumab half-dosage group was hospitalised for worsening of psoriasis (see Table 28). There were no reported malignancies or withdrawals due to adverse events.

One participant in the standard dosage ustekinumab group had a mild injection site reaction. There were no incidences of serious infection, tuberculosis, malignancy or withdrawals due to adverse events during the initial 12-week treatment period.

Table 28 Reported safety outcomes of Ustekinumab (Trial CNTO1275PSO3006 CADMUS) at week 12

Treatment	Participants with safety reports (%)						
	AE	SAEs	Infections	Serious infections	Injection site reactions	Malignan-cies	Withdrawals due to adverse events
UST 0.75mg/kg	16/36 (44.4)	0/36 (0.0)	8/36 (22.2)	0/36 (0.0)	1/36 (2.8)	0/36 (0.0)	0/36 (0.0)
UST 0.375mg/kg	19/37(51.4)	1/37 (2.7) *	12/37 (32.4)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)
PLB	21/37 (56.8)	0/37 (0.0)	14/37 (37.8)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)

*= one participant in the half ustekinumab dosage group was hospitalised for worsening of psoriasis

4.5.4.2 Discontinuation through week 40

Through Week 40, 8.2% (9/110) of participants discontinued the trial. The most common reasons for discontinuation were lack of efficacy and adverse events (Table 29). Five participants (13.5%) who were originally randomised to half-standard dosage ustekinumab group discontinued the trial compared with two participants (5.6%) in the standard dosage group. Two patients who crossed over from placebo to half-dose ustekinumab withdrew due to adverse events.

Table 29 Reported number of participants discontinuing ustekinumab treatment (CADMUS) through week 40

Treatment	Participants with safety reports (%)			
	Total discontinued	Due to AEs	Due to death	Due to lack of efficacy
UST 0.75mg/kg	2/36 (5.6)	0/36 (0.0)	0/36 (0.0)	2/36 (5.6)
UST 0.375mg/kg	5/37 (13.5)	1/37 (2.7)	1/37 (2.7)	3/37 (8.1)
PLB→ UST 0.75mg/kg	0/18 (0.0)	0/18 (0.0)	0/18 (0.0)	0/18 (0.0)
PLB→ UST 0.375mg/kg	2/19 (10.5)	2/19 (10.5)	0/19 (0.0)	0/19 (0.0)

4.5.4.3 Adverse events through week 60

Through Week 60, 81.8% (90/110) of participants in the ustekinumab combined group reported one or more AEs. Of the 74 participant recorded infections, 18 (24%) were considered reasonably related to ustekinumab treatment.

A total of 5.5% (6/110) of participants in the ustekinumab combined group (5 participants in the half-standard dosage group and 1 participant in the standard dosage group) reported SAEs (Table 30). Four (one due to worsening of psoriasis) of the 110 of participants in the ustekinumab combined group discontinued the trial due to an adverse event by week 60.

Table 30 Reported safety outcomes of Ustekinumab (Trial CNTO1275PSO3006 CADMUS) through week 60‡

Treatment	Participants with safety reports(%)						
	AE	**SAEs**	**Infections**	**Serious infections**	**Injection site reactions**	**Malignancies**	**Withdrawals due to adverse events**
UST 0.75mg/kg	29/36 (80.6)	1/36 (2.8)*	24/36 (66.7)	1/36 (2.8)*	1/36 (2.8)	0/36 (0.0)	0/36 (0.0)
UST 0.375mg/kg	33/37 (89.2)	5/37[+†] (13.5)	26/37 (70.3)	1/37† (2.7)	0/37 (0.0)	0/37 (0.0)	2/37 (5.4)
PLB→ UST 0.75mg/kg	13/18 (72.2)	0/18 (0.0)	11/18 (61.1)	0/18 (0.0)	0/18 (0.0)	0/18 (0.0)	0/18 (0.0)
PLB→ UST 0.375mg/kg	15/19 (79.0)	0/19 (0.0)	13/19 (68.4)	0/19 (0.0)	0/19 (0.0)	0/19 (0.0)	2/19 (10.5)

‡incorporates week 12 and 40 data; * ear infection; †pyelonephritis; [+]in addition to events recorded before week 60: 1 death due to automobile accident; 1 allergic contact dermatitis; 1 laboratory values for ALC, ANC and white blood cells of: 0.53, 0.87 and 1.62 x 103/μL, respectively while undergoing treatment with acyclovir for a concurrent AE of herpes simplex

4.5.5 Summary of the efficacy and safety of ustekinumab

In this multicentre trial (CADMUS) of children 12 to 17 years of age:

- Both the standard dosage and half dosage of ustekinumab were significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50,75 and 90, PGA cleared or minimal and PGA cleared scores at 12 weeks.
- Both ustekinumab dosages also lead to significantly greater improvements in health-related quality of life measurements (CDLQI and PedsQL) at 12 weeks than the placebo group.
- Among participants originally allocated to ustekinumab, PASI and PGA effects observed at 12 weeks appeared to be largely sustained at 52 weeks, with few withdrawals due to lack of efficacy.
- Participants originally allocated to placebo showed substantial improvements in PASI and PGA response at 52 weeks, after crossing over to ustekinumab treatment at week 12. There

was some indication that the gains were greater among those received standard dosage ustekinumab than those received half-standard dosage treatment.

- There were no notable differences between the ustekinumab and placebo in terms of short-term and longer-term adverse events, though the number of observations was small and longest the follow-up time was just 60 weeks. Few participants withdrew due to adverse effects.

4.6 Additional observational evidence

4.6.1 Retrospective case series

Two retrospective case series reported the use of adalimumab, etanercept and ustekinumab from 4 to 165 weeks in children with moderate-to-severe psoriasis.[75, 76] Key characteristics and results from these studies are reported in Table 31.

Garber et al reported a retrospective chart review of 27 participants (19 males, 8 females) attending a single US general dermatology clinic from 2008-2014. Insufficient details were reported to establish how many patients received more than one biologic over this period. Clearance rates (defined as 99% reduction on the simple measure for assessing psoriasis severity; S-MAPA) were reported (see Table 31). No serious adverse events were reported. Though the authors concluded that adalimumab, etanercept and ustekinumab are safe and efficacious in paediatric psoriasis, this study provides insufficient data on the efficacy or safety profiles of these agents in practice.

Klufas et al similarly reported a retrospective case series evaluating 51 children with moderate to severe psoriasis treated with systemic therapies for adverse event occurrence and PGA-measured disease response. For all biologics (alone or in combination with methotrexate), mean PGA values fell at 5-7 months follow-up. 29 adverse events were reported in relation to 80 treatment data points (some patients received more than one biologic); most were minor subjective side effects, with no infections or SAEs reported. Again, limitations in the sample size and study design preclude strong inferences being drawn from these data.

Table 31 Retrospective case series of adalimumab, etanercept, or ustekinumab in children and young people with psoriasis

Study (Year) Country	Treatment (dose)	Number of	Treatment duration (weeks)	Median age (range)	Mean PGA at baseline	Reported outcomes / key adverse events
Garber et al (2015) **USA**	Adalimumab (40mg eow)	7	146	-	-	4/6 achieved clearance; 3 secondary failure, 1 injection site reaction, 3 minor infections†
	Etanercept (50mg weekly)	13	87	-	-	6/9 achieved clearance; 1 injection site reaction, 6 secondary failure, 3 lack of response, 4 minor infections*
	Ustekinumab (45mg at weeks 0 and 4, then every 12 weeks)	3	165	-	-	1/3 achieved clearance
	Adalimumab + Methotrexate	2	11	-	-	1/2 achieved clearance
	Etanercept + Methotrexate	2	121	-	-	2/2 achieved clearance
	Etanercept + Cyclosporine	1	20	-	-	-
Klufas et al (2016) **USA**	Adalimumab (40mg eow)	11	3-134	16.5 (7.0-18.0)	2.4	Mean PGA‡ 0.7; 1 injection site reaction
	Etanercept (25 or 50 mg once or twice weekly)	23	8-135	14.0 (8.0-18.0)	3.0	Mean PGA‡ 1.5; 2 injection site reactions
	Ustekinumab (45mg or 90mg at weeks 0 and 4, then every 12 weeks)	6	4-72	16.5 (7.0-18.0)	2.6	Mean PGA ‡1.5
	Adalimumab (40mg eow) + Methotrexate (7.5 to 15mg weekly)	9	8-118	15.0 (11.0-17.0)	2.4	Mean PGA‡ 1.0; 1 injection site reaction
	Etanercept (50mg once or twice weekly + Methotrexate (7.5 to 15mg weekly)	5	4-30	15.0 (13.0-17.0)	3.1	Mean PGA‡ 1.8

Ustekinumab (45mg at weeks 0 and 4, then every 12 weeks) + Methotrexate (12.5mg weekly)	2	NR	16.5 (16.0-17.0)	3.8	Mean PGA‡ 1.3

*across all participants who received etanercept (n=16); †across all participants who received adalimumab (n=9), ‡at 5-7 months

4.6.2 Registry data

Published findings or papers detailing study design were identified for 16 registries. Information on biologic drug safety in their psoriasis cohorts was published by nine registries, where 11 published articles on biologic efficacy and nine included drug survival data. This does not necessarily mean the other registries did not record these outcomes, but they were not covered in the identified literature output.

4.6.2.1 Registry data for children

Further screening was carried out to find publications with explicit reference to children with psoriasis within each registry; specifically on information on survival of biologic treatment. Two registries (Child-CAPTURE and DERMBIO) were found to include children with psoriasis who were treated with biologics. Child-CAPTURE (Netherlands) contained 7 children treated with etanercept,[77] but did not differentiate between biologic and non-biologic therapies in drug survival analyses. We identified from the 2014 annual report by the DERMBIO (Denmark) registry that there are 37 children enrolled who are undergoing treatment with adalimumab, etanercept, or ustekinumab, though data for this group were not reported separately. Cox regression modelling of covariates in two studies found no significant predictive relationship between patient age and drug survival, suggesting treatment withdrawal rates among children were similar to those in adults.[78, 79]

4.6.2.2 Wider registry data

In one 2015 DERMBIO study following 1277 (predominately adult) psoriasis patients for up to 10 years, median drug survival in etanercept was 30 months (CI 25.1 - 34.9), which was significantly lower than for adalimumab (59 months, CI 45.6 – 72.4) and ustekinumab (median not reached).[78] Year-on-year survival for etanercept (estimated from Kaplan-Meier curve) was 0.7 at one year, 0.53 at year two, and 0.3 at year five, compared to 0.85 after one year, 0.78 at two, and 0.65 at year five for ustekinumab (**Table 32**). Loss of efficacy was the most likely reason for drug discontinuation, but this was of greater significance proportionally in etanercept than in the other biologics analysed.

Findings from the British Association of Dermatologists Biologic Interventions Register (BADBIR) were broadly similar to those seen in the Danish cohort. A study by Warren *et al*. on drug survival over three years in 3523 biologic-naïve patients found that 77% of patients remained on biologic treatment over the first year, falling to 53% by the third year.[80] There were again significant differences in the treatment withdrawal rates between biologics; ustekinumab exhibited the highest first-course survival rate at 0.89 for year one and 0.75 at year three. Adalimumab showed the highest survival of the anti-TNFα drugs, at 0.79 after one year and 0.59 after three. Disregarding the very small population of patients on infliximab, etanercept was consistently the worst-performing in terms of treatment withdrawal; with a one year survival rate of 0.70, dropping to 0.40 at three years (Table 33). Etanercept was also found to be a significant predictor of discontinuation of therapy due to loss of efficacy. Other significant predictors of treatment withdrawal were female gender, smoking status, and a higher baseline DLQI.

Table 32 Survival of first biologic in the DERMBIO registry

Biologic	Drug survival		
	1 year	2 years	5 years
Adalimumab (n=567)	0.77	0.67	0.48
Etanercept (n=364)	0.70	0.53	0.30
Infliximab (n=176)	0.75	0.62	0.43
Ustekinumab (n=170)	0.85	0.78	0.65

Table 33 Survival of first biologic in the BADBIR registry

Biologic	Drug survival		
	1 year	2 years	3 years
Adalimumab (n=1879)	0.79	0.67	0.59
Etanercept (n=1098)	0.70	0.51	0.40
Infliximab (n=96)	0.65	0.50	0.35

Ustekinumab (n=450)	0.89	0.82	0.75

4.7 Overview of RCT results

Despite differences in inclusion criteria, the relative lack of younger children in the in the adalimumab and etanercept trials meant that the median age of children across the three trials did not differ greatly. Similarly, measures of disease duration and the component measures of severity did not appear to differ markedly between the three trials. Few participants in any trial had prior experience of biologic treatment.

The biologics and their respective comparators in relevant RCTs in children and young people are summarised in Table 34.

Table 34 summary of biologics and their comparators based on RCTs

Treatment	Class of therapy	Dosage	Comparator
Adalimumab (ADA)	Anti TNF-α	• Standard (0.8mg/kg) • Half-standard (0.4mg/kg)	Methotrexate
Etanercept (ETA)	Anti TNF-α	• Standard (0.8mg/kg)	Placebo
Ustekinumab (UST)	Anti IL-12/IL-23	• Standard (0.75mg/kg) • Half-standard (0.375mg/kg)	Placebo

However, there were no head-to-head comparative data available for the three biologics. In addition, while the etanercept and ustekinumab trials had a placebo as a common comparator, the adalimumab trial used methotrexate as a comparator.

Table 35 shows the relative effects for all three biologics from the three RCTs. However, an implicit comparison is not useful for the purposes of the decision analytic modelling required for the economic evaluation. Section 5 therefore describes a formal evidence synthesis to inform the relative efficacy of these interventions.

Table 35 Relative risks of PASI outcomes for biologic trials in children

Trial	Relative risk and 95% CI		
	PASI 50	**PASI 75**	**PASI 90**
Adalimumab vs. Methotrexate (M04-717); 16 weeks			
Standard dosage (0.8mg/kg)	[redacted]	1.79 (1.04 to 3.06)*	1.34 (0.61 to 2.95)
Half-standard dosage (0.4mg/kg)	[redacted]	1.34 (0.75 to 2.42*	1.42 (0.65 to 3.08)
Etanercept vs. placebo (20030211); 12 weeks			
Standard dosage (0.8mg/kg)	3.26 (2.26 to 4.71)	4.95 (2.84 to 8.65)*	4.10 (1.88 to 8.95)
Ustekinumab vs. placebo (CADMUS); 12 weeks			
Standard dosage (0.75mg/kg)	2.99 (1.79 to 4.97)	7.5 (2.9 to 19.1)	11.0 (2.8 to 43.5)
Half-standard dosage (0.375mg/kg)	2.72 (1.62 to 4.48)	7.3 (2.8 to 18.6)	10.0 (2.5 to 39.8)

*stated as primary outcome

5 Evidence synthesis to inform the relative efficacy of the interventions

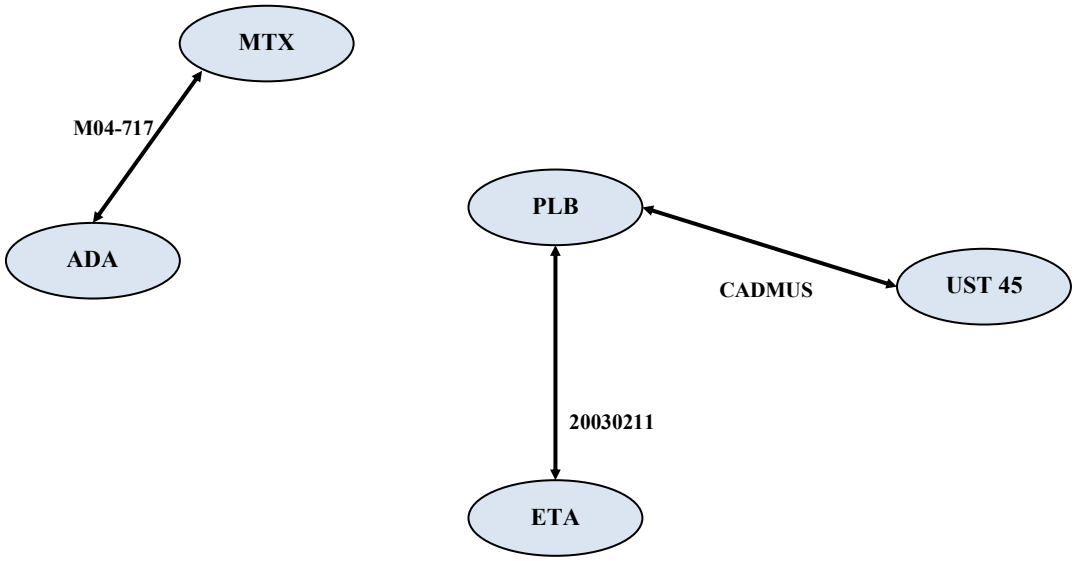
5.1 Overview

RCTs of the effectiveness of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people have been discussed and summarised in Section 4. The efficacy endpoint consistently reported across the trials was PASI response rates, which is the key efficacy parameter used in the economic analysis. In order to determine the relative efficacy of the interventions, it would be ideal to have the results from good quality adequately powered RCTs comparing the active treatments with one another in the population of children and young people. However, the evidence base presents a number of challenges for informing the relative efficacy of the interventions in this population. Firstly, the interventions of interest have not been directly compared in head-to-head RCTs. Secondly, no common comparator (e.g. placebo) exists across all the RCTs. Thirdly, the age of the populations included in the trials differs across the RCTs and the interventions of interest have marketing authorisation for different age groups. Fourthly, the severity of plaque psoriasis is defined differently in the populations included in the RCTs and the interventions are licensed for different levels of severity in children and young people. These challenges mean that a number of assumptions are required in order to inform the benefits of the active treatments relative to the appropriate comparators and each other.

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. The statistical synthesis method of network meta-analysis (NMA) enables the comparison of multiple treatment options using both direct comparisons of interventions from RCTs and indirect comparisons across trials based on a common comparator. [81, 82] As suggested by the term, NMA needs a 'network of evidence' to be established between all of the interventions of interest. However, with neither direct comparisons nor a common comparator in the evidence base for children and young people from which to derive indirect comparisons of comparator treatments, the evidence base is structured as a 'disconnected network').

In the following sections we build on the challenges listed above by firstly exploring the treatment efficacy by age subgroup and by performing a naive indirect treatment comparison of adalimumab and etanercept, highlighting the limitations of such analysis. Furthermore, a framework of analysis is described that uses different levels of evidence from the adult population to specifically address the issue of having a disconnected network structure.

Figure 3 Network of evidence for children and young people



ADA=adalimumab 0.8mg/kg, max 40 mg/week; MTX=methotrexate 0.1-0.4mg/kg/week; ETA=etanercept 0.8mg/kg, max 50mg/week; UST 45 =ustekinumab 0.75mg/kg or 45mg/week; PLB=placebo. Trial names are stated where trial evidence informs the network treatment link.

5.2 Efficacy differences by age subgroup

Adalimumab, etanercept and ustekinumab have marketing authorisation for different age groups in the population of children and young people (≥ 4 years for adalimumab, ≥ 6 years for etanercept, and ≥ 12 years for ustekinumab). This is the result of variation in the age of the patient populations included in the RCTs for these interventions. Furthemore, the trial population for etanercept also includes patients younger than the licensed age group (i.e. the inclusion criteria for the etanercept trial is children and adolescents aged 4-17 years old and 9 children were included in the trial who were younger than the subsequent licensed age group of 6 years old and over). In order to establish the relative efficacy of the interventions it is necessary to either i) assume that the PASI response rates for the treatments are independent of age within the full population of children and young people; or ii) consider outcomes in a subgroup population by age.

Section 4 presents the PASI response rates for each study by age subgroup. On inspection of the PASI response rates, there does not appear to be a pattern across the efficacy outcomes for the different age subgroups within the same study which could explain any differences in efficacy as a result of age. This would seem to suggest that the PASI response rates for the study as a whole are reflective of the outcomes expected in a particular subpopulation by age. This was examined further by using standard parametric statistical tests to assess equality of proportions (i.e. probability of PASI 50/75/90 response rates) across different age subgroups within each study. Within each study, there were no statistically

significant differences identified across the age subgroups for each of the PASI response rates of 50, 75 or 90 (see Table 36). Therefore, in order to compare the relative efficacy of the interventions, it is assumed that the PASI response rates for the treatments are independent of age within the full population of children and young people and that the studies are comparable for this population.

Table 36 Hypothesis testing results of age subgroup PASI response by study and by treatment arm

Study: M04-717	**All**	**Age subgroups**					**Hypothesis test of equality of proportions, p-value**
		4-6 years	**> 6-9 years**	**> 9-12 years**	**>12-15 years**	**> 15 years**	
Adalimumab	**n=38**	**n=0**	**n=7**	**n=8**	**n=13**	**n=10**	
PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.72**
PASI 75	57.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.84**
PASI 90	28.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.47**
Methotrexate	**n=37**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**------**
PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.91**
PASI 75	32.4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.44**
PASI 90	21.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.77**
Study: CADMUS	All	**Age subgroups**					**Hypothesis test of equality of proportions, p-value**
		<= 15 years		**> 15 years**			
Placebo	**n=37**	[redacted]		[redacted]			
PASI 50	[redacted]	N/A		N/A			N/A
PASI 75	[redacted]	[redacted]		[redacted]			**p = 0.90**
PASI 90	[redacted]	N/A		N/A			N/A
Ustekinumab	**n=36**	[redacted]		[redacted]			**------**
PASI 50	[redacted]	N/A		N/A			N/A
PASI 75	[redacted]	[redacted]		[redacted]			**p = 0.60**
PASI 90	[redacted]	N/A		N/A			N/A
Study: 20030211	**All**	**Age subgroups**					**Hypothesis test of equality of proportions, p-value**
		4-11 years		**> 12-17 years**			
Placebo	**n=105**	**n=38**		**n=67**			
PASI 50	22.9%	21.1%		23.9%			**p = 0.93**
PASI 75	11.4%	10.5%		11.9%			**p = 1.00**
PASI 90	6.7%	N/A		N/A			N/A
Etanercept	**n=106**	**n=38**		**n=68**			**------**
PASI 50	74.5%	76.3%		73.5%			**p = 0.93**
PASI 75	56.6%	57.9%		55.9%			**p = 1.00**
PASI 90	27.4%	N/A		N/A			N/A

Adalimumab 0.8mg/kg, max 40 mg/week; Methotrexate 0.1-0.4mg/kg/week; Etanercept 0.8mg/kg, max 50mg/week; Ustekinumab 0.75mg/kg or 45mg/week. N/A= not available

5.3 Indirect treatment comparison

Figure 3 shows that there is no common comparator arm between the adalimumab trial (M04-717) and the trials of etanercept (study 20030211) and ustekinumab (CADMUS), where the former trial is compared against methotrexate (MTX) and the latter trials against placebo. Therefore, it is not possible to establish an indirect comparison between adalimumab and etanercept or ustekinumab without drawing on evidence from other sources (e.g. evidence on the relative efficacy of the interventions in adults) or by creating a common comparator (e.g. assuming that MTX and placebo response rates are exchangeable between the trials). In this section, attention is focused on the indirect comparison that can be established between etanercept and ustekinumab.

An indirect treatment comparison of PASI response rates at 12 weeks was performed between the licensed dose of etanercept (0.8mg/kg up to a maximum dose of 50mg) and ustekinumab (standard dose) using placebo as a common comparator. A Bayesian indirect treatment comparison was undertaken using a probit model for ordered multinomial outcomes of PASI response rates (using a fixed-effect model with multinomial likelihood and a probit link, see appendix 12.8. Table 37 presents the absolute probability of PASI 50, 75 and 90 for etanercept and ustekinumab, while Table 38 presents the relative treatment effect expressed as a relative risk, with 95% Bayesian credible intervals (CrI).

The results demonstrate that ustekinumab appears more effective than etanercept in this population. The PASI 75 absolute probability of response for ustekinumab at 12 weeks is estimated to be 78% (95% CrI 63% to 90%), while for etanercept it is estimated to be 57% (95% CrI 44% to 69%). The 95% credibility intervals are wide and overlap, which reflects the small sample size and limited number of data points used in this analysis. The pooled relative risk (RR) presented in Table 38 for ustekinumab compared to etanercept is 1.41, but is not statistically significant with 95% CrI including 1. The indirect comparison results are in line with the direct evidence from the clinical trials.

Table 37 Absolute probabilities of PASI 50/75/90 results of the indirect treatment comparison for etanercept and ustekinumab

	PASI 50	PASI 75	PASI 90
	Mean (95% CrI)	Mean (95% CrI)	Mean (95% CrI)
Placebo	0.265 (0.190 to 0.346)	0.131 (0.082 to 0.191)	0.042 (0.021 to 0.073)
Etanercept	0.744 (0.631 to 0.841)	0.565 (0.437 to 0.688)	0.330 (0.218 to 0.454)
Ustekinumab SD	0.896 (0.797 to 0.962)	0.781 (0.632 to 0.898)	0.571 (0.395 to 0.742)

SD= Standard dose

Table 38 Relative effect estimates (as relative risks, RR, mean and 95% CrI) for each treatment combination for PASI 75 of the direct trial comparisons (upper diagonal) and of the indirect treatment comparison for etanercept and ustekinumab (lower diagonal)

PLB	**4.95 (2.84 to 8.65)**	**7.50 (2.90 to 19.10)**
4.48 (2.99 to 6.64)	**ETA**	--- ---
6.27 (3.80 to 10.00)	1.41 (0.99 to 1.93)	**UST SD**

PLB = Placebo; ETA = Etanercept 0.8mg/kg, max 50mg/week; USK SD = Ustekinumab 0.75mg/kg or 45mg/week; Lower diagonal: pooled RRs from NMA model. RRs above one favour the row agent; Upper diagonal: RRs from direct comparison. RRs above one favour the column agent; Significant differences in the relative effects between a pair of agents are given in bold.

The company submission for ustekinumab presented a similar indirect treatment comparison for ustekinumab vs. etanercept. The company's analysis produced results for the full population and for a subgroup aged 12-17 years. The results of the company's full population NMA are broadly similar to the results from the AG analysis, e.g. ustekinumab PASI 75 response was estimated to be 79.8% compared to 78.1% in Table 37.

It is important to note that this analysis is limited for a number of reasons:

- It only draws conclusions regarding short-term use of ustekinumab and etanercept in the population of children and young people from the corresponding trials;
- The placebo arm in study 20030211 and CADMUS is assumed to be exchangeable between the trials;
- Inclusion criteria for age were different between the trials;

- There is uncertainty in both the within-trial and between-trial treatment effect estimates due to small sample sizes in the trials;
- There are differences between the trials in terms of baseline characteristics and trial design – these differences have been explored separately in Section 4;
- The indirect treatment comparison does not provide sufficient information to inform the economic analysis since the intervention of adalimumab has been excluded from the analysis due to a lack of common comparator.

As a consequence of the above limitations, in particular, the exclusion of the adalimumab trial evidence (M04-717 study), the results in Table 37 could not be used to assess the relative cost-effectiveness of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people.

5.4 Framework of analysis for informing the relative efficacy of the interventions

Due to the lack of a common comparator arm between the adalimumab trial (M04-717) and the ustekinumab (CADMUS) and etanercept (study 20030211) trials, an analysis plan was developed which entailed exploring the possibility of using PASI response data from adults with moderate to severe plaque psoriasis to fill the evidence gap in the population of children and young people. The use of data from the adult population was supported by our clinical advisor who did not see any reason that precluded the use of the relative effectiveness of the interventions in adults to infer relative effectiveness in children and young people, especially in the absence of evidence in the latter population.

A framework of analysis was thus developed for the NMA approach which allowed all available and relevant evidence to be included was pursued. The framework explored two separate networks which differed according to the extent of evidence utilised from the adult trials:

- The network of trials in children and young people was connected by bringing the *minimum* amount of evidence required from the adult population in order to link the adalimumab trial with the other trials in the disconnected network of Figure 3;
- The network of trials in children and young people was connected by bringing together *all relevant evidence* on the efficacy of all the interventions in adults.

This approach allows treatment specific estimates to be modelled in each population by drawing strength from the network of evidence available. The use of a NMA in preference to pairwise meta-analyses enables the inclusion of all relevant evidence, allowing for precise estimates of treatment effects to be calculated. In addition, the results from the NMA will feed directly into the economic

model to provide the relevant cost-effectiveness of adalimumab, etanercept and ustekinumab against relevant comparators and each other. This approach has been used in previous NICE technology appraisals for the treatment of plaque psoriasis in adults (TA 103, 134, 146, 180, 350, and 368).[83-89]

In each of the NICE technology appraisals in adults the evidence network was updated with new studies reported since the previous appraisal. Therefore we took the most recent single technology appraisals in adults (TA 368 and TA 350) as the starting point for developing a network of studies which could potentially connect the adalimumab trial in children and young people to the other interventions. The Evidence Review Groups (ERGs) for these appraisals generally rated the systematic reviews underpinning the identification of trials for inclusion in the NMA as appropriate, and the evidence networks were subsequently used to inform NICE recommendations in these appraisals. Therefore, it was assumed that the vast majority of relevant evidence for the interventions in adults has been captured in the most recent appraisals in 2015. Relevant adult trials were identified based on the indirect comparison and/or multiple treatment comparisons reported within these appraisals. Lists of excluded trials and reasons for exclusion were also reviewed and relevant trials identified. To supplement this review, the results of a recently published systematic review and NMA, which adjusted for cross-trial differences in the comparative efficacy of biologic treatments for moderate to severe psoriasis in adults, was also examined to cross-check that the majority of relevant studies had been identified in the previous appraisals [90]. Furthermore, we also considered studies reported in the original multiple technology appraisal in adults (TA 103) which included interventions such as methotrexate and cyclosporine. The key inclusion and exclusion criteria used to identify relevant trials for the NMA are shown in Table 39. A list of excluded trials (n=18) and reasons for exclusion can be found in appendix 12.9. Table 40 presents a summary of the trials in adults and the comparator agents in each trial, which was used to inform the NMA.

Table 39 Key inclusion and exclusion criteria for adult studies

Inclusion criteria	Exclusion criteria
• RCT adult studies that considered one or more of the three treatments of interest in recommended dosages: adalimumab, etanercept and ustekinumab; • RCT adult studies that considered the systemic treatment methotrexate - a key comparator in the M04-717 study; • RCT adult studies that directly or indirectly inform comparisons between agents or comparator of interest (adalimumab, etanercept, ustekinumab and methotrexate) or of these against placebo/best supportive care	• RCT adult studies and/or arms that considered irrelevant doses or comparators; • RCT adult studies that reported PASI outcome data at irrelevant time points.

Table 40 Summary of trials in adults selected to inform the NMA

No. trials	Trial reference	Adalimumab (dose)	Etanercept (dose)	Ustekinumab (dose)	Methotrexate	Apremilast	Cyclosporine	Fumaric Acid	Infliximab	Placebo
5	Saurat 2008 [91] (CHAMPION)	✓ (40)			✓					✓
	Gordon 2006 [92]	✓ (40)								✓
	Menter 2008 [93] (REVEAL)	✓ (40)								✓
	Asahina 2010 [94]	✓ (40)								✓
	Bissonnette 2013 [95]	✓ (40)								✓
6	Gottlieb 2003 [96]		✓ (50)							✓
	Leonardi 2003 [97]		✓ (50)							✓
	Elewski 2004 [98]		✓ (50)							✓
	Papp 2005 [99]		✓ (50)							✓
	Van de Kerkhof 2008 [100]		✓ (50)							✓
	PSOR-010 [101] (LIBERATE)		✓ (50)			✓				✓
7	Tsai 2011 [102] (PEARL)			✓ (45)						✓
	Zhu 2013 [103] (LOTUS)			✓ (45)						✓
	Krueger 2007 [104]			✓ (45,90)						✓
	Leonardi 2008 [105] (PHOENIX I)			✓ (45,90)						✓
	Papp 2008 [106] (PHOENIX II)			✓ (45,90)						✓
	Igarashi 2012 [107]			✓ (45,90)						✓

No. trials	Trial reference	Adalimumab (dose)	Etanercept (dose)	Ustekinumab (dose)	Methotrexate	Apremilast	Cyclosporine	Fumaric Acid	Infliximab	Placebo
	Griffiths 2010 [108] (ACCEPT)			✓ (45,90)						
4	Heydendael 2003 [109]				✓		✓			
	Flytstrom 2008 [110]				✓		✓			
	Barker 2011 [111] (RESTORE I)				✓				✓	
	Fallah 2011 [112]				✓			✓		
3	Papp 2012 [113]					✓				✓
	Papp 2015 [114] (ESTEEM I)					✓				✓
	Paul 2015 [115] (ESTEEM II)					✓				✓
2	Guenther 1991 [116]						✓			✓
	Meffert 1997 [117]						✓			✓
1	Altmeyer 1994 [118]							✓		✓
6	Chaudhari 2001 [119]								✓	✓
	Gottlieb 2004 [120] (SPIRIT)								✓	✓
	Reich 2005 [121] (EXPRESS I)								✓	✓
	Menter 2007 [122] (EXPRESS II)								✓	✓
	Torii 2010 [123]								✓	✓
	Yang 2012 [124]								✓	✓

Thirty-four trials in adults with moderate to severe plaque psoriasis were found to be relevant for the NMA; twenty-nine of these considered a placebo arm and six were three-arm trials. As described in the ERG reports for the previous technology appraisals, selected studies were mostly comparable in

terms of their inclusion criteria regarding prior and concomitant medication use. The majority of studies included patients who had failed or had an insufficient response to prior topical therapy and conventional systemic agents such as cyclosporine or methotrexate. Some studies included only biologic-naïve individuals, whereas others allowed prior biologic therapy use. Almost all of the studies did not allow concomitant treatment with systemic agents or phototherapy. A few studies did not mention their criteria regarding concomitant medication use.

The full set of interventions and comparators include adalimumab, etanercept, ustekinumab 45mg, ustekinumab 90mg, apremilast, methotrexate, cyclosporine, fumaric acid, infliximab and placebo. PASI response rates for PASI 50, 75 and 90 from the selected trials were identified and extracted, together with sample size and key baseline patient characteristics by treatment arm. Table 41 presents a summary of the data extracted together with the corresponding data from the three trials in children and young people.

Table 41 Summary of PASI response data used in the NMA and key baseline patient characteristics by treatment arm.

Study reference	Treatment / weekly dose	Population	Time point (weeks)	N	Age (mean years)	Male (%)	PASI 50 (n)	PASI 50 (%)	PASI 75 (n)	PASI 75 (%)	PASI 90 (n)	PASI 90 (%)
20030211 [46, 48-70]	Placebo	Children and young people	12	105	---	50	24	22.9	12	11.4	7	6.7
	Etanercept 0.8mg/kg (max 50mg)		12	106	---	52	79	74.5	60	56.6	29	27.4
CADMUS 2015 [71-74]	Placebo	Children and young people	12	37	16	54	11	29.7	4	10.8	2	5.4
	Ustekinumab SD (max 45mg)		12	36	15	44	32	88.9	29	80.6	22	61.1
M04-717 [36-45]	Adalimumab 0.8mg/kg (max 40mg)	Children and young people	16	37	13	45	30	78.9	22	57.9	11	28.9
	Methotrexate		16	38	13	30	20	54.1	12	32.4	8	21.6
Guenther 1991 [116]	Placebo	Adults	10	11	---	---	1	9.0	---	---	---	---
	Cyclosporine		10	12	---	---	12	100.0	---	---	---	---
Altmeyer 1994 [118]	Placebo	Adults	16	51	---	---	---	---	1	2.0	---	---
	Fumaric acid		16	49	---	---	---	---	12	24.5	---	---
Meffert 1997 [117]	Placebo	Adults	10	43	---	---	---	---	2	4.7	---	---
	Cyclosporine		10	41	---	---	---	---	4	9.8	---	---
Chaudhari 2001 [119]	Placebo	Adults	10	11	45	73	---	---	2	18.2	---	---
	Infliximab 5mg/kg		10	11	51	64	---	---	9	81.8	---	---

Study reference	Treatment / weekly dose	Population	Time point (weeks)	N	Age (mean years)	Male (%)	PASI 50 (n)	PASI 50 (%)	PASI 75 (n)	PASI 75 (%)	PASI 90 (n)	PASI 90 (%)
Gottlieb 2003 [96]	Placebo	Adults	12	55	47	67	6	10.9	1	1.8	0	0.0
	Etanercept 50mg		12	57	48	58	40	70.2	17	29.8	6	10.5
Heydendael 2003 [109]	Methotrexate	Adults	16	43	42	65	---	---	26	60.5	---	---
	Cyclosporine		16	42	38	69	---	---	30	71.4	---	---
Leonardi 2003 [97]	Placebo	Adults	12	166	46	63	24	14.5	6	3.6	1	0.6
	Etanercept 50mg		12	162	45	67	94	58.0	55	34.0	19	11.7
Elewski 2004 [98]	Placebo	Adults	12	193	45	64	18	9.3	6	3.1	1	0.5
	Etanercept 50mg		12	196	45	65	126	64.3	67	34.2	2	1.0
Gottlieb 2004 [120] (SPIRIT)	Placebo	Adults	10	51	45	61	11	21.6	3	5.9	1	2.0
	Infliximab 5mg/kg		10	99	44	74	96	97.0	87	87.9	57	57.6
Papp 2005 [99]	Placebo	Adults	12	193	44	64	18	9.3	6	3.1	1	0.5
	Etanercept 50mg		12	196	46	65	126	64.3	67	34.2	21	10.7
Reich 2005 [121] (EXPRESS)	Placebo	Adults	10	77	44	79	6	7.8	2	2.6	1	1.3
	Infliximab 5mg/kg		10	301	43	69	274	91.0	242	80.4	172	57.1
Gordon 2006 [92]	Placebo	Adults	12	52	43	65	7	13.5	2	3.8	0	0.0
	Adalimumab 40mg		12	45	46	71	34	75.6	24	53.3	11	24.4
Krueger 2007 [104]	Placebo	Adults	12	64	44	72	7	10.9	1	1.6	1	1.6
	Ustekinumab 45mg		12	64	45	61	59	92.2	43	67.2	28	43.8

Study reference	Treatment / weekly dose	Population	Time point (weeks)	N	Age (mean years)	Male (%)	PASI 50 (n)	PASI 50 (%)	PASI 75 (n)	PASI 75 (%)	PASI 90 (n)	PASI 90 (%)
	Ustekinumab 90mg		12	64	44	81	59	92.2	52	81.3	33	51.6
Menter 2007 [122] (EXPRESS II)	Placebo	Adults	10	208	44	69	---	---	4	1.9	1	0.5
	Infliximab 5mg/kg		10	314	45	65	---	---	237	75.5	142	45.2
Flytstrom 2008 [110]	Methotrexate	Adults	12	37	48	76	24	64.9	9	24.3	4	10.8
	Cyclosporine		12	31	45	87	27	87.1	18	48.6	9	24.3
Leonardi 2008 [105] (PHOENIX I)	Placebo	Adults	12	255	45	72	26	10.2	8	3.1	5	2.0
	Ustekinumab 45mg		12	255	46	69	213	83.5	171	67.1	106	41.6
	Ustekinumab 90mg		12	256	45	68	220	85.9	170	66.4	94	36.7
Menter 2008 [93] (REVEAL)	Placebo	Adults	16	398	45	65	60	15.1	28	7.0	8	2.0
	Adalimumab 40mg		16	614	44	67	667	81.9	578	71.0	366	45.0
Papp 2008 [106] (PHOENIX II)	Placebo	Adults	12	410	47	69	41	10.0	15	3.7	3	0.7
	Ustekinumab 45mg		12	409	45	69	342	83.6	273	66.7	173	42.3
	Ustekinumab 90mg		12	411	47	67	367	89.3	311	75.7	209	50.9
Saurat 2008 [91] (CHAMPION)	Placebo	Adults	16	53	41	66	16	30.2	10	18.9	6	11.3
	Adalimumab 40mg		16	108	43	65	95	88.0	86	79.6	55	50.9
	Methotrexate		16	110	42	66	68	61.8	39	35.5	15	13.6
Van de Kerkhof 2008 [100]	Placebo	Adults	12	46	44	54	4	8.7	1	2.2	1	2.2
	Etanercept 50mg		12	96	46	62	66	68.8	36	37.5	13	13.5

Study reference	Treatment / weekly dose	Population	Time point (weeks)	N	Age (mean years)	Male (%)	PASI 50 (n)	PASI 50 (%)	PASI 75 (n)	PASI 75 (%)	PASI 90 (n)	PASI 90 (%)
Asahina 2010 [94]	Placebo	Adults	16	46	44	89	9	19.6	2	4.3	0	0.0
	Adalimumab 40mg		16	43	44	83	35	81.4	27	62.8	17	39.5
Griffiths 2010 [108] (ACCEPT)	Ustekinumab 45mg	Adults	12	209	45	64	182	87.1	141	77.5	76	53.9
	Ustekinumab 90mg		12	347	45	67	319	91.9	256	80.3	155	60.5
Torii 2010 [123]	Placebo	Adults	10	19	43	74	2	10.5	0	0.0	0	0.0
	Infliximab 5mg/kg		10	35	47	63	29	82.9	26	68.6	19	54.3
Barker 2011 [111] (RESTORE I)	Methotrexate	Adults	16	215	42	69	130	60.5	90	41.9	41	19.1
	Infliximab 5mg/kg		16	653	44	67	567	86.8	508	77.8	356	54.5
Fallah 2011 [112]	Methotrexate	Adults	12	27	41	59	15	55.6	6	22.2	2	7.4
	Fumaric acid		12	27	43	74	11	40.7	5	18.5	1	3.7
Tsai 2011 [102] (PEARL)	Placebo	Adults	12	60	40	88	8	13.3	3	5.0	1	1.7
	Ustekinumab 45mg		12	61	41	82	51	83.6	41	67.2	30	49.2
Igarashi 2012 [107]	Placebo	Adults	12	31	49	84	4	12.9	2	6.5	1	3.2
	Ustekinumab 45mg		12	64	45	83	53	82.8	38	59.4	21	32.8
	Ustekinumab 90mg		12	62	44	76	52	83.9	42	67.7	27	43.5
Papp 2012 [113]	Placebo	Adults	16	88	44	60	22	25.0	5	5.7	1	1.1
	Apremilast		16	88	44	57	53	60.2	36	40.9	10	11.4
Yang 2012 [124]	Placebo	Adults	10	45	40	78	6	13.2	1	2.2	0	0.0

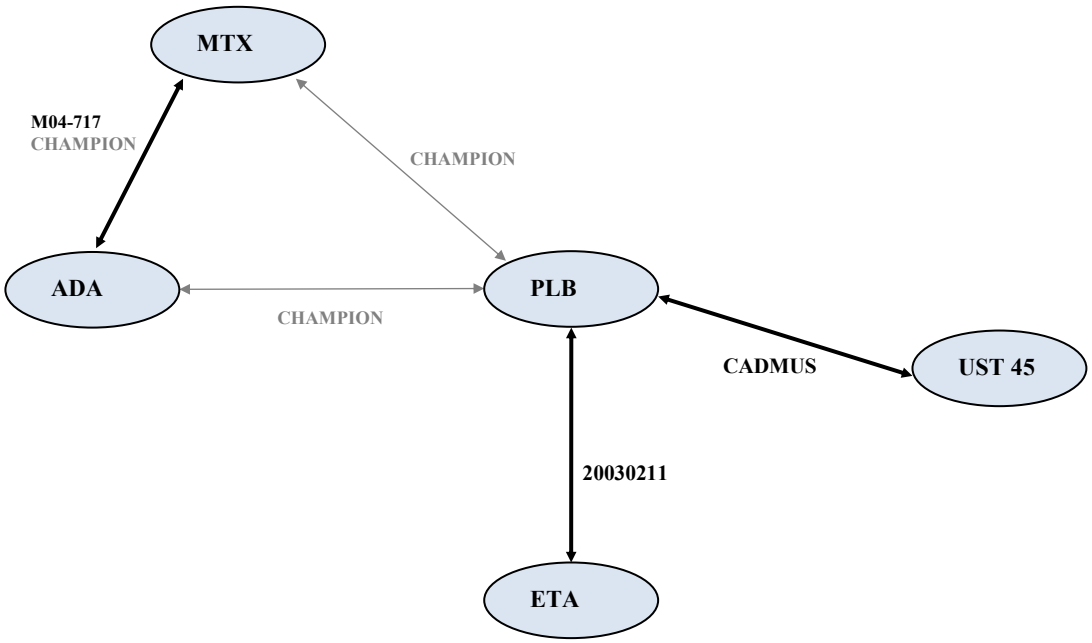
Study reference	Treatment / weekly dose	Population	Time point (weeks)	N	Age (mean years)	Male (%)	PASI 50 (n)	PASI 50 (%)	PASI 75 (n)	PASI 75 (%)	PASI 90 (n)	PASI 90 (%)
	Infliximab 5mg/kg		10	84	39	71	79	94.0	68	81.0	48	57.1
Bissonnette 2013 [95]	Placebo	Adults	16	10	57	60	---	---	2	20.0	---	---
	Adalimumab 40mg		16	20	56	85	---	---	14	70.0	---	---
Zhu 2013 [103] (LOTUS)	Placebo	Adults	12	162	40	78	32	19.8	18	11.1	5	3.1
	Ustekinumab 45mg		12	160	49	84	146	91.3	132	82.5	107	66.9
Papp 2015 [114] (ESTEEM I)	Placebo	Adults	16	282	47	69	48	17.0	15	5.3	1	0.4
	Apremilast		16	562	46	67	330	58.7	186	33.1	55	9.8
Paul 2015 [115] (ESTEEM II)	Placebo	Adults	16	137	46	73	27	19.7	8	5.8	1	0.7
	Apremilast		16	274	45	64	152	55.5	79	28.8	24	8.8
PSOR-010 [101] (LIBERATE)	Placebo	Adults	16	84	---	---	28	33.3	10	11.9	---	---
	Etanercept 50mg		16	83	---	---	69	83.1	40	48.2	---	---
	Apremilast		16	83	---	---	---	---	33	39.8	---	---

Outcome data measured at weeks 10-16 was generally used with preference for data at 12 weeks if outcomes were reported at multiple time points. SD = standard dose

5.4.1 NMA using minimum evidence from the adult population

The disconnected network of evidence in children and young people was connected in the first instance by bringing together the minimum amount of evidence required from the adult population in order to link the adalimumab trial with the other trials (Figure 4). Among the studies presented in **Table 40**, there was only one trial in adults which could directly connect methotrexate with placebo and adalimumab with placebo (CHAMPION [91]). There were a number of trials comparing adalimumab with placebo alone but inclusion of these trials would mean that methotrexate is only connected indirectly through adalimumab and placebo, potentially undermining the evidence from M04-717 on this agent. Therefore, the CHAMPION study represented the best way to connect adalimumab and methotrexate to etanercept and ustekinumab using the least amount of evidence drawn from the adult population.

Figure 4Network of evidence using minimum evidence from the adult population



ADA=adalimumab 0.8mg/kg, max 40 mg/week; MTX=methotrexate 0.1-0.4mg/kg/week; ETA=etanercept 0.8mg/kg, max 50mg/week; UST 45 =ustekinumab 0.75mg/kg or 45mg/week; PLB=placebo. Trial names are stated where trial evidence informs the network treatment link.

In the CHAMPION study, the primary efficacy endpoint was the proportion of individuals achieving PASI 75 at 16 weeks. Adalimumab was found to have significantly greater efficacy (79.6% achieving PASI 75) compared with either methotrexate (35.5%) or placebo (18.9%). PASI outcome data and

key baseline characteristics for the CHAMPION study can be found in Table 41. The average age of patients recruited in CHAMPION was approximately 42 years of age. CHAMPION is a larger trial compared to the trials in children and young people (n=271 vs. n=75 (M04-717)), with approximately 10-20% higher proportion of males.

The PASI 75 response rates for adalimumab and methotrexate in CHAMPION are similar to those reported in study M04-717 in children and young people. An important difference between the CHAMPION study and the trials in children and young people is the observed placebo effect for the primary endpoint of PASI 75. While for study 20030211 and CADMUS the proportion of individuals achieving PASI 75 in the placebo arms was approximately 11%, the proportion observed in placebo-treated patients in the CHAMPTION study was approximately 19%. The authors of the CHAMPION study identified two reasons for this anomalous placebo response: i) placebo response rates are generally greater in European studies; and ii) that the observed placebo response may partly have resulted from the correction of an underlying folate deficiency following folate supplementation, which was mandatory for all study patients.

Given that the CHAMPION study connects the adalimumab trial in children and young people (M04-717) to etanercept and ustekinumab through placebo, it is important to ensure that the differences in placebo response rates do not 'artificially' inflate or deflate the PASI response outcomes for the interventions of interest. Therefore, as well as using a baseline *unconstrained* prediction model, whereby baseline risk (placebo response rates) is predicted using evidence from all studies included in the network (analysis 1a), a baseline *constrained* prediction model was also considered, whereby placebo response rates are predicted based on the placebo-arm trials in children and young people only (i.e. study 20030211 and CADMUS) (analysis 1b). As the number of trials to inform each treatment effect is small, a fixed-effect model was used. The results of this analysis are presented in Section 5.4.3 (Results).

5.4.2 NMA using full evidence from the adult population

The second approach to the NMA involved connecting the evidence from the adalimumab trial in children and young people to the evidence from the other trials (study 20030211 and CADMUS) by drawing strength from the full network of evidence available in adults. The relative efficacy of adalimumab, etanercept and ustekinumab has been evaluated extensively in adults with moderate to severe plaque psoriasis. Given the limited evidence base in children and young people, and the expectation that the difference in response rates between the interventions is predominantly due to the relative efficacy of the biologics rather than age or other patient characteristics, it would seem appropriate to combine the weight of evidence from all relevant trials and comparators, including

those in adults. This wider network of evidence can be used to facilitate an indirect comparison of adalimumab with etanercept and ustekinumab by examining the relationships that exist between the different treatments and study populations and drawing strength from the full network of evidence.

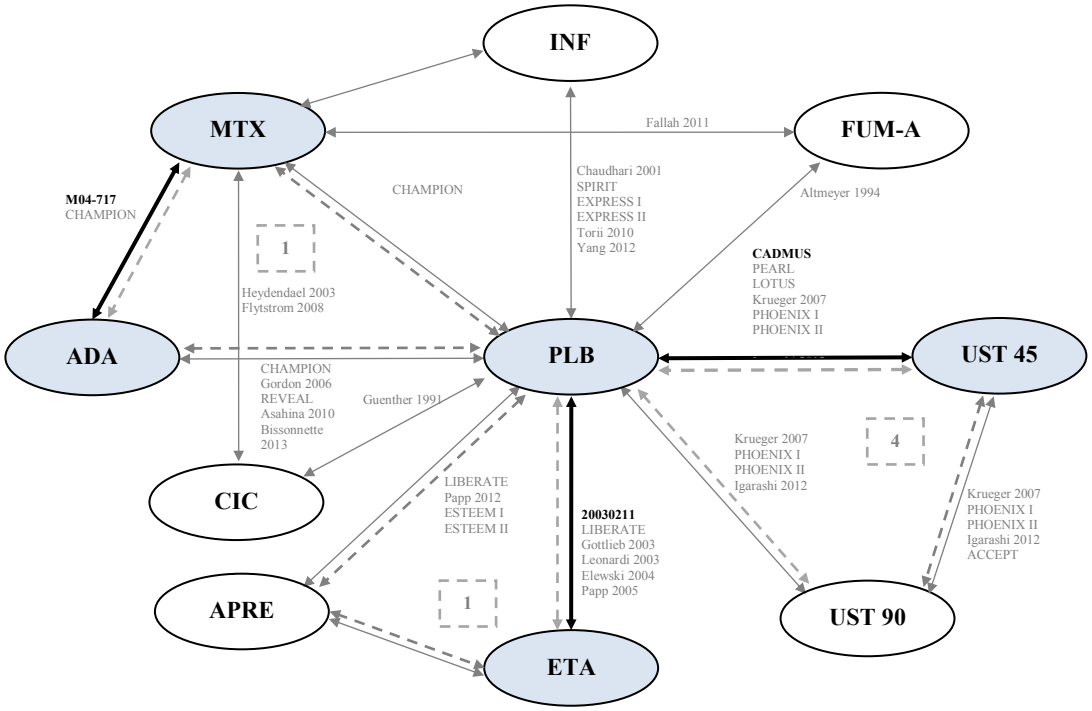
Figure 5 presents the full network of evidence in both populations. This wider network considers 9 active treatments and placebo, which encompass 37 RCTs in total (3 in children and young people and 34 in adults) with 6 of these being three-arm trials. The majority of network links ('head-to-head trial comparisons') are populated by more than one study.

A Bayesian evidence synthesis approach was employed which draws on the relationships that exist between treatments and populations, while also preserving differences that exist across populations by adjusting for age and placebo response rates. NMA meta-regression models on baseline risk (i.e. placebo response) were explored. [90] These models impose a common interaction effect between baseline risk and relative effectiveness that account for variation in reference arm response across trials. NMA meta-regression models that explore variability caused by age effects were also implemented. These models impose an age group interaction effect at the study level (binary variable: 1 if study is from a children or young adult population, 0 otherwise) that attempts to explain the heterogeneity between treatment effects when considering both adult treatment response data and data from children and young people. The age adjusted meta-regression models provided pooled PASI response rates by treatment for both children and young people and adults. A common treatment by age interaction effect was imposed. The common interaction assumption is the least data demanding (i.e. only one extra parameter is needed to be estimated), but it also imposes the strongest assumption as it implies that the same age group effect exists regardless of treatment (excluding placebo).[125] For example, if the age interaction effect (of children and young people vs. adults) is estimated to be positive and of average magnitude 25% on the absolute PASI scale, PASI response rates in children and young people will be approximately 25% higher, on average, relative to adults, irrespective of treatment. Further details on the implemented synthesis models and their assumptions, including WinBUGS code can be found in appendix 12.9.

Fixed- and random-effects analyses were explored for two separate scenarios: (a) meta-regression model with adjustment for baseline risk (i.e. placebo response rates); and (b) meta-regression model with adjustment for baseline risk and age. Irrespective of scenario and according to deviance information criterion (DIC) and total residual deviance statistics, the random-effects approach provided a better fit to the data than the fixed-effect counterpart. Therefore, only results from the random-effects model are presented and discussed herein. Results from the fixed-effect model can be found in appendix 12.10.

Table 42 provides a summary of the models implemented together with the key modelling assumptions. As no evidence was found to support the existence of a class effect, all models considered treatments to be independent of each other. Models in analyses 2a and 2b assume treatments are independent of each other, but treatment effects are adjusted with the trial-specific baseline effects assuming a common interaction term. In addition, models in analysis 2b adjust for trial-specific age effects, also assuming a common interaction term. This age adjustment enables the estimation of treatment effects separately by age populations (adults and children and young people). All implemented synthesis models assumed fixed effects on PASI response cut-off points.

Figure 5 Wider network of evidence in children and young people and adult populations



ADA=adalimumab 0.8mg/kg, max 40 mg/week; MTX=methotrexate 0.1-0.4mg/kg/week; ETA=etanercept 0.8mg/kg, max 50mg/week; UST 45=ustekinumab 0.75mg/kg or 45mg/week; INF= infliximab 5mg/kg; FUM-A=fumaric acid; CIC=cyclosporine; APRE=apremilast; UST 90=ustekinumab 90mg/week; PLB=placebo. Trial names are stated where trial evidence informs the network treatment link. Discontinued lines indicate where 3-arm trials inform the evidence network, with the number of 3-arm trials stated in a discontinued line box.

Table 42 Summary of models implemented and key modelling assumptions.

Analysis	Study	Meta-regression	Baseline prediction
1a	FE	No adjustment	Unconstrained
1b	FE	No adjustment	Constrained to studies of children and young people

2	RE	No adjustment	Unconstrained
2a	RE	Common interaction term for baseline effect	Unconstrained; baseline adjusted
2b	RE	Common interaction term for baseline effect and for age effect	Unconstrained; baseline adjusted

5.4.3 Results

5.4.3.1 Analysis 1 – Results using minimum evidence from the adult population

Table 43 summarises the results of the NMA in terms of absolute PASI response rates for the unconstrained (no explicit adjustment for differences in placebo response rates across the trials) and constrained (placebo response rates are predicted based on the placebo-arm trials in children and young people only) models. The results of both sets of analyses show that all active treatments are more effective than placebo. In terms of mean response rates, ustekinumab is estimated to have the highest probability of achieving PASI 50 (90%, 95% CrI: 81% to 96%), PASI 75 (79%, 95% CrI: 64% to 90%) and PASI 90 (57%, 95% CrI: 39% to 74%) compared to any of the other treatments, suggesting that it is the most effective intervention. This is followed by adalimumab, etanercept and methotrexate in both sets of analyses, i.e. the ranking of treatments based on mean response rates is unchanged by the different models.

The unconstrained baseline model (analysis 1a), however, predicts a placebo effect for PASI 75 of 20.3% (95% CrI: 14% to 27%) compared to 13.1% (95% CrI: 8% to 19%) for the constrained baseline model. This difference is driven by the CHAMPION study which had a substantially higher placebo response rate of approximately 19% for PASI 75 compared to the placebo response rates observed in the trials of children and young people (approximately 11% in study 20030211 and CADMUS). The constrained baseline model (analysis 1b) adjusts the baseline predictions to consider only placebo effect evidence from trials in the younger population. In this analysis, the mean PASI 75 response rate for placebo is reduced and closer to the observed response in the children and young people trials.

Table 43 NMA results of absolute PASI response for analysis 1a and 1b: probability of achieving PASI 50/75/90

Analysis	1a				1b			
	PASI 50 Mean (95% CrI)	**PASI 75** Mean (95% CrI)	**PASI 90** Mean (95% CrI)	r	**PASI 50** Mean (95% CrI)	**PASI 75** Mean (95% CrI)	**PASI 90** Mean (95% CrI)	r

Placebo	0.371 (0.29 to 0.46)	0.203 (0.14 to 0.27)	0.071 (0.04 to 0.11)	5	0.267 (0.19 to 0.35)	0.131 (0.08 to 0.19)	0.039 (0.02 to 0.07)	5
Etanercept	0.830 (0.73 to 0.91)	0.676 (0.54 to 0.79)	0.431 (0.30 to 0.57)	3	0.747 (0.63 to 0.84)	0.566 (0.43 to 0.69)	0.321 (0.21 to 0.44)	3
Ustekinumab	0.941 (0.87 to 0.99)	0.859 (0.73 to 0.95)	0.677 (0.49 to 0.85)	1	0.901 (0.81 to 0.96)	0.787 (0.64 to 0.90)	0.569 (0.39 to 0.74)	1
Adalimumab	0.832 (0.74 to 0.91)	0.678 (0.56 to 0.79)	0.433 (0.31 to 0.56)	2	0.746 (0.60 to 0.87)	0.567 (0.40 to 0.73)	0.324 (0.19 to 0.49)	2
Methotrexate	0.432 (0.33 to 0.54)	0.251 (0.17 to 0.34)	0.096 (0.06 to 0.15)	4	0.323 (0.20 to 0.47)	0.170 (0.09 to 0.28)	0.057 (0.02 to 0.11)	4
Residual deviance	46.6*	39.7	57.6		46.6*	39.7	57.6	
DIC		158.60				158.60		

r-– ranking of treatments according to point estimates; FE-fixed effect; *Compared with 27 data points. DIC and total residual deviance are marginally lower in analysis 1b than in 1a, implying a better fitting model.

As shown by the credible intervals around the mean response rates, which are wide and overlap, there is uncertainty around these response rates. This is also shown in terms of the relative risks of each treatment compared with placebo and their credibility intervals for the best fitting model 1b (Table 44).

Table 44 Relative effect estimates (as relative risks, RR, mean and 95% CrI) for each treatment combination for PASI 75 of the direct trial comparisons (upper diagonal) and of the NMA results of analysis 1b (lower diagonal)

PLB	**4.95 (2.84 to 8.65)**	**7.50 (2.90 to 19.10)**	--- ---	--- ---
4.37 (3.02 to 6.56)	**ETA**	--- ---	--- ---	--- ---
6.10 (3.84 to 10.01)	**1.39 (1.00 to 1.97)**	**UST 45**	--- ---	--- ---
4.36 (3.10 to 6.31)	1.00 (0.71 to 1.39)	0.72 (0.48 to 1.01)	**ADA**	**0.49 (0.38 to 0.59)**
1.28 (0.78 to 1.98)	**0.29 (0.16 to 0.50)**	**0.21 (0.11 to 0.38)**	**0.29 (0.19 to 0.43)**	**MTX**

PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate; Lower diagonal: pooled RRs from NMA model. RRs above one favour the row agent; Upper diagonal: RRs from direct comparison (pooled using fixed-effects when multiple studies exist). RRs above one favour the column agent; Significant differences in the relative effects between a pair of agents are given in bold.

5.4.3.2 Analysis 2 – Results using all relevant evidence from the adult population

Table 45 summarises the absolute PASI response rates from the NMA which uses the full network of evidence in both populations for the unadjusted random-effects model (analysis 2). Relative treatment effects for analysis 2 and for PASI 75 response are presented in Table 46. The random-effects approach outperformed the fixed-effect one in terms of model fit, suggesting that accounting for between-study heterogeneity is an important factor ($\tau^2 = 0.02$).

The results of this analysis suggest that ustekinumab is the most effective intervention with the highest mean probability of PASI response (PASI 75: 73%, 95% CrI: 67% to 79%), followed by adalimumab (PASI 75: 63%, 95% CrI: 55% to 70%), etanercept (PASI 75: 40%, 95% CrI: 34% to 47%) and methotrexate (PASI 75: 34%, 95% CrI: 25% to 42%). Ustekinumab is statistically significantly more effective than any other agent based on relative effect estimates for PASI 75 (vs. etanercept, RR 1.78, 95% CrI 1.50 to 2.12; vs. adalimumab, RR 1.15, 95% CrI 1.01 to 1.35) and adalimumab is statistically significantly more effective than etanercept (RR 1.54, 95% CrI 1.25 to 1.88). The estimated pooled placebo absolute effect is in line with that observed, on average, across all studies in all populations.

These unadjusted results, however, do not consider an explicit adjustment for differences in placebo response rates across trials or differences across the populations (i.e. children and young people compared to adults). In the following sections, the results from the adjusted analyses are presented.

Table 45 NMA results of absolute PASI response for analysis 2: probability of achieving PASI 50/75/90

Analysis	2			
	PASI 50 Mean (95% CrI)	**PASI 75** Mean (95% CrI)	**PASI 90** Mean (95% CrI)	r
Placebo	0.141 (0.12 to 0.16)	0.049 (0.04 to 0.06)	0.010 (0.01 to 0.01)	5
Etanercept	0.633 (0.57 to 0.70)	0.404 (0.34 to 0.47)	0.172 (0.13 to 0.22)	3
Ustekinumab	0.885 (0.85 to 0.92)	0.732 (0.67 to 0.79)	0.466 (0.40 to 0.53)	1
Adalimumab	0.818 (0.76 to 0.87)	0.629 (0.55 to 0.70)	0.354 (0.28 to 0.43)	2
Methotrexate	0.562 (0.47 to 0.65)	0.336 (0.25 to 0.42)	0.130 (0.08 to 0.18)	4
Residual deviance	378.1*	355.6	404.0	
DIC		1241.07		

r-– ranking of treatments according to point estimates; *Compared with 209 data points.

Table 46 Relative effect estimates (as relative risks, RR, mean and 95% CrI) for each treatment combination for PASI 75 of the direct trial comparisons (upper diagonal) and of the NMA results of analysis 2 (lower diagonal)

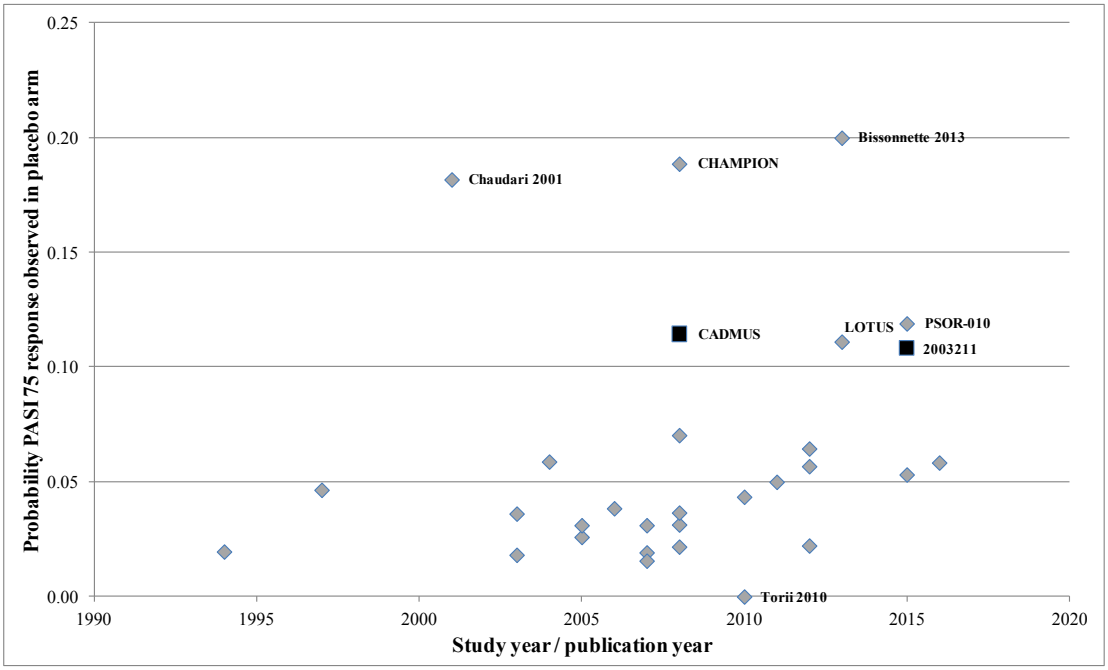
PLB	**9.52 (7.46 to 12.35)**	**14.49 (11.43 to 18.28)**	**8.08 (6.18 to 10.53)**	**1.88 (1.02 to 3.47)**
8.03 (6.61 to 9.64)	**ETA**	--- ---	--- ---	--- ---
14.24 (12.17 to 16.58)	**1.78 (1.50 to 2.12)**	**UST 45**	--- ---	--- ---
12.34 (10.10 to 14.82)	**1.54 (1.25 to 1.88)**	**0.87 (0.74 to 0.99)**	**ADA**	**0.49 (0.38 to 0.59)**
6.72 (4.83 to 8.90)	0.84 (0.60 to 1.11)	**0.47 (0.35 to 0.60)**	**0.55 (0.42 to 0.68)**	**MTX**

PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate; Lower diagonal: pooled RRs from NMA model. RRs above one favour the row agent; Upper diagonal: RRs from direct comparison (pooled using fixed-effects when multiple studies exist). RRs above one favour the column agent; Significant differences in the relative effects between a pair of agents are given in bold.

5.4.3.3 Adjustment for differences in placebo response rates across the trials

The NMA in the full population compares treatment outcomes across a large number of separate clinical trials. The reliability of these comparisons depends on the cross-trial similarity of the patient populations included in the network. An important difference between the included trials is the observed PASI response rates in the placebo arms of the trials, which is a common reference treatment across the majority of the trials. Table 41 showed that the PASI response rates in the placebo arm of the trials ranged from zero to 20% (0% in Torii et al [123] and 20% in Bissonnette et al [95]). All of the trials varied by design, eligibility criteria, prior medication use, average age and other characteristics. All of these variations could contribute to differences in placebo response rates and, therefore, to differences in the relative efficacy of the intervention to placebo. However, there is no systematic way to identify the reasons for these differences. A 'placebo creep' phenomenon has been discussed in the literature, which identifies a relationship between placebo response rates and time since publication of trial results. [126] However, such a phenomenon has not been identified in the trials considered in the NMA (Figure 6). The average PASI 75 response rate in the placebo arm across all trials is 6.2%, while the average rate is 5.9% in studies of adult populations and 11.1% in studies of children and young people. Three adult studies, [91, 95, 119] including CHAMPION, have substantially higher placebo response rates of approximately 18-20% compared to the other studies. Four studies, which include the two trials in children and young people and two in adults [101, 103], have approximately double the average placebo rate.

Figure 6 Probability of PASI 75 response in placebo arms of trials in NMA by study year



It is not clear exactly how these varying placebo rates affect treatment effects; however, it is clear that any differences will affect the relative efficacy of the interventions compared to placebo. Therefore, a potential relationship between baseline risk and relative treatment effect was explored [90] in analysis 2a.

Table 47 and Table 48 present the results of a model that adjusts for differences in placebo response rates. As for the unadjusted analysis (i.e. analysis 2), the baseline adjusted random-effects model was found to fit the data considerably better than the fixed-effect counterpart [DIC: 1303.7 (FE) vs. 1177.6 (RE); total residual deviance: 473.5 (FE) vs. 380.9 (RE)]. Furthermore, the 95% credible intervals for the estimated mean baseline effect derived in the baseline adjusted model do not include zero (-0.93, 95% CrI: -0.97 to -0.88). This suggests that adjusting for baseline risk heterogeneity is important to explain existing between-study variation.

Table 47 NMA results of absolute PASI response for analyses 2a: probability of achieving PASI 50/75/90

Analysis	**2a**			
	PASI 50	**PASI 75**	**PASI 90**	
	Mean (95% CrI)	Mean (95% CrI)	Mean (95% CrI)	r

Placebo	0.151 (0.13 to 0.17)	0.053 (0.04 to 0.06)	0.010 (0.01 to 0.01)	5
Etanercept	0.642 (0.57 to 0.71)	0.414 (0.35 to 0.49)	0.180 (0.12 to 0.25)	3
Ustekinumab	0.882 (0.84 to 0.92)	0.727 (0.66 to 0.79)	0.461 (0.37 to 0.56)	1
Adalimumab	0.839 (0.78 to 0.89)	0.660 (0.58 to 0.74)	0.349 (0.25 to 0.45)	2
Methotrexate	0.570 (0.46 to 0.67)	0.344 (0.25 to 0.44)	0.178 (0.10 to 0.28)	4
Residual deviance	381.7*	357.5	409.4	
DIC		904.5		

r-– ranking of treatments according to point estimates; *Compared with 209 data points.

Table 48 Relative effect estimates (as relative risks, RR, mean and 95% CrI) for each treatment combination for PASI 75 of the direct trial comparisons (upper diagonal) and of the NMA results of analysis 2a (lower diagonal)

PLB	**9.52 (7.46 to 12.35)**	**14.49 (11.43 to 18.28)**	**8.08 (6.18 to 10.53)**	**1.88 (1.02 to 3.47)**
7.86 (6.46 to 9.44)	**ETA**	--- ---	--- ---	--- ---
13.82 (11.70 to 16.32)	**1.77 (1.48 to 2.11)**	**UST 45**	--- ---	--- ---
12.53 (10.34 to 15.01)	**1.60 (1.31 to 1.95)**	0.91 (0.78 to 1.04)	**ADA**	**0.49 (0.38 to 0.59)**
6.52 (4.68 to 8.55)	0.84 (0.58 to 1.12)	**0.47 (0.34 to 0.61)**	**0.52 (0.38 to 0.67)**	**MTX**

PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate. Lower diagonal: pooled RRs from NMA model. RRs above one favour the row agent; Upper diagonal: RRs from direct comparison (pooled using fixed-effects when multiple studies exist). RRs above one favour the column agent; Significant differences in the relative effects between a pair of agents are given in bold.

The results of analysis 2a suggests that ustekinumab is the most effective intervention with the highest mean probability of PASI response (PASI 75: 73%, 95% CrI: 66% to 79%), followed by adalimumab (PASI 75: 66%, 95% CrI: 58% to 74%), and etanercept (PASI 75: 41%, 95% CrI: 35% to 49%) and methotrexate (PASI 75: 34%, 95% CrI: 25% to 44%). Ustekinumab is statistically significantly more effective than etanercept based on relative effect estimates for PASI 75 (RR 1.77, 95% CrI 1.48 to 2.11), but not when compared to adalimumab (RR 1.10, 95% CrI 0.96 to 1.28). Adalimumab is also statistically significantly more effective than etanercept (RR 1.60, 95% CrI 1.31 to 1.95).

5.4.3.4 Adjusting for differences in population and placebo response rates

While evidence from trials in both children and young people and adults contributed to the full network of evidence (effectively assuming independence between age and treatment effectiveness), it is important to recognise that the age of the population could contribute to differences in treatment efficacy. Therefore, analysis 2b adjusts for differences in population and differences in placebo response rates (since the placebo response rates were considerably different in the trials of children and young people compared to adults). Table 49 summarises the results of this analysis in terms of PASI response outcomes for both populations. Table 50 presents the corresponding relative risks for PASI 75 for children and young people.

The model from analysis 2b fits the data as well as model 2a, as both present similar average total residual deviance [380.8 (2b) vs. 381.7 (2a)]. However, DIC is substantially higher for 2b. This suggests that this model is being penalised due to issues of parsimony. The children and young people subgroup effect is estimated not to be statistically significantly different from the adults' subgroup effect, implying that PASI absolute effect distributions of these populations overlap. This is not unexpected due to the limited number of existing studies in the population of children and young people.

The adjustment for population resulted in similar treatment rankings for children and young people when compared with the whole population results (Table 47). The pooled placebo response rate for children and young people is estimated to be higher than for adults (PASI 75: 12%, 95% CrI 5% to 20% in children and young people vs. 5%, 95% CrI 4% to 6% in adults), reflecting the higher placebo response rates observed in the trials for children and young people. This impacts on the efficacy of treatments by substantially increasing the estimated absolute PASI response rates across all treatments, but affecting the relative effects to a smaller extent. On average, PASI 75 response rates are estimated to be 10 to 15% higher in children and young people compared to adults. The treatment rankings, however, remain unchanged. This is consistent with clinical opinion, where efficacy rates are expected to be generally higher in children and young people compared to adults, since the biological interventions tend to work better in individuals with a lower body weight. Also children and young people tend to have less comorbidities and generally get more UV light from participating in outside activities. The credible intervals for PASI 75 for children and young people and adults overlap as shown in Figure 7.

The results of analysis 2b in children and young people suggests that ustekinumab is the most effective intervention with the highest mean probability of PASI response (PASI 75: 82%, 95% CrI:

71% to 90%), followed by adalimumab (PASI 75: 79%, 95% CrI: 64% to 90%), etanercept (PASI 75: 54%, 95% CrI: 39% to 69%) and methotrexate (PASI 75: 49%, 95% CrI: 31% to 68%). The relative efficacy of ustekinumab and adalimumab is similar based on relative effectiveness estimates for PASI 75 (ADA vs. UST 45, RR: 0.96, 95% CrI 0.85 to 1.05). In children and young people, ustekinumab (RR 1.47, 95% CrI 1.28 to 1.92) and adalimumab (RR 1.47, 95% CrI 1.23 to 1.79) are statistically significantly more effective than etanercept.

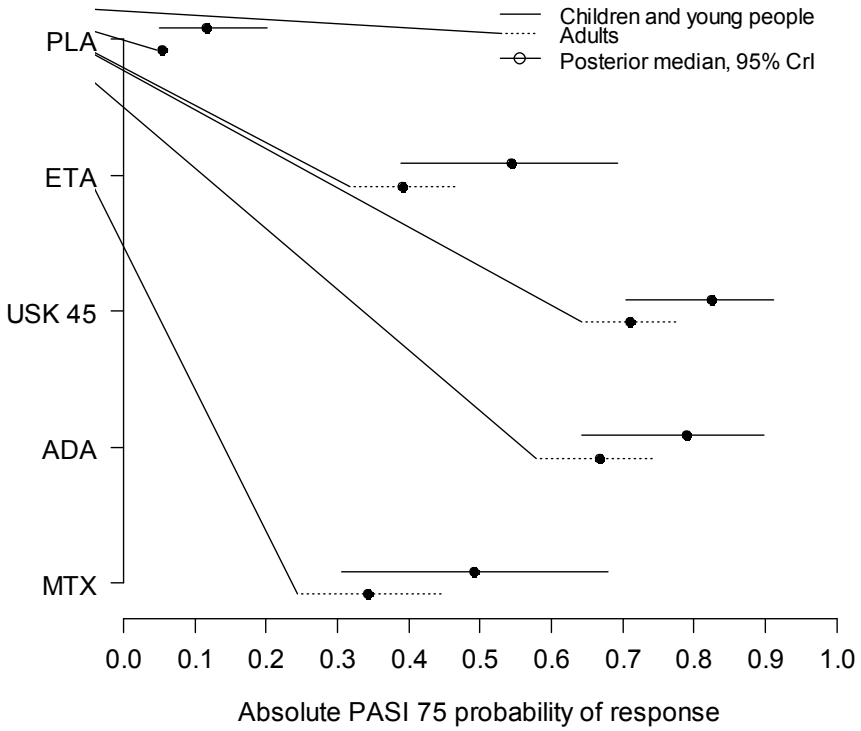
Table 49 NMA results of PASI response for analysis 2bii: probability of achieving PASI 50/75/90 for children and young people and adults

Analysis	Children and young people population				Adults			
	PASI 50	**PASI 75**	**PASI 90**		**PASI 50**	**PASI 75**	**PASI 90**	
2b	Mean (95% CrI)	Mean (95% CrI)	Mean (95% CrI)	r	Mean (95% CrI)	Mean (95% CrI)	Mean (95% CrI)	r

Placebo	0.265 (0.15 to 0.40)	0.115 (0.05 to 0.20)	0.029 (0.01 to 0.06)	5	0.151 (0.13 to 0.17)	0.053 (0.04 to 0.06)	0.010 (0.01 to 0.01)	5
Etanercept	0.752 (0.62 to 0.86)	0.544 (0.39 to 0.69)	0.279 (0.16 to 0.42)	3	0.619 (0.54 to 0.69)	0.390 (0.32 to 0.47)	0.162 (0.12 to 0.22)	3
Ustekinumab	0.934 (0.87 to 0.97)	0.824 (0.71 to 0.91)	0.594 (0.43 to 0.74)	1	0.872 (0.83 to 0.91)	0.711 (0.64 to 0.78)	0.441 (0.36 to 0.52)	1
Adalimumab	0.915 (0.83 to 0.97)	0.790 (0.64 to 0.90)	0.546 (0.37 to 0.72)	2	0.844 (0.78 to 0.90)	0.667 (0.58 to 0.75)	0.393 (0.30 to 0.48)	2
Methotrexate	0.708 (0.53 to 0.85)	0.492 (0.31 to 0.68)	0.240 (0.11 to 0.40)	4	0.567 (0.45 to 0.68)	0.342 (0.24 to 0.45)	0.134 (0.08 to 0.20)	4
Residual deviance	380.8*	356.2	408.6		380.8*	356.2	408.6	
DIC		1229.5				1229.5		

r-– ranking of treatments according to point estimates; *Compared with 209 data points.

Figure 7 Absolute PASI 75 probability of response for children and young people and adult population from NMA model 2b



PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate.

Table 50 Relative effect estimates (as relative risks, RR, mean and 95% CrI) for each treatment combination for PASI 75 of the direct trial comparisons (upper diagonal) and of the NMA results of analysis 2b in the children and young people subgroup of the population (lower diagonal)

PLB	**9.52 (7.46 to 12.35)**	**14.49 (11.43 to 18.28)**	**8.08 (6.18 to 10.53)**	**1.88 (1.02 to 3.47)**
5.09 (3.30 to 8.05)	**ETA**	--- ---	--- ---	--- ---
7.91 (4.46 to 14.14)	**1.54 (1.28 to 1.92)**	**UST 45**	--- ---	--- ---
7.53 (4.37 to 12.98)	**1.47 (1.23 to 1.79)**	0.96 (0.85 to 1.05)	**ADA**	**0.49 (0.38 to 0.59)**
4.55 (3.01 to 6.94)	0.91 (0.66 to 1.15)	**0.59 (0.41 to 0.77)**	**0.62 (0.44 to 0.78)**	**MTX**

PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate. Lower diagonal: pooled RRs from NMA model. RRs above one favour the row agent; Upper diagonal: RRs from direct comparison (pooled using fixed-effects when multiple studies exist). RRs above one favour the column agent; Significant differences in the relative effects between a pair of agents are given in bold.

A consistency assessment was undertaken which involved excluding the trials of children and young people from the evidence network. This assessment indicated that the results were consistent across populations – see appendix 12.12 for further details.

5.4.4 Summary of findings of relative efficacy from NMA

There is no direct trial evidence that allows establishing the relative effectiveness of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people. Furthermore, there is no common comparator across the three trials, which precludes establishing an indirect comparison between all the interventions without drawing on evidence from other sources, namely from a different age population (i.e. adults).

In this section several NMA analyses were conducted to overcome the challenges in formally assessing the relative efficacy of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people.

First, statistical testing was performed on age subgroup efficacy data from the clinical trials in children and young people to establish whether it is reasonable to assume that the PASI response rates for the treatments are independent of age within the full population of children and young people, as the trials included participants in different age ranges. An indirect treatment comparison based solely

on children and young people trial data for etanercept and ustekinumab was then performed and results presented. However, this analysis was of limited use for the economic analysis as the network did not incorporate the full set of relevant interventions. Finally, a framework of analysis using different levels of evidence from the adult population was developed to address the issue of having a disconnected network structure. Previously appraised adult trial evidence was reviewed and extracted, and assumed exchangeable with children and young adult evidence for inclusion in the evidence base. Two main approaches were considered, one where the network of trials in children and young people was connected by bringing the *minimum* amount of evidence required from the adult population in order to link the three existing trials, and another where *all relevant efficacy evidence* identified in adults was incorporated in the network. For each NMA model fixed- and random-effects model approaches were investigated. The latter approach was shown to be preferable, highlighting that variability across trials was important to account for. The rate of placebo response was identified as a source of heterogeneity. Also, population adjusted models allowed obtaining subpopulation specific estimates for i) children and young people and ii) adults. The different model adjustments were explored and the age and placebo adjusted model identified as the best fitting model. For comparison and comprehensiveness, unadjusted and adjusted model results were also presented.

PASI response results were generally consistent across the different models, adjusted and unadjusted. Ustekinumab was identified as the most efficacious treatment followed by adalimumab and etanercept. Methotrexate was the least efficacious active agent, followed by placebo. The economic model in Section 7 uses the results for the children and young people subgroup of the placebo and population random-effects adjusted NMA (2b, Table 49) to inform the effectiveness estimates. This NMA model was considered to provide the most appropriate set of efficacy estimates to inform the economic analysis because: a) it considers all relevant evidence; b) it adjusts for placebo heterogeneity; c) it adjusts for age effects; and d) it enables the estimation of age subgroup-specific effects. Scenario analyses are also conducted where the results from the unadjusted baseline constrained model with minimum adult evidence (1b, Table 43) are applied in the model. Partial comparisons with direct trial data and the indirect comparison reported in Section 5.3 are also incorporated in a scenario analysis for completeness.

6 Assessment of existing cost-effectiveness evidence

6.1 Introduction

This section aims to provide an overview of existing evidence on the cost-effectiveness of adalimumab, etanercept, ustekinumab and relevant comparators for the treatment of plaque psoriasis in children and young people. The overview includes the company submissions from Janssen (ustekinumab) and AbbVie (adalimumab), while Pfizer (etanercept) did not submit a company submission. An overview of cost-effectiveness evidence from related NICE Technology Appraisals (TAs) for the treatment of plaque psoriasis in adults (TA 103, 134, 146, 180, 350, and 368) is also presented. The differences in the model structures and assumptions used across the studies are examined in order to identify any important differences in approaches and areas of uncertainty. The findings from the review provide the basis for the development of a new decision-analytic model in children and young people reported in Section 7.

6.2 Methods

Systematic searches of the literature were conducted to identify potentially relevant studies for inclusion in the assessment of cost-effectiveness of the interventions against any comparator in children and young people. A broad range of studies was considered for inclusion in the assessment of cost-effectiveness, including economic evaluations conducted alongside clinical trials and modelling studies. Only full economic evaluations that compared two or more options and considered both costs and consequences in children and/or young people were considered. The inclusion criteria allowed for studies in adults as long as data were reported separately for a subpopulation of children and/or young people. The searches were not restricted to biologic therapy or level of disease severity, as a dearth of evidence was anticipated in the population of children and young people.

The following resources were searched for relevant published literature: 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). The search strategy was the same as that reported for the systematic review described in Section 4 (see Appendix 12.1) but was restricted to include studies with ‘cost’ in the title or abstract. Titles and abstracts were assessed independently by two reviewers for inclusion and any discrepancies were resolved by consensus. Additional hand-searching of related TAs in adults was undertaken.

6.3 Results

6.3.1 Identified published studies

A total of 293 unique records were identified from the systematic literature review of existing cost-effectiveness evidence in children and young people, of which only one study subsequently met the inclusion criteria [127]. This study was from the All Wales Medicines Strategy Group (AWMSG) advice for the use of etanercept for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years in NHS Wales who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies [127].

One previous NICE MTA appraisal (TA 103) [88, 89] and five STA appraisals (TA 134, 146, 180, 350, and 368) [84-87, 128] were identified in adults with chronic plaque psoriasis..

6.3.2 Review of existing published cost-effectiveness studies

This review starts with an overview of the AWMSG cost-effectiveness model for the assessment of etanercept in children and adolescents from the age of 8 years and then considers the cost-effectiveness evidence submitted by the companies for ustekinumab and adalimumab in children and young people. The final section provides an overview of the cost-effectiveness modelling used in the previous TAs in adults.

6.3.3 Etanercept AWMSG cost-effectiveness model in children and young people

The only economic model identified in published studies was that reported as part of the AWMSG advice No. 138 for the use of etanercept within NHS Wales for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years. The cost-effectiveness evidence presented was deemed insufficient for AWMSG to recommend the use of etanercept in NHS Wales. The cost-effectiveness modelling is not reported in sufficient detail to be very informative. The AWMSG considered that it was not possible to judge whether or not the analysis presented by the company (Pfizer) in their submission represented the most plausible estimate of the cost-effectiveness of etanercept compared to placebo in this population. This was due to a number of limitations of the economic evidence and decision analytic model submitted by the company.

The economic model was a Markov model with a 28-day cycle length to represent intermittent treatment with etanercept compared to placebo/non-systemic therapy over a 10-year time horizon. The perspective of the evaluation was NHS Wales. For treatment with etanercept 0.8 mg/kg weekly (up to a maximum of 50 mg), individuals were modelled to receive initial therapy for a 'trial period' of 12 weeks, after which their PASI 50 response was used to determine whether or not they were considered responders or non-responders to treatment. Those who achieved a PASI 50 response were considered

responders and continued treatment with continuous etanercept up until week 24. At week 24, those who did not achieve a PASI 50 response discontinued treatment, while those with a PASI response between 50 and 75 remained on continuous etanercept. Of those with PASI 75 response, 25% were assumed to remain on continuous etanercept and the remainder received intermittent etanercept (comprising of a treatment-free period, with treatment reinitiated in those who experience relapse). Non-responders at 12 and 24 weeks were assumed to discontinue treatment.

The effectiveness evidence was sourced from a placebo controlled RCT of etanercept in children and adolescents aged 4-17 years with moderate to severe psoriasis and with previous or current treatment with phototherapy or systemic therapies, or psoriasis considered by the investigator as poorly controlled with topical treatments [56]. The AWMSG estimated that only 57% of the trial population met the licensed indication for etanercept at the time of the submission.

The Health-related quality of life (HRQoL) estimates applied in the model were derived from adult studies of etanercept through the mapping of adult Dermatology Quality of Life Index (DLQI) scores to EQ-5D utility values. The utility gains from baseline were assumed to be independent of treatment and varied according to severity of disease based on PASI response rates. The AWMSG noted that there was no discussion of the uncertainty surrounding the use of utility values from adults to inform the population of children and adolescents.

The drug costs of etanercept were based on the doses used in the RCT in children and adolescents, at 0.8 mg/kg body weight up to a maximum dose of 50mg and delivered in pre-filled syringes. However, the AWMSG noted discrepancies between that reported and the doses used in the model, with a lower dose of 25 mg weekly used in the model for all patients instead of 44% of patients receiving the maximum dose of 50 mg per week and 56% of patients receiving a weekly dose of 0.8 mg/kg in the trial. The median weight in the trial was approximately 60 kg which equates to a median dose closer to 50 mg per week than 25 mg per week. The AWMSG noted that the model was very sensitive to the assumed weekly cost of etanercept.

The number of clinic visits was informed by the British Association of Dermatologist (BAD) guidelines and length of hospital stay for patients who failed treatment was sourced from TA103 for adults. A number of other model parameters were not discussed in the company's submission but appeared to have been sourced from the original NICE MTA (TA 103) in adults. The use of adult data to populate the model and the implications of assuming transferability of adult data to inform the decision problem in children and adolescents did not appear to have been discussed by the company during the AWMSG appraisal.

The results of the company's model showed that etanercept was both less expensive and more effective (i.e. etanercept was the dominant treatment strategy) compared to placebo in children and adolescents of age 8 years and older. Sensitivity analysis was poorly reported and it was uncertain whether probabilistic sensitivity analysis had been performed. The AWMSG considered it impossible to establish whether the base-case analysis represented the most plausible estimate of the cost-effectiveness of etanercept in this population based on the limited information provided in the company's submission. As a result, the AWMSG were unable to recommend etanercept for children and young people due to the uncertainties inherent in the economic model.

6.3.4 Janssen submission for ustekinumab in children and young people

Within their submission supporting this appraisal, Janssen explored the possibility of constructing an economic model to assess the cost-effectiveness of ustekinumab for the treatment of moderate to severe psoriasis in children and young people. However, given the limited clinical evidence identified in their systematic review of effectiveness, Janssen decided not to pursue the development of an economic model. Janssen noted that the only previous economic evaluation in this population (i.e. etanercept for AWMSG) resulted in an adaptation of an adult model in psoriasis and relied on simplifying assumptions for the cost-effectiveness analysis. Therefore, due to the limitations of the evidence base, they concluded that any estimation of the cost-effectiveness of biologics in children and young people with psoriasis will be subject to a number of insuperable uncertainties and will largely be based upon a number of assumptions taken from the adult population. Janssen's submission does, however, provide an overview of the available evidence in children and adults to aid the development of an economic model by the Assessment Group. However, no cost-effectiveness results are presented in Janssen's submission for children and young people.

6.3.5 AbbVie submission for ustekinumab in children and young people

AbbVie undertook a targeted review to identify publications and major HTA bodies that report cost-effectiveness analyses for adalimumab in children and young people with plaque psoriasis. Their submission indicates that only one relevant study was identified (Langley et al 2014).[129] This study estimated the number needed to treat to achieve PASI 75 response based on a Bayesian network meta-analysis of efficacy outcomes for adalimumab, etanercept, infliximab and ustekinumab and evaluated the incremental cost per PASI 75 responder for biologic treatments during the first 10 to 16 weeks of treatment. Based on the results of this study, AbbVie indicates that adalimumab was found to be the most cost-effective treatment option in terms of incremental cost per PASI 75 responder compared to the other biologics. However, the Assessment Group notes that the study by Langley et al 2014 is not based on a population of children and young people and does not present cost-effectiveness of the

biologics in terms of costs and quality-adjusted life years (QALYs) over a time horizon sufficiently long to capture differences between the interventions. Furthermore, the study is only presented in the form of an abstract rather than a full publication, therefore limited details are available to adequately critique the study. AbbVie's submission did not include an economic model for the assessment of adalimumab in children and young people.

6.4 Cost-effectiveness models in adults

6.4.1 Overview

Given that the literature review only identified one unpublished model assessing the cost-effectiveness of etanercept in children and young people and that this model was adapted from TA 103 in adults and largely populated with adult data, additional hand-searching of published documents associated with the previous NICE TAs of plaque psoriasis in adults was carried out. The aim was to examine existing decision-analytic models, to identify important structural assumptions, highlight key areas of uncertainty and outline the potential issues associated with generalising evidence from the adult population to a population of children and young people.

The first NICE TA on biologic therapies for the treatment of psoriasis was a Multiple Technology Appraisal (MTA) examining the cost-effectiveness of etanercept and efalizumab within their licensed indications in adults (TA 103 published in July 2006).[88, 89] As part of this appraisal, the York Assessment Group developed a *de novo* cost-effectiveness model, which was subsequently referred to as 'the York model'. Six subsequent Single Technology Appraisals (STAs) followed TA 103:

- TA 134 – Infliximab for the treatment of adults with psoriasis (published in January 2008);[87]
- TA 146 – Adalimumab for the treatment of adults with psoriasis (published in June 2008);[86]
- TA 180 – Ustekinumab for the treatment of adults with moderate to severe psoriasis (published in September 2009);[85]
- TA 350 - Secukinumab for the treatment of adults with moderate to severe plaque psoriasis (published in July 2015);[84]
- TA 368 - Apremilast for the treatment of adults with moderate to severe plaque psoriasis (published in November 2015).[128]

All of these STAs employed a similar modelling approach to the original York model in TA 103. The only study identified which deviated from the original model was the most recent STA of apremilast (TA 368) which included the modelling of sequences of treatment. Therefore, the main differences between the TAs lies in the evidence base, intervention and comparators rather than any major structural

differences in the modelling approach used. A summary of the York model and the key differences between the assumptions and evidence base used in subsequent adaptations of the model are described in the following section. Table 51 provides an overview of the NICE TAs in adults

Table 51 Overview of NICE TAs for psoriasis in adults

Appraisal	**Etanercept and efalizumab** **TA103**	**Infliximab** **TA134**	**Adalimumab** **TA146**	**Ustekinumab** **TA180**	**Secukinumab** **TA350**	**Apremilast** **TA368**
Modelling approach	Markov model, which became known as the 'York model'	Based on the York model	Based on the York model	Based on the York model	Based on the York model, but explicitly incorporates a decision tree for trial period followed by a Markov model	Based on the York model but with treatment sequences
Intervention	EFA ETA 25 mg BIW continuous ETA 50 mg BIW intermittent	INF	ADA	UST 45 mg UST 90 mg	SEC	Primary analysis: APR→ADA→ ETA → BSC Subgroup analysis: APR → BSC Scenario analysis APR→ADA→ ETA/UST → BSC
Comparators	Primary analysis: BSC Secondary analysis: CS, fumaderm, MTX, INF	EFA ETA 25 mg BIW continuous ETA 25 mg BIW intermittent ETA 50 mg BIW intermittent BSC	INF EFA ETA 25 mg BIW continuous ETA 25 mg BIW intermittent ETA 50 mg BIW intermittent BSC	ADA INF EFA ETA 25 mg BIW continuous ETA 25 mg BIW intermittent ETA 50 mg BIW intermittent BSC	ADA UST INF ETA BSC	Primary analysis: ADA→ ETA → BSC Subgroup analysis: BSC Scenario analysis ADA→ ETA/UST → BSC
Time horizon & justification	10 years NR	10 years Sufficient time for all future costs and	10 years Based on the York model	10 years Based on the York model	10 years Time horizon reflective of treatment duration of	10 years

Appraisal	**Etanercept and efalizumab** **TA103**	**Infliximab** **TA134**	**Adalimumab** **TA146**	**Ustekinumab** **TA180**	**Secukinumab** **TA350**	**Apremilast** **TA368**
		outcomes to be included			moderate to severe plaque psoriasis	Maintain consistency with previous analyses and in the base case majority of patients are on BSC by the end of 10 years
Cycle length	12 months (not explicit)	12 months	12 months	3 months	12 months	28 days
Discount rates	6.0% on costs, 1.5% on QALYs	3.5%	3.5%	3.5%	3.5%	3.5%
Mortality	Not considered	Not considered	Not considered	Not considered	Not considered	All-cause mortality incorporated
HRQoL instrument	DLQI mapped to EQ-5D	Utilities from York model	EQ-5D	DLQI mapped to EQ-5D; SF-6D in sensitivity analysis	EQ-5D	Utilities from York model & EQ-5D; DLQI mapped to EQ-5D
Link between utility and clinical efficacy	EQ-5D mapped from ΔDLQI by ΔPASI (coefficients not reported)	Base-case used the estimates from the York model, but only for those in the 4th quartile of DLQI (worst HRQoL). Additional analyses used utility values estimated by mapping SF-36 data collected in EXPRESS I and II to EQ-5D using an	Trial collected EQ-5D association with DLQI and changes in PASI	EQ-5D mapped from ΔDLQI by ΔPASI (used a mapping algorithm based on the published scatter-plot in the York model): EQ-5D = -0.0162*DLQI + 0.8554	Changes in EQ-5D from baseline at a given time point as function of: - PASI response at that time point - baseline DLQI difference from the pooled mean baseline DLQI - interaction between these terms	Changes in utility associated with changes from baseline PASI were taken from the York model for the DLQI>10 population. For the DLQI≤10, EQ-5D data collected in trials was used; direct link between %ΔPASI and ΔEQ5D in patients with DLQI≤10 The same baseline utility

Appraisal	**Etanercept and efalizumab** **TA103**	**Infliximab** **TA134**	**Adalimumab** **TA146**	**Ustekinumab** **TA180**	**Secukinumab** **TA350**	**Apremilast** **TA368**
		unpublished mapping algorithm.				score (0.7) from a published study was used for both populations.
Total costs	Incremental vs. supportive care: Supportive Care: £0 ETA 25 mg: £7,743 EFA £9,382 ETA 25 mg Continuous: £9,665 ETA 50 mg: £14,860	Incremental vs. supportive care: Continuous ETA 25 mg: £1,531 INF: £4,562	Incremental vs. supportive care: - MTX £-3,844 - Cyclosporine £-1,987 - Supportive Care £0 - ETA intermittent £4,114 - ETA High Intermittent £4,699 - EFA £4,942 - ADA £4,993 - ETA £5,058 - INF £7,736	Incremental vs. supportive care: - Supportive care £0 - EFA £5,264 - ETA 25 mg intermittent £3,989 - ETA 25 mg continuous £4,829 - ETA 50 mg continuous £5,333 - ADA £4,660 - UST £4,615 - INF £6,327	Standard of care: £73,610 ETA 25 mg BIW: £75,788 SEC 300 mg:£76,361 ADA 40 mg: £76,981 UST 45 mg: £79,544 UST 90 mg: £79,732 INF 5 mg/kg: £93,539	DLQI>10 Apremilast sequence: £89,374 Comparator sequence: £92,589
Total QALYs	Supportive Care: 0 ETA 25 mg: 0.116 EFA: 0.112 ETA 25mg continuous: 0.116 ETA 50 mg: 0.123	Continuous ETA 25 mg: 0.089 INF: 0.205	Incremental vs supportive care - MTX 0.129 - Cyclosporine 0.079 - ETA intermittent 0.11	Incremental vs. supportive care: - EFA 0.1308 - ETA 25 mg intermittent 0.1325 - ETA 25 mg continuous 0.1409	Standard of care: 0.97 ETA 25 mg BIW: 1.13 SEC 300 mg: 1.36 ADA 40 mg: 1.22 UST 45 mg: 1.30	DLQI>10 Apremilast sequence: 6.83 Comparator sequence: 6.69

Appraisal	**Etanercept and efalizumab** **TA103**	**Infliximab** **TA134**	**Adalimumab** **TA146**	**Ustekinumab** **TA180**	**Secukinumab** **TA350**	**Apremilast** **TA368**
			- ETA high intermittent 0.123 - EFA 0.124 - ADA 0.164 - ETA 0.134 - INF 0.182	- ETA 50 mg continuous 0.1483 - ADA 0.1502 - UST 0.156 - INF 0.1616	UST 90 mg: 1.33 INF 5 mg/kg: 1.36	

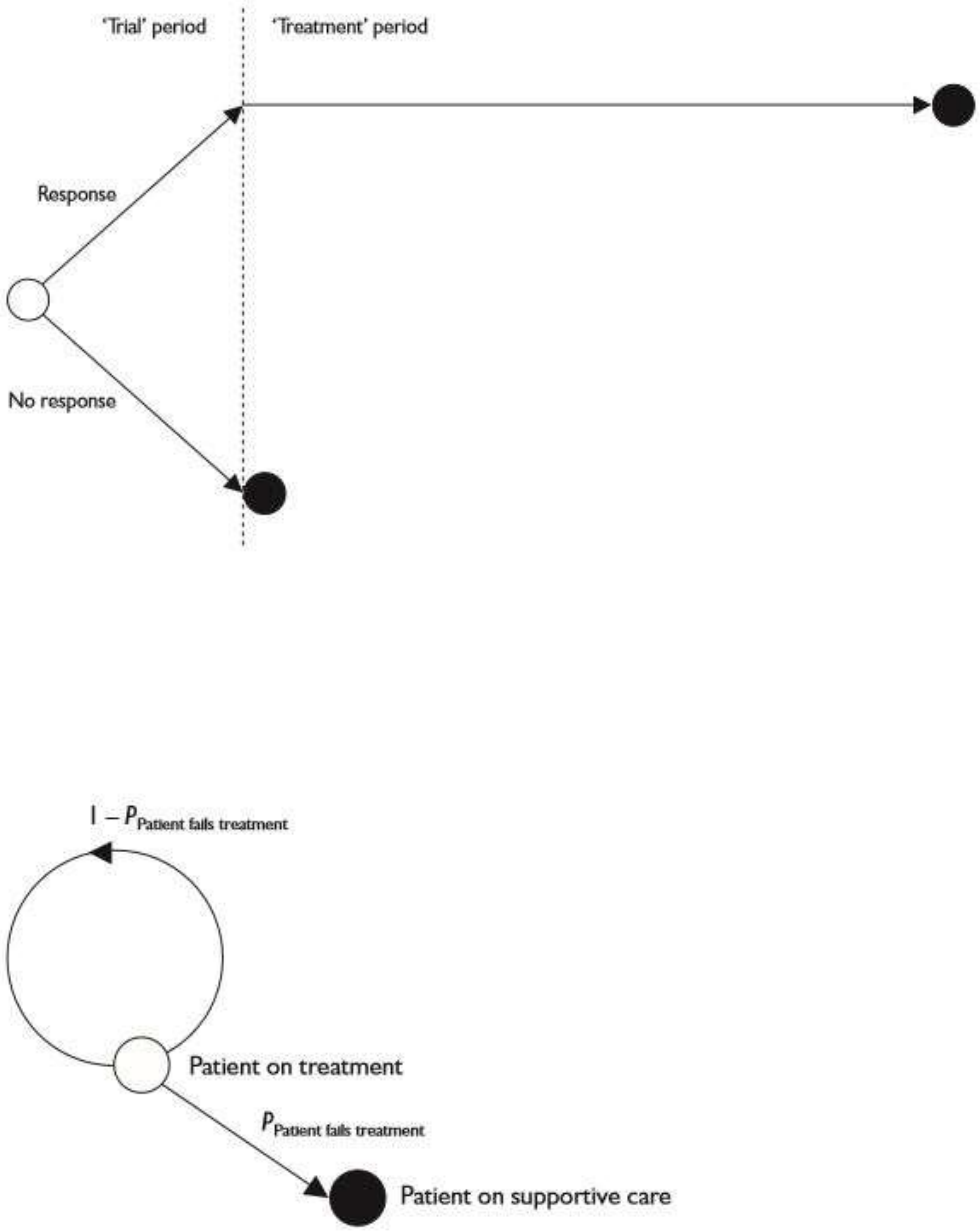
ADA, adalimumab; APR, apremilast; BIW, twice weekly; BSC, Best supportive care; CS, cyclosporine; EFA, efalizumab; ETA, etanercept; INF, infliximab; MTX, methotrexate; NR, not reported; SEC, secukinumab; SF-6D, Short Form–6 Dimension; UST, ustekinumab.

6.4.2 Summary of the York model (TA 103) and subsequent adaptations (TA 134, 146, 180, 350, 368)

The York model was a cohort Markov model, which was developed to estimate the costs and QALYs of etanercept and efalizumab compared to best supportive care (BSC) over a time horizon of 10 years (primary analysis). A secondary analysis was also conducted to compare the interventions with additional systemic therapies of cyclosporine, fumaderm, methotrexate and infliximab. The model adopted the perspective of the UK NHS. The price year for costs was 2004-2005 and an annual discount rate of 6% for costs and 1.5% for outcomes was applied (in line with NICE Guidance at the time of the appraisal).

The model consisted of a two part structure: a 'trial' period for initial response and a 'treatment' period for long-term response to treatment (see Figure 8). The initial response period was used to determine initial response rates and the decision to continue treatment. The duration of the trial period was based on the period over which response was assessed in the efficacy trials for each treatment – this was 12 weeks for etanercept and efalizumab and between 10 and 16 weeks for the other systemic therapies. Individuals with a PASI 75 response were considered 'responders' and continued treatment after the trial period (i.e. they entered the treatment period), while individuals who were 'non-responders' discontinued treatment and received best supportive care. The treatment duration for responding individuals was based on an annual withdrawal rate of 20%. Upon withdrawal, individuals were assumed to receive BSC.

Figure 8 Structure of the York model (Source: TA 103)



The base case analysis considered a single line of therapy consisting of a biologic treatment (etanercept or efalizumab) followed by BSC. While specific sequences of treatments were not considered in the York model, an analysis showing the expected costs and QALYs associated with each treatment option compared to BSC was used to determine the most 'cost-effective order' in which to give the treatments, which varied according to the cost-effectiveness threshold.

The same model structure based on a single line of treatment was used in subsequent TAs of TA 134, 146, 180 and 350, and to a lesser extent in TA 368, where it was only used for the subpopulation of

patients with DLQI ≤ 10. The only difference in the modelling approach across the appraisals was a variation in the cycle length of the Markov model (12 months in TA 134, 146, 350; 3 months in TA 180; and 28 days in TA 368), which was adapted to reflect the different length of the trial periods when treatment response was assessed. All appraisals used a time horizon of 10 years in their base case analysis and used additional scenarios to show the implications of a change in the time horizon.

In TA 368, the company adapted the model structure to allow a comparison of treatment sequences, with up to five sequential lines of treatment. The model structure followed the same approach as the York model but if treatment response was considered inadequate at the end of the trial period, individuals moved into the trial period of the next line of treatment (or to BSC if the end of the treatment sequence had been reached). The company's original economic model only considered apremilast as first treatment in the sequence and compared different treatment sequences with apremilast as an additional line of therapy, rather than replacing an existing biological therapy in the sequence. However, following the Evidence Review Group critique additional analyses were presented which compared the use of apremilast at different positions within a sequence.

6.4.3 Clinical effectiveness evidence in the York model and subsequent appraisals

The response rates used in the York model were based on a Bayesian network meta-analysis comparing the interventions to a broad range of comparators including systemic therapies. An ordered probit model was used to predict PASI 50, PASI 75 and PASI 90 response rates, with PASI 75 used as the primary measure of response at the end of the trial period. If the trial only reported PGA 0/1 (clear or almost clear) as the endpoint, it was assumed to be equivalent to PASI 75 response. A similar Bayesian network meta-analysis was used in subsequent appraisals but was updated with additional evidence as more interventions and comparators became available. There were some differences across the appraisals in terms of how heterogeneity was accounted for in the meta-analysis and whether any adjustment had been made for differences in placebo response rates across the trials.

The effectiveness data was considered to be an area of uncertainty in the previous appraisals, mainly due to the lack of direct head-to-head comparisons between the biologic treatments and the paucity of longer-term data. Although the evidence base expanded over time with many more RCTs included in the network meta-analysis, other concerns were raised relating to differences between the trial populations in the network (e.g. exposure to prior therapies and severity of disease). The definition of placebo or best supportive care across the different trials included in the network meta-analysis was also a contentious issue.

6.4.4 Health-related quality of life in the York model and subsequent appraisals

The utility values associated with treatment in the York model were based on the proportion of patients in the different PASI response categories (<50, 50-75, 75-90, ≥90) and the change in utility from baseline associated with the PASI response category. Utility values were estimated based on a two stage process:

- Mean change in DLQI score between baseline and week 12 in the etanercept trials was estimated for patients with different levels of PASI response and different baseline DLQI scores. This analysis was facilitated by access to patient-level data from the trials, and the placebo and treatment groups were pooled.
- The DLQI data collected in the etanercept trials was then mapped onto EQ-5D values. This was achieved through access to data from the Health Outcomes Data Repository (HODaR), which included patients who had completed both the DLQI and EQ-5D. This data was used to map the change in DLQI associated with PASI responses to changes in EQ-5D utility values.

The two-stage process estimated average EQ-5D gains in utility from baseline for the different PASI response categories: 0.05 for PASI <50, 0.17 for PASI 50-75, 0.19 for PASI 75-90 and 0.21 for PASI ≥90. Estimated gains in utility were also presented for individuals in the fourth quartile of baseline DLQI, i.e. for patients with the worst baseline quality of life. The utility values from the York model were applied directly in TA 368 for the population with DLQI >10 and in TA 134 (values for the fourth quartile of baseline DLQI). For TA 146, TA 350, and TA 368 (scenario analysis), the company had access to EQ-5D data collected in the trials, which were pooled across treatment groups and reported by PASI response category. For TA 180, a similar modelling approach was used but the mapping algorithm used in the York model was applied to ustekinumab trial data to generate utility gains by PASI response category based on DLQI scores in the trial. The utility values applied in the TAs are summarised in Table 52.

None of the TAs included a disutility associated with adverse events from treatment. Only one TA considered a disutility from flare-ups associated with time off treatment with intermittent etanercept (TA 146); however the value applied was not reported in the published documentation.

The modelling approach used in the previous TAs assume that:

- PASI response is a perfect proxy for the change in utility arising from treatment. In other words, by conditioning on PASI response, utility is independent of treatment;
- Similarly, if utility is conditioned on DLQI change, then utility is independent of PASI response;

- The relationship between DLQI and utility is linear;
- The impact of adverse events on health-related quality of life is unimportant.

The main critique of the approach used in the York model relates to the uncertainty introduced by mapping from DLQI to EQ-5D, based on a small sample of 86 patients. The NICE Appraisal Committees favoured the use of EQ-5D data collected directly from the trials when available. Scenario analysis in TA 103 showed that the cost-effectiveness results were very sensitive to the selection of utility values, with greater QALY gains from treatment in the fourth quartile of baseline DLQI (subgroup with worse baseline HRQoL) compared to the overall trial population. Furthermore, since the utility values were conditioned on PASI response at the end of the trial period, these values were extrapolated over the time horizon of the model, which is a key driver of differences between the treatments.

Table 52 Summary of utility values applied in previous TAs

	TA 103		TA 134**	TA 146			TA 180		TA 350***	TA 368			
Population*	All	4th qtl DLQI	4th qtl DLQI	All	DLQI >10	DLQI≤10	DLQI≥10	DLQI≥10	All	DLQI>10		DLQI≤10	
Analysis	BC	SA	BC	SA	BC	SA	BC	SA	BC	BC	SA	BC	SA
BL PASI	-	-	-	-	-	-	-	-	0.642	0.7	0.7	0.7	0.7
Source	NR	NR	NR	NR	NR	NR	NR	NR	RCT	Revicki et al, 2008 [130]			
Incremental gain in utility from baseline													
PASI<50	0.050	0.120	0.120	0.054	0.063	0.045	0.04	0.0016	0.109	0.05	0.0134	0	-0.0024
PASI50-75	0.170	0.290	0.290	0.140	0.178	0.102	0.17	0.0424	0.193	0.17	0.0537	0.02	0.0275
PASI75-90	0.190	0.380	0.380				0.22	0.0970	0.226	0.19	0.1150	0.03	0.0256
PASI>90	0.210	0.410	0.410	0.219	0.308	0.130	0.25	0.1276	0.264	0.21	0.1333	0.07	0.0704
Source	Trial collected DLQI data by PASI category, mapped to EQ-5D		TA103	Pooled trial EQ-5D data. Relationship with PASI established by mixed model.			Trial DLQI data by PASI category, mapped to EQ-5D	RCT sourced SF-6D data by PASI	Pooled trial EQ-5D data and a statistical model predicted	TA103	Pooled trial EQ-5D data by PASI respons	Pooled trial EQ-5D data by PASI respons	Pooled trial EQ-5D data by PASI response category. Includes all available

				using TA103's mapping algorithm.	response category	the change in HRQoL from BL by categories of PASI response.		e category .	e category .	apremilast trial data available

BC; base-case; BL, baseline; NR, not reported; qtl, quartile; RCT, randomised clinical, trial; SA, scenario analysis

*Populations are defined based on baseline DLQI HRQoL; **A scenario analysis with utilities estimates from the all population in TA103 was also conducted; ***A scenario analysis with utilities estimates from the all population in TA146 was also conducted.

6.4.5 Resource use and costs in the York model and subsequent appraisals

Resource use and costs included in the York model and subsequent appraisals consisted of drug acquisition costs, administration and monitoring, outpatient visits and inpatient hospitalisation stay. The cost of tests to assess eligibility for biologic treatment was excluded. All treatments with the exception of infliximab were assumed to be self-administered. Drug costs were sourced from the most recent information in the British National Formulary (BNF). A range of monitoring and laboratory costs were considered, including full blood count, liver function tests and regular physician visits. No adverse event costs associated with treatment were included in the York model. TA 350 was the only appraisal where costs of adverse events were considered. The rates of adverse events applied were sourced from the secukinumab trials and published literature and included non-melanoma skin cancer, other malignancies and severe infections.

Resource use and costs included in the earliest TAs (TA 134, TA 146 and TA 180) mostly followed the assumptions of the York model and sourced their resource use and unit costs from TA 103. There were small differences in resource use for drug monitoring and administration between the TAs but these differences had only a minor impact on the cost-effectiveness results. Later TAs (TA 350, TA 368) based their resource use and cost estimates on the NICE Clinical Guideline on psoriasis (CG 153) for the cost-effectiveness of second-line biologics and on the accompanying costing report. .[131, 132] The CG 153 included the same categories of costs as the York model but expanded upon them to better characterise the costs of BSC. The costs associated with BSC were identified as a key driver of the cost-effectiveness results in TA 103 and were considered to be an area of substantial uncertainty in subsequent TAs.

In all of the appraisals, non-responders to treatment were assumed to receive BSC (with the exception of TA 368 where sequential use of treatments was considered and non-responders only moved to BSC when all other treatment options were exhausted). The costs associated with BSC differ across the appraisals as there is no clear guidance on what BSC consists of. Table 53 details the elements of cost for BSC included in each of the TAs, as well as those reported in CG 153.

Table 53 Summary of resource use and costs for best supportive care included in the previous TAs and NICE guidance

Study	Treatments included as part of BSC	Outpatient visits (annual)	Day centre care (annual)	Hospitalisations (annual)	Reported total annual cost of BSC
TA 368	45% of patients on MTX 45% of patients on continuous CS 16% of patients have 24 sessions of NBUVB per year	10% of patients have 5 visits	All patients have 5 visits	82% of patients (high need) have one hospitalisation with a 20.8 days mean LOS, 18% (very high need) have 2.55 hospitalisations with a 53.04 days mean LOS. On average 26.6 days.	£11,542.73
TA 350	45% of patients on MTX 15 mg/week 45% of patients on continuous CS 300 mg/day for a maximum of 2 years 3.84 sessions of NBUVB per year	4	5	10.7	£9,015.00
CG 153	45% of patients on MTX 45% of patients on continuous CS for a maximum of 2 years 16% of patients have 24 sessions of NBUVB per year	10% of patients have 5 visits	All patients have 5 visits	82% of patients (high need) have one hospitalisation with a 20.8 days mean LOS, 18% (very high need) have 2.55 hospitalisations with a 53.04 days mean LOS. On average 26.6 days.	£10,730.00
TA 180	No treatments	2	0	21	£6,209.54

TA 146	No treatments	2	0	21	£5,493.00
TA 134	No treatments	18*	0	21	£7,365.00
TA 103	No treatments	2	0	0/21**	£113.20/£5,327.71

BSC, Best supportive care; CS, cyclosporine; LOS, length of stay; MTX, methotrexate; NBUVB, narrow band UVB therapy.

*Non-responders that switch to BSC, responders have 2 outpatient visits; **Zero in the base-case analysis and 21 days in a scenario analysis.

The cost of BSC for non-responders in the York model was limited to two annual outpatient visits in the base-case analysis, but included one annual hospitalisation with a 21 day length of stay (LOS) in a scenario analysis. The rate of hospitalisation for patients on BSC was based on expert opinion with LOS sourced from Hospital Episode Statistics (HES) data and two local surveys. Subsequent TAs (TA 134, TA 146, TA 180) used the 21 days of inpatient stay for BSC in their base-case analysis. In each of these appraisals it was assumed that no treatments were given as part of BSC.

The NICE Clinical Guideline CG 153 departed from this definition of BSC (see Appendix P of the guideline) because they believed that it does not reflect what currently happens in clinical practice for patients who require a second line biologic. They assumed that 45% of patients would receive treatment with methotrexate, 45% would receive continuous cyclosporine for a maximum of 2 years, and 16% would have 24 sessions of narrow band UVB therapy per year, while on BSC. Furthermore, it was reported in CG 153 that patients meeting the eligibility criteria for biologic therapy are generally high-need patients who utilise sizeable health care resources through inpatient admissions, lengthy hospital stays, frequent visits to day clinics for specialist-applied topical treatments and UVB, and require monitoring for toxicity due to the use of systemic treatments. The NICE Guideline Development Group (GDG) sourced the resource use estimates for BSC from two published cohorts of patients with high need (i.e. those with severe psoriasis), which were conducted in tertiary dermatology units in the UK (n=76) [130] and the Netherlands (n=67). [133]. Both of these studies estimated mean inpatient days in the year preceding initial treatment with biologic therapy. In addition, estimates of LOS from a multicentre prospective service review based on four specialist dermatology centres in the UK [134] were used in a scenario analysis. The GDG for CG 153 emphasised that there is substantial variability in the long-term costs reported for patients with psoriasis. As a result, CG 153 included extensive sensitivity analyses for the elements of cost associated with BSC. These included variations in number of hospitalisations per year and average LOS by level of need. The cost-effectiveness of second line biologic therapy compared to BSC in CG 153 was highly sensitive to the assumptions about BSC.

The more recent TAs (TA 368 and TA 350) largely followed the resource use reported in CG 153 for BSC (see Table 54). The NICE Appraisal Committees for TA 350 and TA 368 noted that in both cases the costs of BSC were likely to have been overestimated. The committees considered that the patient population in CG 153 and Fonia et al (2010) did not match that of the appraisals and reflected a sicker group of patients. In particular, Fonia et al (2010) described care in a tertiary care centre, which is known to be associated with treating the most severely affected cases of psoriasis. Furthermore, during consultation of TA 368, the company provided NHS hospital episode statistics data that showed that the average length of hospital stay associated with BSC was 3.5 days. However, this was argued by the

company to be an underestimate as it includes patients with different disease severities and patients receiving concomitant medication. The duration of hospital stay for BSC in adults with moderate to severe psoriasis remains highly uncertain.

Table 54 Summary of CG 153 assumptions for scenario analysis

Severity of psoriasis	Proportion of patients	Number of admissions (annual)	Assumed average LOS (days)	Patient days in hospital	Number of bed days per annum in the model	Base-case assumptions and variations in scenario analysis
High need	82%	1	20.8	20.8		**Base case:** Proportion of patients by level of need sourced from Driessen et al, 2010. Average LOS taken from Wood et al, 2008 for patients with baseline PASI of 10-20 (20.8 days). Number of hospitalisations calculated to match Driessen et al, 2010, average LOS for very high need patients in the year prior to biologic therapy (53 days).
Very high need	18%	2.55	20.8	53.0	26.6	
High need	82%	1	**23.7**	23.7		**Scenario 1:** Average LOS taken from Wood et al 2008 for patients with baseline PASI greater than 20 (23.7 days).
Very high need	18%	2.55	**23.7**	60.4	30.3	
High need	**70%**	1	20.8	20.8		**Scenario 2:** 30% very high need
Very high need	**30%**	2.55	20.8	53.0	30.5	
High need	**95%**	1	20.8	20.8		**Scenario 3:** 5% very high need
Very high need	**5%**	2.55	20.8	53.0	22.4	
High need	82%	**0.25**	20.8	5.2		**Scenario 4 –** Aims to match Driessen et al, 2010, estimates of average LOS (53 days for patients with LOS equal or greater than 30 days and 14.9 days for the full study population) by changing the number of hospitalisations per year. However, the number of hospitalisations per year for the high need patients would have to be 0.75 to yield an average of 14.9 days LOS as reported in the study.
Very high need	18%	2.55	20.8	53.0	13.8	
High need	82%	**0.5**	20.8	10.4		**Scenario 5:** 0.5 hospitalisations for high need and 2 hospitalisations for very high need
Very high need	18%	**2**	20.8	41.6	16.0	
High need	82%	**1**	20.8	20.8		**Scenario 6:** 1 hospitalisation for all
Very high need	18%	**1**	20.8	20.8	20.8	

High need	82%	**0.312**	20.8	6.49	6.5	**Scenario 7:** Aims to match Fonia et al, 2010 estimate of average LOS (6.49 days) by changing the number of hospitalisations per year.
Very high need	18%	**0.312**	20.8	6.49		

Elements varied in sensitivity analysis are shown in bold; all of the variations result in a different estimate for number of bed days per annum applied in the model.

6.4.6 Cost-effectiveness results from the York model and subsequent appraisals

The cost-effectiveness results for the base-case analysis in previous NICE TAs in adults are summarised in Table 55, alongside the drivers of cost-effectiveness stated in the TAs documentation. The results reported for TA 134, 146, 180, 350 and 368 correspond to those in the company submissions.

Table 55 Summary of cost-effectiveness results and key drivers of cost-effectiveness for previous adult TAs

Appraisal	**Etanercept and efalizumab** **TA 103**	**Infliximab** **TA 134**	**Adalimumab** **TA 146**	**Ustekinumab** **TA 180**	**Secukinumab** **TA 350**	**Apremilast** **TA 368**
Base-case analysis results ICERs (/QALY)	Incremental analysis: ETA 25 mg vs BSC: £66,703 EFA: dominated ETA 25mg continuous: dominated ETA 50 mg vs ETA 25 mg : £1,035,121 ICER vs Supportive care: ETA 25 mg: £66,703 EFA: £84,018 ETA 25 mg continuous: £83,258 ETA 50 mg £120,855	Incremental analysis: - ETA 25 mg vs BSC: £8,044 -EFA: dominated - ETA 25mg continuous vs ETA 25 mg: £17,208 - ETA 50 mg: Extendedly dominated - INF vs ETA 25mg continuous: £ £26,095 ICER relative to supportive care: - INF: £22,240	Incremental analysis: (biologics only): ETA Intermittent: extendedly dominated ETA High Intermittent: extendedly dominated EFA: extendedly dominated ADA compared to BSC: £30,538 ETA: Dominated Infliximab: £147,906 ICER relative to supportive care: - MTX: £-29,759 - CS: £-25,135 - ETA Intermittent: £37,284 - ETA High Intermittent: £38,358 - EFA: £39,948 - ADA: £30,538	ICERs vs. supportive care: - EFA: £40,250 - ETA 25 mg intermittent: £30,111 - ETA 25 mg continuous: £34,281 - ETA 50 mg continuous: £35,964 - ADA: £31,022 - UST:£29,587 - INF: £39,153 ICER UST vs other treatments: - Supportive care: £29,587 - EFA: UST dominant - ETA 25 mg intermittent: £26,637 - ETA 25 mg continuous: UST dominant	Incremental analysis: ETA 25 mg BIW compared to BSC: £13,948[a] SEC compared to BSC: £2,464 ADA 40 mg: Dominated by SEC UST 45 mg: Dominated by SEC UST 90 mg: Dominated by SEC INF: Dominated by SEC	Apremilast sequence dominated the comparator sequence.

			- ETA: £37,676 - INF: £42,492	- ETA 50 mg continuous: UST dominant - ADA: UST dominant - INF vs. UST: £304,566		
Stated drivers of cost-effectiveness	Identified by scenario analysis in the AG report: - Source of utility gain by PASI response: use of estimates from subgroup with lower baseline HRQoL (higher DLQI) improves the cost-effectiveness of biologic drugs. - Inclusion of 21 days of hospitalisation on the costs of non-responders favours the cost-effectiveness of the more effective drugs	Identified by one way sensitivity analysis in the MS: - Non-responders' inpatient LOS - Mean patient weight in the model - Response rates to treatment for infliximab - Utility gain for responders	Identified by scenario analysis in the MS: - Source of utility gain by PASI response: use of estimates from subgroup with lower baseline HRQoL (higher DLQI) improves the cost-effectiveness of biologic drugs. - Annual length of inpatient stays for non-responders	Identified by one way sensitivity analysis in the MS: - Number of hospital days for BSC - Estimated cost of dosing for intermittent ETA 25 mg - SF-6D utility scores instead of EQ-5D (mapped from DLQI)	Identified by scenario analysis in the MS: - Costs assumed for BSC including hospitalisation costs, day care costs and, to a lesser extent costs of phototherapy. - Small changes in incremental health benefits between different biological treatments, thus ICERs could vary considerably with small QALY changes	Differences in costs (mostly because of hospitalisation LOS for those on BSC) and outcomes with APR compared with BSC were the main driver, given high assumed costs of BSC and the assumption of no PASI response for BSC

[a] ETA extendedly dominated by SEC.

ADA, adalimumab; AG, Assessment Group; APR, apremilast; BIW, twice weekly; BSC, Best supportive care; CS, cyclosporine; EFA, efalizumab; ETA, etanercept; ICER, incremental cost-effectiveness ratio; INF, infliximab; LOS, length of stay; MS, manufacturer's submission; MTX, methotrexate; SEC, secukinumab; SF-6D, Short Form–6 Dimension; UST, ustekinumab.

In the base-case full incremental analysis for TA 103, which compared etanercept in three dosing regimens (25 mg intermittent, 50 mg intermittent and 50 mg continuous), efalizumab and BSC, and with the assumed no hospitalisations for non-responders to biologic treatment, BSC was the most cost-effective strategy at cost-effectiveness thresholds below £66,703 per QALY gained. At a threshold equal or greater than £66,703 per additional QALY, intermittent etanercept 25 mg would be the cost-effective intervention, dominating (i.e. being less costly and more effective than) continuous etanercept 25 mg and efalizumab. Intermittent etanercept at 50 mg had an ICER exceeding £1 million per QALY gained compared to etanercept at a lower dose (25 mg intermittent).

Inclusion of 21 days of hospitalisation for the non-responders to biologic drugs, reduced the ICER of intermittent etanercept 25 mg compared to BSC to £29,420 per additional QALY. When in addition to the 21 hospitalisation days, the estimates of utility gains per PASI response were sourced from the subgroup of patients at the highest (worst HRQoL) quartile of baseline DLQI in the analysis (group with the highest gain in utility from improvement in PASI score), the ICER for intermittent etanercept 25 mg vs. BSC further reduced to £15,297 per QALY. In both these scenario analyses, continuous etanercept 25 mg and efalizumab remained dominated by intermittent etanercept 25 mg, while the ICER of intermittent 50 mg etanercept vs. 25 mg decreased but not sufficient to make it cost-effective at commonly accepted cost-effectiveness threshold ranges. In the secondary analysis that compared the full range of systemic therapies (namely, infliximab, methotrexate, cyclosporine and fumaderm) and assumed 21 days of hospitalisation for non-responders, methotrexate dominated all interventions including BSC, with the exception of infliximab. Infliximab was more costly and more effective than methotrexate but the resulting ICER for this comparison exceeded £1 million per QALY gained, with methotrexate emerging as the cost-effective intervention for this analysis.

Appraisals subsequent to TA 103 (TA 134, 146, 180, 350 and 368) all included a cost associated with hospitalisation stay for non-responders (LOS ranging from 10.7 to 26.6 days per annum). This generally resulted in more favourable cost-effectiveness estimates when biologic therapies were compared to BSC. Consistent with the findings of the York model, duration of hospitalisation for non-responders was identified as a key driver of cost-effectiveness for biologic therapies in psoriasis across these appraisals. The base-case analysis of the majority of the appraisals in adults sourced their estimates of utility gains by PASI response on a subgroup of lower baseline HRQoL (TA 134, 146, and 180) leading to higher QALY gains for the most effective drugs in terms of PASI response. This parameter can be considered the second driver of cost-effectiveness in the adult models.

The base-case cost-effectiveness results in the company submissions for infliximab, adalimumab and ustekinumab (TA 134, 146 and 180, respectively) place the ICERs for these drugs at the upper end of the currently accepted NICE cost-effectiveness threshold range, as long as the assumptions for HRQoL and costs of hospitalisation for non-responders referred above hold. The estimates of cost-effectiveness for secukinumab and apremilast presented by the manufacturers in TA 350 and 368 were considered overly optimistic by the NICE appraisal committees, and largely driven by the costs of BSC in non-responders to biologic therapy. These costs were considerably higher than in previous appraisals due to the assumption of a higher consumption of health care resources for non-responders in line with CG 153 (Table 54).

NICE recommended the following biologic treatments in adults with psoriasis: efalizumab, etanercept, infliximab, adalimumab, ustekinumab and secukinumab. With the exception of infliximab the biologic treatments were recommended for severe psoriasis defined as baseline PASI equal or greater than 10 and DLQI greater than 10 for patients who had previously failed or had a contraindication/intolerance to non-biologic systemic therapy. The recommendation for efalizumab further required that patients had failed on etanercept or had a contraindication/intolerance to the drug. Efalizumab is no longer marketed in the UK.

Infliximab was recommended only for very severe psoriasis defined as baseline PASI equal or greater than 20 and DLQI greater than 18 for patients who had previously failed or had a contraindication/intolerance to non-biologic systemic therapy. The recommendation for ustekinumab and secukinumab was conditional on Patient Access Schemes (PAS). The PAS for ustekinumab guarantees a flat price for ustekinumab 45 mg and 90 mg, so that the 90 mg dose is provided at the same price as 45 mg for patients weighing more than 100 kg, while the one for secukinumab consists of a confidential discount over the drug list price.

The NICE recommendations for all these biologic treatments require treatment termination if response is not produced at the end of the 'trial' period (12 weeks for etanercept and secukinumab, 10 weeks for infliximab and 16 weeks for adalimumab and ustekinumab). Treatment response is defined as achieving PASI 75 or PASI 50 accompanied by a five point reduction in DLQI from baseline.

6.5 Summary of the key areas of uncertainty in adult models and motivation for de-novo model in children and young people

There are no studies comparing the cost-effectiveness of biologic therapies for plaque psoriasis in children and young people. Furthermore, none of the companies participating in this appraisal have

submitted an economic evaluation. Our review of previous NICE TAs of plaque psoriasis in adults was conducted to examine existing decision-analytic models, and identified important structural assumptions, highlight key areas of uncertainty and the potential issues associated with generalising evidence from the adult population to a population of children and young people. In this section we summarise the key areas of uncertainty identified in adults in light of potential implications for the *de novo* model in children and young people.

Model structure

Although in clinical practice treatment with biologic therapy is expected to be sequential, i.e. patients are switched to further lines of biologic therapy upon failure of first line biologic; the majority of TAs did not consider treatment sequencing. Lack of evidence to inform treatment sequencing, especially on the efficacy of the treatments conditional on prior therapies received, appears to be the main reason for not formally modelling treatment sequences in all but one appraisal (TA 368). Given that there is very limited evidence to support the cost-effectiveness of sequential use of treatments in adults and that no evidence exists in children and young people (see Section 4), any attempt to model treatment sequences in the population of children and young people will be highly uncertain.

Clinical effectiveness evidence

Due to a lack of head-to-head trials comparing the treatments with each other, network meta-analysis was used to compare the treatments to each other indirectly. There was concern that not all trial populations matched those of the decision problem due to variation in the inclusion criteria, with some trials not explicitly excluding individuals who had not failed non-biologic systemic therapy. Placebo or best supportive care was not defined consistently across trials, which introduced heterogeneity in placebo response rates. Similar issues were identified in the clinical effectiveness evidence for children and young people (see Section 4), where the evidence base is even more sparse with only three RCTs and no common comparator across the trials. Section 5 describes how network meta-analysis was used to expand the evidence base in children and young people by drawing strength from the full network of evidence available for adults, while attempting to account for heterogeneity between trial populations (i.e. children and young people vs. adults) and placebo response rates.

Long-term response and withdrawal rates

To extrapolate data beyond the clinical trials, previous appraisals in adults have assumed that responders to treatment maintain their PASI response rate over time until treatment withdrawal. The same all-cause withdrawal probability of 20% per annum has been assumed for all biological

therapies in the absence of any long-term withdrawal data. Given the paucity of long-term data in children and young people, this parameter will also be uncertain in this population.

Health-related quality of life (HRQoL)

Most of the previous TAs in adults 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. Although some TAs applied EQ-5D data collected directly in RCTs, this was limited to data collected in the trials sponsored by the company and no evidence synthesis methods were used to synthesise the utility estimates. The estimates of utility gains from treatment were variable across subgroups of patients defined by baseline DLQI, with greater gains achieved for individuals with worse baseline HRQoL. The size of the utility gains in previous appraisals was considered to be largely uncertain and it represented a key driver of the cost-effectiveness results. It is expected that utility gains associated with treatment will also be highly uncertain in the population of children and young people due to an absence of EQ-5D values in this population. In Section 7, a review of HRQoL data in children and young people is reported. Scenario analyses will be used to explore the impact of uncertainty on the cost-effectiveness results.

Resource use and costs

The resource use and costs associated with best supportive care has been one of the key drivers of cost-effectiveness in adult appraisals. In particular, the duration and costs associated with inpatient hospitalisation stay for individuals who do not respond adequately to treatment has been highly uncertain. Until the publication of CG 153, the resource use and costs associated with BSC in adult TAs was largely informed by assumptions and expert opinion. The two TAs which followed the guideline (TA 350 and TA 368) used CG 153 but supplemented it with data from cohort studies that collected resource use data for patients treated for psoriasis with biologic treatments. However, the patient population in which the data was collected was likely to reflect a sicker population than that defined by the NICE scope for these appraisals, and the uncertainty associated with the estimates was not sufficiently explored. The search described in Section 6.2 did not identify any evidence on the resource use and costs of BSC in children and young people. The use of evidence in adults supplemented by clinical expert opinion to inform the costs of BSC in this population is discussed in depth in Section 7. Scenario analyses will be used to explore the implications of uncertainty in the assumptions used for BSC, particularly those in relation to hospitalisation length of stay, on the cost-effectiveness results.

Each of these areas of uncertainty are considered in more detail as part of the decision-analytic model developed to evaluate the cost-effectiveness of adalimumab, etanercept and ustekinumab in children and young people described in the next section.

7 Independent economic assessment

7.1 Introduction

The review of cost-effectiveness evidence in the population of children and young people and the absence of company models highlights the challenges of developing an economic model in this population. The fundamental challenge is the limited clinical evidence base for both short- and long-term outcomes to inform a model. Therefore, any estimation of the cost-effectiveness of biologics in children and young people will be subject to a number of uncertainties. These uncertainties cannot be avoided but a clear and transparent approach, which highlights the assumptions entering the economic model, can be pursued in order to help the decision maker come to an assessment regarding the cost-effectiveness of biologics in this population.

Plaque psoriasis is a chronic non-progressive disease, which manifests in children and young people in a similar manner to adults. The main difference between the younger population and adults is the presence of co-morbidities in adults (such as high blood pressure, liver impairment and renal impairment), which tend to make adults less well with psoriasis compared to a younger population. Currently, there is no treatment pathway specific to psoriasis in children and young people in the UK. The management and approach to care of treatment seems to mirror that used in adults. Our clinical advisor, Dr Ruth Murphy, indicated that where there is an absence of evidence it would be reasonable to extrapolate data from the adult population to children and young people. The company submission for ustekinumab also supports this approach for the development of an economic model given that there are few significant differences in the posology or management of chronic plaque psoriasis in children, young people and adults.

Management and treatment of plaque psoriasis depends on the extent and severity of an individual's disease, local custom and practice. If an individual patient does not respond to or tolerate a particular treatment option, an alternative one is usually tried. This means that treatments are usually 'trialled' on an individual basis until an effective option is found. If an effective treatment is not found, then a patient will receive some form of best supportive care. This approach to treatment appears to be the same for children and young people and adults, but usually more caution is exercised in the younger population due to the limited availability of licensed treatment options.

The trialling of treatments upon treatment failure, or intolerance, suggests that sequences of treatments is a consideration for the cost-effectiveness model, whereby after failure of a first treatment option patients would then be trialled on a second option, and so on, until all options are exhausted. However, this would require additional clinical evidence on the efficacy of the treatments conditional on prior therapies received. There is very limited evidence to support the cost-effectiveness of sequential use of treatments in adults and no evidence exists in children and young people (see Section 4). Therefore, although the model should ideally explore the sequential use of treatments, any attempt in the population of children and young people would be highly uncertain. Furthermore, the optimum treatment sequence may not be suitable for an individual patient with specific characteristics and where treatment in this population is usually tailored to the child or adolescent due to needle phobia or the presence of psoriatic arthritis. Therefore, an alternative approach may be better whereby the optimum ordering of treatments, in terms of their cost-effectiveness, is established. This is achieved by comparing each of the alternative treatment options to BSC and then indicating the most cost-effective order in which to give the therapies based on total expected costs and QALYs associated with each treatment option.

The previous York model appears to be the most widely accepted model of chronic plaque psoriasis. The five NICE TAs which followed TA 103 for the treatment of moderate to severe psoriasis in adults (infliximab TA 134, adalimumab TA 146, ustekinumab TA 180, secukinumab TA 350 and apremilast TA 368) have followed the framework of the York model and these have been accepted by NICE as relevant to plaque psoriasis. The main changes which have followed since the advent of the York model has been the availability of new evidence, the methodology for linking efficacy estimates to health-related quality of life utility values, the parameters used in the model to inform BSC, updated unit costs, time on treatment, and the modelling of treatment sequences in the most recent appraisal of apremilast. It would therefore seem appropriate that the same modelling framework is used for children and young people but with an evidence base informed by outcomes in the younger population. Hence, the structure of the model is very similar to that used in previous TAs in adults and, where evidence is lacking or limited in the population of children and young people, data has been extrapolated from the adult population and supplemented by expert opinion.

7.2 Decision problem and patient population

The decision problem addresses the cost-effectiveness of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people. The population in the model reflects the marketing authorisation of the three interventions. However, the marketing authorisation

for the use of each of the interventions in this population differs by age and severity of psoriasis at baseline, but also in terms of the positioning of the biologic in the pathway of care. A stepwise approach to treatment for the management of plaque psoriasis is usually pursued where topical therapies are offered as first-line treatment following by phototherapies and/or systemic non-biological therapies such as methotrexate as second-line treatment, and then biological treatments are offered as third-line where previous therapies are found to be ineffective. However, adalimumab is licensed in a paediatric population for individuals who have an inadequate response to, or who are inappropriate candidates for, topical therapy and phototherapies, whereas etanercept and ustekinumab are licensed for individuals inadequately controlled by, or intolerant to, other systemic therapies or phototherapies. Therefore, adalimumab is the only biologic treatment indicated in the population of children and young people who have not failed prior systemic therapies.

The biologic interventions also differ in their marketing authorisation by age and severity of psoriasis (see

Figure **9**). Both adalimumab (age ≥4 years) and etanercept (age ≥6 years) are indicated for younger ages and severe psoriasis, whereas ustekinumab is indicated for an adolescent population (age ≥12 years) and moderate to severe psoriasis. The definition of severity also differs in the corresponding trials of the biologics in children and young people (see Table 56). In adults, severe psoriasis is defined by a total PASI score of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10. However, there is not a clear consensus on the definition of moderate or severe psoriasis in children and young people. This is partly due to the fact that PASI has not been validated as a disease severity assessment tool for use in this population and no other tool is available. Mean PASI scores at baseline in the trials were 18.6 for etanercept, 18.3 for adalimumab and 21.1 for ustekinumab. Therefore, although the license for ustekinumab is moderate to severe psoriasis, patients in the CADMUS trial (ustekinumab) had disease severity more comparable to patients in study 20030211 (etanercept) and M04-717 (adalimumab) with severe disease. Hence, the population in the model is chosen to reflect severe psoriasis as defined by the baseline characteristics of the trial populations in children and young people.

Figure 9 Licensed age and severity of biologic therapies in children and young people

Table 56 Definition of disease severity in the trial populations for children and young people

Etanercept	Ustekinumab	Adalimumab
License: Severe chronic plaque psoriasis Trial population: Moderate to severe plaque psoriasis with - Baseline PASI≥12, PGA≥3 and involvement ≥10% of BSA	License: Moderate to severe plaque psoriasis Trial population: Moderate to severe plaque psoriasis with - Baseline PASI≥12, PGA≥3 and involvement ≥10% of BSA for ≥6 months	License: Severe chronic plaque psoriasis Trial population: Severe plaque psoriasis with – Baseline PASI≥20, PGA≥4, involvement ≥20% of BSA or very thick lesions and ≥10% of BSA – or baseline PASI≥10 and one of the following: • Active psoriatic arthritis non-responsive to NSAIDS nonsteroidal • Clinically relevant facial involvement • Clinically relevant genital involvement • Clinically relevant hand or foot involvement • CDLQI>10

In order to reflect the differences in marketing authorisation by age and positioning of treatment in the pathway, the base case cost-effectiveness analysis considers three separate populations:

4. Before systemic therapy – Children and young people **aged 4-17 years** with **adalimumab** as the only licensed intervention for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **topical therapy and phototherapies, i.e. as an alternative to systemic therapies.**
5. After systemic therapy (1) – Children and young people **aged 6-11 years** with **adalimumab** and **etanercept** for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **systemic therapies or phototherapies.**
6. After systemic therapy (2) – Children and young people **aged 12-17 years** with **adalimumab, etanercept** and **ustekinumab** for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **systemic therapies or phototherapies.**

The population aged 4-5 years with adalimumab as the only licensed intervention for the treatment of severe plaque psoriasis after systemic therapy was not considered as a separate population because no children under 6 years were included in the adalimumab trial (M04-717); therefore efficacy estimates for this age group were assumed to be the same as those for ages 6-11 years, which results in similar cost-effectiveness estimates for adalimumab compared to best supportive care for ages 6-11 years.

The starting age used in the model is 4 years, 6 years and 12 years for the populations above, respectively. The time horizon of the model extends until individuals reach 18 years of age. At this point, the population becomes adults and separate NICE recommendations for the use of the interventions in adults apply. The difference in marketing authorisation of the interventions by age inevitably means that the time horizon of the model will differ according to population. In order to explore the impact of the time horizon, a separate scenario analysis is presented which considers a common time horizon of 14 years for all populations. The time horizon of 14 years (which is greater than the time horizon of 10 years used in previous TAs in adults) is sufficient to capture differences in costs and effects between the interventions under comparison.

7.3 Intervention and comparators

The interventions considered in the cost-effectiveness analysis are adalimumab, etanercept and ustekinumab within their marketing authorisation. The following comparators were considered in the NICE scope:

- Non-biological systemic therapy (including, but not limited to, cyclosporine 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)
- When appropriate, adalimumab, etanercept and ustekinumab will be compared with each other.

Due to the positioning of adalimumab in the stepwise management of psoriasis, non-biological systemic therapy is only a relevant comparator for adalimumab since it is the only licensed

intervention representing an alternative to systemic therapy; etanercept and ustekinumab are licensed for individuals who are inadequately controlled by, or intolerant to, prior use of systemic therapies. Standard systemic therapies such as methotrexate, cyclosporine and acitretin are not licensed for psoriasis in children and young people. However, it is evident from the UK audit of the assessment and management of psoriasis in children that 19% of children have received systemic drugs (9% methotrexate, 5% acitretin, 4% cyclosporine and 1% dapsone) outside their licensed indication [135,Burden-The,2015]. The non-biologic systemic therapy considered as a comparator in the cost-effectiveness analysis for adalimumab is methotrexate since it is the most widely used systemic in the population of children and young people and was used as a comparator in study M04-717.

If biological treatments are found not to be effective, individuals are usually offered some form of best supportive care (BSC) rather than no treatment. Therefore, BSC is considered a relevant comparator for individuals who have exhausted all treatment options including conventional systemic therapy and phototherapy. BSC tends to include a mix of active non-biologic systemic therapies such as methotrexate and cyclosporine and palliative care, including phototherapy, even though these treatments may have been proven to be largely ineffective.

The interventions of etanercept, adalimumab and ustekinumab are compared with each other as appropriate to the licensed population. The use of these interventions outside of the age constraints of their license (e.g. the use of etanercept in children under 6 years and ustekinumab in children under 12 years) is considered a relevant comparator in a scenario analysis. The use of other off-label biological treatments such as infliximab outside of its licensed indication in adults is not considered. Advice from our clinical expert suggests that it is very unlikely that an unlicensed TNF inhibitor would be used as an alternative to a biological treatment that is licensed and available in this population. Furthermore, there are no RCTs comparing the use of infliximab to any comparator (or placebo) in the population of children and young people. Infliximab also requires the need for intravenous infusion in hospital and clinical opinion suggests that this is not a favourable option in this young population.

The biosimilar of etanercept, namely Benepali 50 mg, is not licensed for use in children and young people. Therefore, the biosimilar is not considered a relevant comparator in the base case analysis. However, a scenario analysis is considered where the drug cost of etanercept is reduced by approximately 10% to match the cost of Benepali in adults (£164.00 per pre-filled syringe). [136,

The drug doses for the intervention and comparators considered in the cost-effectiveness analysis are shown in

Table **57**. These are based on licensed doses for etanercept, adalimumab and ustekinumab and expected doses for methotrexate and BSC. Continuation of treatment is conditioned on response to treatment at the end of the trial period, which corresponds with the time point specified in the SmPC for children and young people. For etanercept and adalimumab, this corresponds to 12 and 16 weeks, respectively. For ustekinumab, the SmPC specifies that consideration should be given to discontinuation if no response up to 28 weeks. In the analysis, the time point for response with ustekinumab was taken to be 16 weeks corresponding to its administration at 12 weeks after the dose given at 4 weeks. This also corresponds to the same time point that was used to assess response with ustekinumab in adults (TA 180). [85] It is assumed that all treatments are used continuously in responders to treatment, until treatment withdrawal. Cyclosporine (used as part of BSC) is assumed to have a maximum treatment duration of 2 years.

Table 57 : Licensed or guideline doses used in the economic analysis

Treatment	Dose	Response assessment
Etanercept	0.8mg/kg up to a maximum of 50 mg weekly for up to 24 weeks	12 weeks
Adalimumab	0.8mg/kg up to a maximum of 40 mg at weeks 0 and 1, then every 2 weeks thereafter	16 weeks
Ustekinumab	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	16 weeks
Methotrexate	0.1-0.4 mg/Kg weekly	16 weeks
Cyclosporine (as part of BSC)	2-5 mg/Kg daily for up to 2 years	Not applicable

7.4 Methods

7.4.1 Overview

A de novo decision analytic model was developed to estimate the cost-effectiveness of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people. The cost-effectiveness model consists of a Markov cohort transition model developed in Microsoft Excel (2013). The structure of the model is very similar to that used in previous TAs for moderate to severe plaque psoriasis in adults. The model has been developed in accordance with the NICE reference case. The time horizon of the model extends until individuals reach 18 years of age, where they then become adults and current NICE recommendations for the use of the interventions in adults apply. The length of the time horizon varies by the starting age of individuals in the model. As indicated above, three starting ages are considered in the model to reflect the restrictions of the marketing authorisation of the interventions.

Outcomes of the model are expressed using quality adjusted life years (QALYs). The QALY provides a summary measure combining estimates of remaining length of life (life-years) with its associated quality of life. QALYs are derived by multiplying a utility value (quality of life) by the time spent with this utility (length of life). The utility values used in the model are generated via a mapping algorithm from trial collected PedsQL data to EQ-5D. The utilities associated with treatment are based on the proportion of individuals in the different PASI response categories (see Section 7.4.6). All costs are considered from the perspective of the National Health Services and Personal Social Services (NHS & PSS). Healthcare resource use and cost categories include cost of treatment (acquisition, administration, monitoring and adverse event costs) and changes in health service resource utilisation due to loss of response to treatment (see Section 7.4.12).

The parameters of the model were sourced from published literature, information reported in the company submissions and the results of the evidence synthesis described in Section 5. Both costs and QALYs are discounted at 3.5% per annum, in line with current NICE guidance. [137]

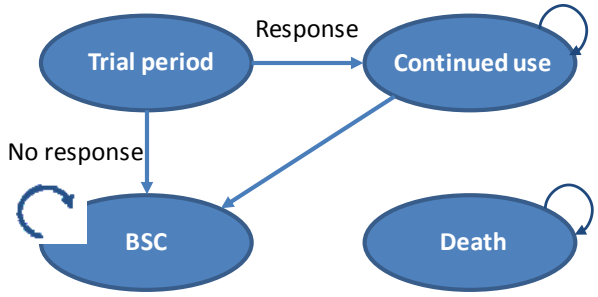
7.4.2 Model structure and assumptions

The model consists of four health states: 'Trial period', 'Continued use', BSC and death (**Figure 10**). Individuals enter the model in the trial period and receive one of the three biologic interventions or a relevant comparator. The length of the trial period is dependent on the intervention and can last from 12 weeks for etanercept to 16 weeks for adalimumab and ustekinumab, corresponding to the time point at which response to treatment is assessed. The cycle length in the model corresponds to 28 days (4 weeks), which takes account of the different lengths of time spent in the trial period.

At the end of the trial period, individuals are assessed as responders or non-responders to treatment based on PASI response rates. PASI response in the base-case analysis is taken to be PASI 75, i.e. response is assessed based on whether an individual achieves a 75% reduction in baseline PASI score. Individuals who do not have an adequate response to treatment at the end of the trial period, move to the health state of BSC. Individuals who are considered responders to treatment transition to the health state of continued use, where they remain in this state until they withdraw from treatment and move to BSC. During the period of continued use, individuals continue to receive the active therapy and are assumed to maintain their level of PASI response until treatment discontinuation due to any cause, such as lack of efficacy, the presence of adverse events or non-compliance to treatment (modelled together as an overall risk of all cause withdrawal).

Upon treatment discontinuation (in either the trial period or continued use state), individuals transition to BSC. BSC consists of non-biologic supportive therapies. The only transition out of the BSC state is death. 'Death' is an all-cause mortality state to which transition is possible from any health state. Mortality is not conditioned on treatment or treatment response. Mortality rates by age were sourced from life tables in England and Wales for the years 2013-15[138] and averaged across gender.

Figure 10 Schematic of model structure



7.4.3 Effectiveness data

The measure of treatment effectiveness used in the model is the proportion of individuals achieving a specific threshold of PASI response relative to baseline. Relative change in PASI response is the most widely reported outcome in clinical trials and has been used as the main outcome in previous models in adults. The PASI response rates used in the model are taken directly from children and young people efficacy estimates of the network meta-analysis which incorporates *all relevant adult evidence* (Section 5.4). Scenario analyses are also conducted where the results from the unadjusted baseline

constrained model with *minimum* adult evidence (Section 5.4) are applied in the model, as well as artial comparisons with direct trial data and the indirect comparison (Section 5.3) are also incorporated in scenario analysis for completeness.

In the base case analysis, PASI 75 response rates are taken as the measure of effectiveness for treatment continuation. Individuals who meet the threshold of PASI 75 are classified as responders at the end of the trial period and assumed to maintain their response for as long as they are in the health state of continued use. In a separate scenario analysis, the threshold of PASI 50 is taken as the measure of effectiveness for treatment continuation.

PASI response rates from the NMA are also used in the model to inform the HRQoL utility values. Gains in utility associated with treatment are conditioned on PASI response rates (see Section 6.4.4), an approach which has been taken in previous models for the treatment of psoriasis in adults. PASI response rates for BSC are assumed to be equivalent to placebo in the NMA.

In the absence of data to model time-varying transition probabilities, response rates are assumed to be constant per cycle in the model. The response rates used to inform the model are presented in Table 70. The uncertainty in the predicted response rates from the NMA is reflected in the model by directly exporting the simulated posterior distributions from the Markov Chain Monte Carlo analysis in WinBUGs to the cost-effectiveness analysis, preserving any correlations in the data.

7.4.4 Treatment withdrawal rates

Responders to treatment are assumed to maintain their response until treatment discontinuation. Discontinuation is modelled as an overall risk of withdrawal due to any cause, such as lack of efficacy, the presence of adverse events or non-compliance to treatment. Previous TAs in adults assumed a constant withdrawal rate of 20% per annum for all treatments.

A literature search described in Section 4 was conducted with the aim of identifying registry data on long-term treatment response to biologics in children and young people with psoriasis. Two registries were identified: the Child-CAPTURE (Netherlands) and DERMBIO (Denmark). However, none of the published studies from these registries allowed the estimation of long-term withdrawal rates in individuals who are responders to treatment and also the DERMBIO registry included only a small number of children. The data indicated that there was no significant predictive relationship between age and treatment continuation, which may suggest that treatment withdrawal rates used in the adult population can be extrapolated to children and young people in the absence of any alternative source

of data. Data from the DERMBIO registry suggests that the withdrawal rate on biological therapies is constant over the treatment period (with no obvious plateau), which supports the use of a constant withdrawal rate over time.[78`]

A recent study on the long-term drug survival rates of four biologics (adalimumab, etanercept, infliximab and ustekinumab) based on data from the UK BADBIR audit of 3,523 biologic naïve adult patients indicates that loss of efficacy is a major reason for treatment discontinuation, decreasing from 77% in the first year to 53% in the third year of use. [80] This is consistent with a withdrawal rate of 20% per annum, which has been used in previous TAs of adults. This study also suggests that there may be differences in the withdrawal rate by treatment, with ustekinumab having a significantly higher survival rate compared to adalimumab and etanercept. However, the study does not distinguish between discontinuation due to a lack of treatment response in the short-term, i.e. during the initial trial period, and the long-term for patients who are responders to treatment. Therefore, the differences in withdrawal rates by treatment may reflect the higher efficacy of ustekinumab compared to adalimumab and etanercept, rather than reflecting differences between the treatments conditional upon response at the initial assessment point.

In the absence of sufficient evidence on the long-term withdrawal rates in children and young people, and given that observational data generally suggests that a constant 20% annual withdrawal rate is a reasonable assumption in adults, the same withdrawal rate was assumed in the model (this rate equates to a 28-day discontinuation rate of 1.70% per cycle).

7.4.5 All-cause mortality

All-cause mortality is incorporated in the model by applying a risk of death during each cycle. The mortality risk is assumed to be independent of response status or treatment received. A common mortality risk is thus assumed for all patients based on the general population mortality risks. The general population mortality risk is obtained from gender specific life tables for England and Wales for the period between 2013 and 2015 and is averaged across males and females assuming equal proportion.[138]

7.4.6 Health-related quality of life

7.4.6.1 Review of utility data in children and young people with psoriasis

A systematic literature review was conducted to identify utility values for plaque psoriasis in children and young people. The aim of the search was to identify any studies that reported utility values or

other measures of HRQoL that could be converted into utility values specifically for the population of children and young people. The search criteria were not restricted to biological treatment or level of disease severity since a dearth of evidence in this population was anticipated. The Health Economics Research Centre (HERC) database of mapping studies from the University of Oxford [139] was also searched to identify any suitable mapping algorithms which would allow conversion of clinical measures routinely collected in studies of psoriasis in children and young people into utility values.

The search did not identify any studies that reported utility values collected in children and young people with psoriasis. The search on the HERC mapping algorithm database identified one study on the development of a mapping algorithm to estimate EQ-5D youth (EQ-5D-Y) utility values from PedsQL general core scales (GSC), Khan et al, 2014. [140]. PedsQL is a generic instrument for measuring HRQoL in children and adolescents and those with acute and chronic health conditions. PedsQL measures core dimensions of health as delineated by the World Health Organisation, as well as role (school) functioning. The four multidimensional scales are physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items).[18] EQ-5D-Y is the youth version of the EQ-5D, which has been specifically adapted in terms of language for children aged 8-11 years and for adolescents aged 12-18 years.

Khan and colleagues [140] assessed different mapping methods for estimating EQ-5D-Y health utilities from PedsQL response scores. The study used data collected in a cross-sectional survey conducted in four secondary schools in England amongst children aged 11–15 years. The sample on which the mapping models were estimated included 559 children and the validation sample comprised 337 children. Children in the full study sample (n=896) were on average 13.3 years old (SD 1.3), 54% were male and approximately 40% were of non-white ethnicity. The authors explored both direct and response mapping approaches to predict EQ-5D-Y utility values, as well as a number of functional forms including ordinary least squares (OLS) regression, generalised linear models, two-part logit-OLS regression, Censored Least Absolute Deviations (CLAD) and Tobit regression. Model performance was assessed on the validation sample and models were re-estimated on the full study sample. Table 58 presents the two best fitting models for the mapping algorithm. These correspond to the models estimated using OLS regression with i) age and gender terms included as regressors; and ii) excluding age and gender terms as regressors.

Table 58 Best fitting mapping algorithms from PedsQL to EQ-5D-Y from Khan et al, 2014[140]

Mapping algorithm	**OLS regression with gender and age terms (1)**		**OLS regression without gender and age terms (2)**	
Variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Age (years)	-0.006136	0.004741	-	-
Gender	-0.009385	0.012292		
PedsQL domain scores				
Physical functioning (PF)	0.009067	0.002571	0.009127	0.002568
Emotional Functioning	0.006807	0.002533	0.006611	0.002530
Social Functioning (SF)	0.00563	0.002831	0.005705	0.002829
School Functioning (SchF)	0.005802	0.002371	0.006011	0.002367
Quadratic terms				
PF squared	0.00002	0.000025	0.00002	0.000025
EF squared	-0.000049	0.000018	-0.000048	0.000018
SF squared	0.000011	0.000016	0.000011	0.000016
SchF squared	-0.000017	0.000015	-0.000017	0.000015
Interaction terms				
PF x EF	-0.000005	0.000027	-0.000004	0.000027
PF x SF	-0.000053	0.000029	-0.000055	0.000029
PF x SchF	-0.000066	0.000030	-0.000066	0.000030
EF x SF	-0.000011	0.000023	-0.000009	0.000023
EF x SchF	0.000061	0.000021	0.000059	0.000021
SF x SchF	-0.000026	0.000022	-0.000027	0.000022
Constant	-0.335861	0.118035	-0.428496	0.094210

The two mapping algorithms were considered to have similar prediction accuracy for the mean EQ-5D-Y. Model 1 which included age and gender as regressors had a better fit across a wider range of EQ-5D-Y values than model 2. Model 2 reported better fit for the EQ-5D-Y utility score range of 0.8–1.0 category. There are a number of potential limitations to the use of these algorithms to predict EQ-5D-Y utilities. The sample on which the algorithms were estimated consisted of healthy children aged 11 to 15 years old, which may limit the predictive accuracy in sicker populations or outside this age range. The authors recognise that there is need for further validation and testing of the algorithm but in the absence of an alternative source it remains a useful tool for estimating EQ-5D-Y utility values in situations where only the PedsQL has been administered.

7.4.6.2 Utility data reported in company submissions

HRQoL assessments were collected in study 20030211 (etanercept), CADMUS (ustekinumab) and M04-717 (adalimumab) using the Children's Dermatologic Life Quality Index (CDLQI) and the PedsQL at selected time points. EQ-5D or EQ-5D-Y values were not collected in any of the trials. Therefore, the only possibility to include EQ-5D utility values in the model is via a mapping from either CDLQI or PedsQL. The literature review described above did not identify any studies that estimated the relationship between CDLQI and EQ-5D, while the study by Khan et al (2014) was the only study that estimated the relationship between PedsQL and EQ-5D. [140] The Assessment Group (AG) requested from the companies access to individual level patient data (IPD) for PedsQL domain scores at baseline and follow-up by category of PASI response, and PedsQL summary scores at the domain level by response category. The AG did not receive access to IPD; however, Janssen (ustekinumab) submitted aggregated summary data (mean and standard deviation) from the CADMUS trial for PedsQL subscale and total scale scores by treatment arm (placebo and ustekinumab standard dose) and PASI response categories at 12 weeks (<50, 50-75, 75-90, ≥90) for baseline,12, 28 and 52 weeks. [141]

7.4.6.3 Utility estimates used in the model

The utility values associated with treatment in previous models in adults have been based on the proportion of individuals in the different PASI response categories (<50, 50-75, 75-90, ≥90) and the change in utility from baseline associated with the PASI response category. Therefore, PASI response rates from the NMA are assumed to be a perfect proxy for change in utility arising from treatment.

The relationship between utility and PASI response was estimated in previous TAs in adults using either DLQI data mapped onto EQ-5D utility values or via direct EQ-5D data collected in the trials. In the population of children and young people, the only possibility of obtaining EQ-5D values is via the mapping algorithm from PedsQL to EQ-5D-Y described above. Without access to the IPD, which would allow full uncertainty to be reflected in the values, the mapping algorithm was applied to the summary scores at the domain level from the CADMUS trial.

Validation of the algorithm was performed by examining data reported in a study by Varni et al (2012), which compared self-reported HRQoL (based on PedsQL scores) among paediatric patients with moderate to severe plaque psoriasis with a healthy sample. [142] The sample used to represent the

psoriasis population corresponded to individuals in the main efficacy trial for etanercept (n=208, age 4 to 17 years) and measurements of PedsQL at baseline were pooled across the two treatment arms (etanercept and placebo). The healthy population sample was taken from a US children's health insurance program evaluation (n=5,079) open to children and young people aged 2 to 16 years old. Table 59 summarises the PedsQL subscale scores reported in Varni et al for the psoriasis and healthy population, alongside the estimates obtained by applying the two best fitting mapping algorithms to obtain EQ-5D-Y utility values (model 1 includes age and gender terms, while model 2 excludes these variables).

Table 59 Application of mapping algorithm to estimate EQ-5D-Y utilities in paediatric populations

	Psoriasis population N=208			**Healthy population N=5,079**		
	Mean	**EQ-5D-Y model 1**	**EQ-5D-Y model 2**	**Mean**	**EQ-5D-Y model 1**	**EQ-5D-Y model 2**
Age (years)	12.71	0.869	0.864	9.72	0.936	0.913
Gender[a]	0.519			0.517		
Physical functioning	82.5			87.8		
Emotional Functioning	67.1			79.2		
Social Functioning	80.7			85		
School Functioning	70.2			70.2		
PedsQoL total score	75.5			83.9		

[a] Assumes that the reference category is female

The EQ-5D utility estimates are higher in the healthy population compared to the population with psoriasis irrespective of the model used to map PedsQL to EQ-5D-Y. The distinction between the models is minimal, especially in the psoriasis population: model 1 provides slightly higher utility values compared to model 2 (0.6% and 2.5% higher in the psoriasis and healthy populations, respectively). Model 2 was subsequently used in the base-case analysis since the reference category for the variable gender was unclear in Khan et al (2014). [140]

The mapping algorithm (model 2 in Table 58) was used to estimate change in EQ-5D-Y utility values from baseline based on PedsQL data from the CADMUS trial (ustekinumab) at baseline and 12 weeks

follow-up (the time point at which response to treatment was assessed in the trial and blinding of randomised subjects in the trial was terminated; after this point cross-over between treatment arms was possible). The mean change in EQ-5D-Y between baseline and week 12 was estimated for individuals with different levels of PASI response. Table 60 reports the EQ-5D-Y utility values estimated for the base-case-analysis, with placebo and treatment arms pooled.

Table 60 Baseline utility and mean change in utility by PASI response estimated based on CADMUS PedsQL data mapped onto EQ-5D-Y

	Utility increment at the end of trial period			
Baseline utility[a] (n=73)	**PASI<50 (n=30)**	**PASI 50-75 (n=10)**	**PASI 75-90 (n=9)**	**PASI ≥90 (n=24)**
0.8596	0.0036	0.0255	0.0340	0.0810

[a]Estimated by pooling the EQ-5D-Y utility values at study baseline of patients in the ustekinumab 0.75 mg/Kg and placebo arms of CADMUS

The baseline utility estimate is similar to that derived from study 20030211 for etanercept (0.864 in Table 59) and is lower than the general healthy population estimate of 0.913 based on Varni et al (2012). [142]. The mean change in EQ-5D utility from baseline by PASI response categories is much smaller than that observed in previous TAs of adults. For example, the EQ-5D changes in utility by PASI response categories in the York model of adults were 0.05 for PASI <50, 0.17 for PASI 50-75, 0.19 for PASI 75-90 and 0.21 for PASI ≥90.

In order to examine whether the magnitude of change in EQ-5D-Y was accompanied by similar changes in other measures of HRQoL in the population of children and young people, the change in EQ-5D-Y was compared with reported CDLQI values by PASI response (Table 61). A comparison of EQ-5D and DLQI values by PASI response in adults is also shown in Table 61 (taken from TA 180 for ustekinumab, which was the only TA in adults which reported both outcomes). [85] The mean change in CDLQI by PASI response in the CADMUS trial is much smaller than the mean change in DLQI in TA 180, which is consistent with the smaller mean change estimated for EQ-5D-Y in the paediatric population compared to EQ-5D in adults. These differences, however, should be interpreted with caution since CDLQI and DLQI scores are not directly comparable and the number of observations is much smaller in the population of children and young people compared to the sample of adults in TA 180.

Table 61 Mean change from baseline in CDLQI/DLQI and EQ-5D/Y by PASI response

	CADMUS trial			TA 180		
	Sample size, n	**Mean change in CDLQI**	**Mean change in EQ-5D-Y**	**Sample size, n**	**Mean change in DLQI**	**Mean change in EQ-5D[a]**
PASI<50	30	[redacted]	0.0036	430	-2.5	0.04
PASI 50-75	10	[redacted]	0.0255	160	-10.3	0.17
PASI 75-90	9	[redacted]	0.0340	207	-13.4	0.22
PASI ≥90	24	[redacted]	0.0810	318	-15.3	0.25

[a]Pooled EQ-5D data collected in the Phoenix trials

The EQ-5D-Y utility estimates suggest that improvements in HRQoL associated with reductions in PASI response rates are of a much smaller magnitude in children and young people compared to adults; however, the evidence is highly uncertain due to the small sample size and the limited data available to validate the findings. In the absence of an alternative source to estimate EQ-5D values for the model, this is used in the base-case analysis. However, it is important to highlight a number of limitations with this approach. Firstly, the use of a mapping algorithm to estimate utilities introduces uncertainty compared to direct EQ-5D measurement. Secondly, the Khan et al (2014) mapping algorithm has not been validated in children younger than 11 years old or in a population with psoriasis. [140] Thirdly, the CADMUS trial from where the PedsQL data mapped to EQ-5D was sourced excluded children younger than 12 years; therefore, it remains uncertain whether the mapped utilities are reflective of children younger than 12 years old. Fourthly, in populations younger than 12 years, there may be issues with lack of agreement or consistency between self-reported and proxy (parent)-reported measurements. [143] Therefore, even if PedsQL data were available for younger children, the mapping algorithm might not consistently perform for self-reported and parent-reported measurements of the instrument. These limitations reduce the robustness of the utility estimates used in the model.

Given the uncertainty surrounding the utility estimates for children and young people, scenario analyses are conducted using utility estimates from previous TAs in adults for etanercept, adalimumab and ustekinumab. Table 62 summarises the utility estimates considered in the scenario analyses.

Table 62 Baseline utility values and mean change in EQ-5D by PASI response used in the base-case and scenario analysis

	Baseline utility	Utility gain by PASI response category			
		PASI<50	PASI 50-75	PASI 75-90	PASI ≥90
Base-case analysis	0.0036	0.0255	0.0340	0.0810	0.0036
TA103 utility values	0.7**	0.050	0.170	0.190	0.210
TA146 utility values*	NR***	0.063	0.178	0.178	0.308
TA180	0.692*	0.04	0.17	0.22	0.25

*DLQI>10; **Based on Revicki et al (2008), [130] as it was not reported in the TAs; ***Constrained to this value, so that the absolute utility valuewould not go above one for patients undergoing the maximum utility increment.

7.4.7 Utility estimates by health state

The HRQoL utility values are applied in the model based on PASI response to treatment. The utility values in the 'trial period' and period of 'continued use' for each treatment is based on the proportion of individuals in the different PASI response categories (<50, 50-75, 75-90, ≥90) and the change in utility from baseline associated with PASI response. During the trial period, individuals are assigned utility values based on treatment response at the end of the trial period:

$$u_{trt}^{TP} = [u_{00} \times (1 - p_{trt}^{PASI50}) + u_{50} \times (p_{trt}^{PASI50} - p_{trt}^{PASI75}) + u_{75} \times (p_{trt}^{PASI75} - p_{trt}^{PASI90}) + u_{90} \times (p_{trt}^{PASI90})]$$

where u_{00}, utility gain for individuals not achieving a PASI 50 response; u_{50}, utility gain for individuals achieving a PASI 50 response but not a PASI 75 response; u_{75}, utility gain for individuals achieving a PASI 75 response but not a PASI 90 response; u_{90}, utility gain for individuals achieving ≥ PASI 90 response; p_{trt}^{PASIxx}, probability of a PASI XX response with treatment.

During the period of continued use, individuals are assigned utility values based on maintaining treatment response at the end of the trial period, which is based on meeting the minimum of a PASI 75 response:

$$u_{trt}^{CU} = [u_{75} \times (p_{trt}^{PASI75} - p_{trt}^{PASI90}) + u_{90} \times (p_{trt}^{PASI90})]/p_{trt}^{PASI75}$$

Individuals who discontinue treatment progress to BSC. The utility associated with BSC is based on the proportion of individuals in the different PASI response categories (<50, 50-75, 75-90, ≥90) for BSC (assumed equal to placebo response from the NMA):

$$u_{BSC} = [u_{00} \times (1 - p_{BSC}^{PASI50}) + u_{50} \times (p_{BSC}^{PASI50} - p_{BSC}^{PASI75}) + u_{75} \times (p_{BSC}^{PASI75} - p_{BSC}^{PASI90}) + u_{90} \times (p_{BSC}^{PASI90})]$$

A scenario analysis is considered where the utility of individuals in BSC is set equal to baseline utility, i.e. there are no health benefits from BSC.

On entering the death state, individuals are assigned a utility value of zero. **Table 63** summarises the utility estimates applied in the base-case analysis by treatment and health state.

Table 63 Utility values by treatment and health state used in the base-case analysis

Treatment	Health state in model		
	Trial period	**Continued use**	**BSC**
Adalimumab	0.9156	0.9261	0.8713
Etanercept	0.8974	0.9177	0.8713
Ustekinumab	0.9186	0.9274	0.8713
Methotrexate	0.8994	0.9164	0.8713
BSC	-	-	0.8713

Given the paucity of evidence on adverse events in children and young people undergoing biological treatment for psoriasis and similarly to the majority of previous TAs in adults, no disutility from treatment was applied in the model.

7.4.8 Resource utilisation and costs

Resource use and costs included in the model correspond to direct NHS costs and include: treatment acquisition costs, administration costs, monitoring costs, costs associated with adverse events, and cost of BSC. Costs were sourced from NHS Reference Costs 2014-15, Monthly Index of Medical Specialities (MIMS), British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and published literature. Where costs were not available for 2015-16, costs are inflated to 2014-2015 based on the Hospital & Community Health Services Index published in the PSSRU (2015). [144] The systematic literature review described in Section 4.1 considered broad search terms in order to capture resource utilisation and costs associated with treatment for psoriasis in the population of children and young people. The search identified five studies [145 , 146, 147, 148 , 149] which estimated resource use and costs of biologic therapies in psoriasis from insurance claim databases, but upon further examination of the population included in the studies it became clear that only adults were considered in the databases. In addition, the studies used data from US insurance databases, which are unlikely to reflect health care resource utilisation in the UK.

Given the lack of data on resource use and costs of treatment for psoriasis in children and young people, previous NICE TAs for adults were hand-searched in order to identify relevant resource use categories and potential sources of resource use estimates and unit costs. These were tabulated and sent to our clinical advisor (see Section 6.4.5), who then worked with us in order to help establish the transferability of adult data and resource use assumptions to the population of children and young people.

Based on clinical opinion, the management of psoriasis in children and young people is very similar to that in adults, according to our clinical advisor. Therefore, it seems reasonable to assume that the resource use associated with the administration of the treatments and monitoring costs would be similar to that used in previous TAs in adults. The assumptions used for resource use and costs for each of the cost categories are described in the sections below.

7.4.9 Drug acquisition costs

Table 64 details the dose and frequency of administration for each treatment and comparator, including cyclosporine which forms part of BSC, and the unit costs associated with each treatment.

Table 64 Drug acquisition costs in children and young people

Treatment	Administration route	Dose / frequency	Presentation /Unit cost	Source

Adalimumab	SC	0.8mg/kg up to a maximum of 40 mg at weeks 0 and 1, then every 2 weeks thereafter	Pre filled syringe 40 mg £352.14	MIMS [150]
Etanercept	SC	0.8mg/kg up to a maximum of 50 mg weekly for up to 24 weeks	Pre filled syringe 25 mg /vial £89.38 Pre filled syringe 50 mg £178.75	MIMS [150]
Ustekinumab	SC	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	Injectable solution , vial 45 mg £2,147.00	MIMS [150]
Methotrexate	Oral (72%), SC (24%), IM (4%)	0.1-0.4 mg/Kg weekly	Oral solution 2 mg/mL 65 mL, £125.00 Injectable solution, Vial 50 mg £2.62	MIMS[150] BNF [151]
Cyclosporine	Oral	2-5 mg/Kg daily for up to 2 years	Oral solution, Neoral®, 100 mg/mL, 50 mL £102.30	BNF [151]

BNF, British National Formulary; SC, subcutaneous; IM, intramuscular.

The dose and posology of the biologic therapies were taken from the summary of product characteristics. For methotrexate and cyclosporine, which are currently not licensed for paediatric use, these were sourced from published literature and confirmed with our clinical advisor to ensure that they reflected UK clinical practice in this population. [152, 153, 154] Methotrexate can be administered orally or injected subcutaneously or intramuscularly. In the model, it is assumed that 72% of individuals are given methotrexate in oral solution and 28% in injectable solution, which reflects the distribution of administration identified in the UK psoriasis audit on the use of systemic treatments in

children and young people. [135] Therefore, the unit cost per mg for methotrexate is a weighted average of the unit cost per mg of the oral and injectable solutions (i.e. £0.71/mg). Unit costs were sourced from MIMS and supplemented by the British National Formulary. [135, 155]

Figure 11 illustrates the number of doses administered in the first five cycles of the model for each treatment based on the licensed dose. Adalimumab is administered at weeks 0 (baseline) and 1, and then every 2 weeks thereafter until response assessment at the end of week 16. If individuals are responders to treatment, they continue to receive adalimumab every two weeks until treatment withdrawal (highlighted in grey). Ustekinumab is administered at weeks 0 and 4, and then every 12 weeks thereafter, with response assessment at week 16. Etanercept and methotrexate are administered weekly, with response assessment at weeks 12 and 16, respectively.

Figure 11 Drug dose distribution during the first five cycles in the model

	Cycle 1				Cycle 2				Cycle 3				Cycle 4				Cycle 5			
ADA	●	●		●		●		●		●		●		●		●		●		●
ETA	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
UST	■				■												■			
MTX	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ
Weeks	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13	13-14	14-15	15-16	16-17	17-18	18-19	19-20

ADA, adalimumab; ETA, etanercept; MTX, methotrexate; UST, ustekinumab; ●, ADA administration; ♦ ETA administration; ■, UST administration; Δ, MTX administration.

The dosage of the interventions are dependent on patient weight. The median weight by age and gender in the population of children and young people was extracted from the Royal College of Paediatrics and Child Health's School age growth charts.[156] Table 65 shows the weight used in the model by age. This was based on an average of girls and boys weight (and where the weight estimate in the growth chart did not correspond to an integer, the next highest integer was used).

Table 65 Median weight by age used in the model

Age	Girls median weight (Kg)	Boys median weight (Kg)	Weight in the model (Kg)
4	17	18	17.5
5	19	19	19
6	21	21	21
7	23	23	23
8	26	26	26
9	29	29	29
10	33	32	32.5
11	36	35	35.5
12	41	39	40
13	46	44	45
14	50	50	50
15	54	56	55
16	56	61	58.5
17	57	66	61.5
18	58	67	62.5

The weight by age was used to estimate the correct dosage of each treatment and the corresponding costs. Table 66 summarises the dosages used in the model for each treatment and the corresponding cost per dose. Following clinical advice, it was assumed that the vial with the lowest dose available would be used to allow administration of a single dose in a paediatric population. This inevitably results in wastage of the remainder of the vial. For example, for individuals less than 60 Kg the full cost of the 45mg vial of ustekinumab is assumed as the remaining product in the vial cannot be stored. Vial splitting across individuals is considered unlikely because in most cases the majority of the vial is used for a single patient and treating patients together is less likely to occur in this population due to low patient numbers. Therefore, the cost per dose is fixed for adalimumab and ustekinumab (£352.14 and £2,147.00, respectively). For etanercept, children younger than 10 years old will receive the 25 mg vial (£89.38), while those 10 years and older will receive the 50 mg vial (£178.75).

Table 66 Drug dosages and cost per dose by age in the model

		Adalimumab **0.8 mg/kg, max 40 mg**		**Etanercept** **0.8 mg/kg, max 50 mg**		**Ustekinumab** **0.75mg/kg weight <60kg; 45mg for weight 60-100kg**		**Methotrexate** **0.4 mg/Kg**		**Cyclosporine** **5 mg/Kg**	
Age	**Weight (Kg)**	**Dosage (mg)**	**Cost per dose**	**Dosage (mg)**	**Cost per dose**	**Dosage (mg)**	**Cost per dose**	**Dosage (mg)**	**Cost per dose (£)**	**Dosage (mg)**	**Cost per dose (£)**
4	17.5	14	£352.14	-	-	-	-	7	£6.73	87.5	£1.79
5	19	15.2	£352.14	-	-	-	-	7.6	£7.31	95	£1.94
6	21	16.8	£352.14	16.8	£89.38	-	-	8.4	£8.08	105	£2.15
7	23	18.4	£352.14	18.4	£89.38	-	-	9.2	£8.85	115	£2.35
8	26	20.8	£352.14	20.8	£89.38	-	-	10.4	£10.00	130	£2.66
9	29	23.2	£352.14	23.2	£89.38	-	-	11.6	£11.15	145	£2.97
10	32.5	26	£352.14	26	£178.75	-	-	13	£12.50	162.5	£3.32
11	35.5	28.4	£352.14	28.4	£178.75	-	-	14.2	£13.65	177.5	£3.63
12	40	32	£352.14	32	£178.75	30.0	£2,147.00	16	£15.38	200	£4.09
13	45	36	£352.14	36	£178.75	33.8	£2,147.00	18	£17.31	225	£4.60
14	50	40	£352.14	40	£178.75	37.5	£2,147.00	20	£19.23	250	£5.12
15	55	40	£352.14	44	£178.75	41.3	£2,147.00	22	£21.15	275	£5.63
16	58.5	40	£352.14	46.8	£178.75	43.9	£2,147.00	23.4	£22.50	292.5	£5.98
17	61.5	40	£352.14	49.2	£178.75	45.0	£2,147.00	24.6	£23.65	307.5	£6.29
18	62.5	40	£352.14	50	£178.75	45.0	£2,147.00	25	£24.04	312.5	£6.39

The absence of values in the grey shaded areas reflect the fact that the intervention is not licensed for this age.

7.4.10 Drug administration costs

Adalimumab, etanercept and ustekinumab are assumed to be self-administered. In the case of younger children, it is assumed that a parent or carer would administer the subcutaneous (SC) injection. SC injections are assumed to incur administration costs only for nurse training for self (or parent/carer) administration in the induction phase. In line with previous TAs in adults, this was assumed to require three hours of nurse time, which was costed based on the cost per working hour of a band 5 hospital nurse with qualifications (£43 per hour). [144] A cost of £129 was applied in the first cycle of the model for the administration of the biologics.

7.4.11 Monitoring costs

Table 67 summarises the resource use assumptions for monitoring and corresponding unit costs applied in the model. In the absence of evidence specifically for the population of children and young people, resource use estimates associated with monitoring and routine laboratory tests for biologics and non-biologic systemic treatments have been taken from the NICE Clinical Guideline 153 (CG 153), [131] [157]which used similar assumptions to those in the original York model (TA 103) [88, 89] and in subsequent NICE appraisals of biologics.[84-87, 128]

Table 67 Monitoring resource use and unit costs

Frequency of testing	Biologic drugs		Methotrexate		Cyclosporine	Unit cost	
Item	**Trial period**	**Continued use (annual)**	**Trial period**	**Continued use/BSC (annual)**	**BSC (annual)**	**Per item**	**Source**
Liver function test (LFT)	2	4	2	4	4	£ 0.77[a]	TA103 [88, 89]
Full blood count (FBC)	2	4	2	4	4	£3.05[a]	TA103[88, 89]
Glomerular filtration rate (GFR)	0	0	0	0	1	£195.07[b]	NHS reference costs, 2014-15
Urea and Electrolytes (U&E)	2	4	2	4	4	£ 1.41[a]	TA103[88, 89]

Outpatient/ physician visits	2	4	2	4	4	£ 119.99[c]	NHS reference costs, 2014-15 [158]

[a]Costs inflated to 2014-15 prices based on the Hospital & Community Health Services Index published in the PSSRU (2015); [b]Activity weighted average of GFR as an outpatient procedure (currency codes RN27B and RN27C for ages below 5 years old and 6 to18 years); [c]Activity weighted average of non-admitted Face to Face Attendance, Follow-up , consultant and non-consultant led visits (service code:257 Paediatric Dermatology; currency code: WF01A).

Individuals on biologic therapy are assumed to undertake a series of tests during the initial trial period, namely a Full Blood Count (FBC), Liver Function Test (LFT), Urea and Electrolytes (U&E). During the trial period, the tests are assumed to be carried out during two routine outpatient visits that occur at treatment initiation and at the end of trial period (treatment response assessment visit). Since methotrexate was not included as a comparator in CG 153 (only as part of BSC), it is assumed that the resource use for the monitoring of methotrexate in the trial period is the same as the biologics. In the maintenance period (corresponding to the health state of 'continued use'), individuals on systemic therapies are assumed to be monitored once every three months. [157]The unit costs for Glomerular filtration rate (GFR) and outpatient visits were taken from NHS reference costs 2014-15, [158] while the costs of the remaining monitoring items were inflated to 2014-15 prices based on estimates presented in TA 103.

The cost of tests undertaken solely to screen individuals for eligibility for treatment are excluded from the analysis, namely chest X-rays, tests for tuberculosis or biopsies of lesions atypical of psoriasis. These costs were also excluded in previous appraisals in adults. The cost of acid folic used in conjunction with methotrexate to prevent side effects was also excluded from previous appraisals as the annual cost of this drug is very low (less than £1). Our clinical advisor indicated that children and young people would be tested for Herpes Zoster before treatment initiation. However, as this test would be performed on every patient not immune to the virus regardless of treatment, it was excluded from the analysis. The costs of liver biopsy and Type III Procollagen Peptide (PIIINP) for the purpose of assessing liver function in individuals treated with methotrexate is also excluded from the analysis based on clinical advice; liver biopsy is seldom conducted in children and young people given its invasiveness, while PIIINP is a marker of growth in this population rather than of hepatic toxicity.

7.4.12 Best supportive care costs

Best supportive care (BSC) corresponds to the management of individuals after failure of conventional systemic therapies. BSC is also considered a relevant comparator to biological treatments. If biologics are found not to be effective, individuals are usually offered some form of BSC rather than no treatment. BSC tends to include a mix of active non-biologic systemic therapies such as methotrexate and cyclosporine and palliative care, including phototherapy, as well as outpatient visits and hospitalisations to manage disease flare-ups.

The resource use and costs associated with BSC have represented a significant area of uncertainty in the cost-effectiveness of biologic treatments for moderate to severe psoriasis in adults. In TAs prior to CG 153, the definition of BSC in terms of resource use and costs was restricted to outpatient visits and hospitalisations to manage symptoms of psoriasis, and these were largely informed by assumptions and clinical opinion (TA 103, 134, 146 and 180). In CG 153, the definition of BSC was expanded to also include non-biologic systemic treatments, phototherapy and attendance at tertiary day centres. As discussed previously in Section 6.4.5, this guideline used estimates of resource use from observational studies in the UK (Fonia et al., 2010) [130] and The Netherlands (Driessen et al., 2010) [133] but also relied heavily on clinical opinion and assumptions. In the absence of evidence for children and young people, the definition of BSC in CG153 was used in the model with input from our clinical advisor on the appropriateness of the assumptions for a younger population.

Table 68 summarises the resource use assumptions for BSC by category of cost in CG 153 and those applied in the model, alongside the associated unit costs. Unit costs were sourced from the BNF 2016, [151] MIMS[150] and NHS reference costs 2014-15. [158] The relative proportion of individuals on active treatment with methotrexate and cyclosporine was modified from that used in CG 153 based on clinical opinion that children and young people are less likely to be managed with cyclosporine compared to adults due to the renal toxicity of the drug. Data from a UK psoriasis audit on the use of systemic treatments in children and young people was used to inform the relative proportion of individuals on methotrexate and cyclosporine. [135] In CG 153, it was assumed that 90% of individuals receiving BSC would be on active treatment with systemic drugs. However, in the audit 53 patients were treated with non-biologic systemic treatments; of these, 25 patients were treated with methotrexate and 12 with cyclosporine. Therefore, instead of assuming that individuals are equally distributed between methotrexate and cyclosporine, a ratio (25/37 and 12/37 for those on methotrexate and cyclosporine, respectively) for each treatment was applied to the overall proportion of 90% in order to reflect the distribution of children and young people receiving these treatments in the audit. The corresponding proportion of individuals assumed to receive methotrexate and cyclosporine as

part of BSC is 61% and 29%, respectively. As in CG 153, treatment with cyclosporine was assumed to be discontinued after a maximum duration of 2 years (due to increased risk of renal toxicity). Monitoring costs associated with the use of these non-biologic systemic therapies were applied in the model as presented in section 7.4.11 above.

In line with CG 153, the cost of 24 sessions of phototherapy per year (narrow band UVB) is assumed for 16% of the population, while 5 outpatient visits per annum are assumed for the 10% of individuals not managed with systemic therapies. All individuals are assumed to incur the costs of 5 visits per annum to a specialist dermatology day centre, in line with CG 153.

The resource use associated with hospitalisations for individuals on BSC was identified as an area of high uncertainty and a key driver of cost-effectiveness in the previous TAs in adults. The number of bed days assumed in CG 153 (26.6 days per year) was based on the average length of stay (LOS) for psoriasis patients with a baseline PASI of 10 to 20 points taken from a UK observational study (Wood et al., 2008) [134] combined with the average number of hospitalisations for individuals at high (1 hospitalisation per year) and very high need (2.55 hospitalisations per year) from a Dutch observational study (Driessen et al., 2010). [133] The total of 26.6 days of hospitalisation per annum was considered by NICE appraisal committees for TA 350 (secukinumab) and TA 368 (apremilast) in adults to be too high. Our clinical advisor suggested that hospitalisations in children and young people are very rare. This is largely because children and young people have not yet developed co-morbidities which often lead to hospitalisation with psoriasis in adults. Therefore, in the base-case analysis it is assumed that children and young people do not incur any inpatient stays. In separate scenario analyses, estimates of 26.6 days of hospitalisation per annum (CG 153) and 6.49 days of hospitalisation per annum from Fonia et al (2010) are considered. [157, #6851]

Table 68 Resource use assumptions and unit costs for BSC in CG 153 and current analysis

	CG 153		Current MTA		
	Resource use	**Unit costs**	**Resource use**	**Unit costs**	**Source**
Drug acquisition costs					
Methotrexate	45% of patients on MTX once weekly	£0.05/mg	**61%** of patients on MTX once weekly	£0.71/mg	MIMS [150] BNF [151]

Cyclosporine	45% of patients on CS daily for a maximum of 2 years	£0.02/mg	**29%** of patients on CS daily for a maximum of 2 years	£0.02/mg	BNF [151]
Health care utilisation costs					
NBUVB	16% of patients have 24 sessions of NBUVB per year	£85.16	16% of patients have 24 sessions of NBUVB per year **(same as CG 153)**	£95.53[a]	NHS reference costs 2014-15 [158]
Monitoring	4 monitoring visits per year for all patients on systemic treatment (including each 1 outpatient visit, 1 FBC, 1 LFT, 1 U&E) + 0.04 liver biopsies and 4 PIIINP per year for patients on MTX +1 GFR per year for patients on CS	£86.85 per monitoring visit £553 per liver biopsy £25.29 per PIIINP £233.00 per GFR	4 monitoring visits per year for all patients on systemic treatment (including each 1 outpatient visit, 1 FBC, 1 LFT, 1 U&E) +1 GFR per year for patients on CS **(same as CG 153 but without liver biopsies and PIIINP)**	£125.22 per monitoring visit for all patients on systemic treatment £195.07 per GFR[b]	Calculated (see section 7.2.9.3) For GFR - NHS reference costs 2014-15 [158]
Day centre care	5 visits per year	£362.60 per visit	5 visits per year **(same as CG 153)**	£472.55 per visit[c]	NHS reference costs 2014-15 [158]
Outpatient visits	5 visits per year for the 10 % patients that are not on systemic treatment	£82	5 visits per year for the 10 % patients that are not on systemic treatment **(same as CG 153)**	£119.99[d]	NHS reference costs 2014-15 [158]
Hospitalisations	26.6 bed days.	£271.17	**0 (base-case)** **Alternative values explored in scenario analysis**	£295.80[e]	NHS reference costs 2014-15 [158]

CS, cyclosporine; FBC, Full Blood Count; GFR, glomerular filtration rate; LFT, Liver Function Test; MTX, methotrexate; NBUVB, narrow band UVB phototherapy; PIIINP, Type III Procollagen Peptide; U&E, Urea and Electrolytes.

[a]Activity weighted average of phototherapy (currency codes JC47A and JC47B for ages below 12 years old and 13 and over) across Total HRGs; [b]Activity weighted average of GFR (currency codes RN27B and RN27C for ages below 5 years old and 6 to18 years) across Total HRGs; [c]Activity weighted average of Skin Disorders Without Interventions (currency codes JD07F-K) for day cases. [d]Activity weighted average of non-admitted Face to Face Attendance, Follow-up , consultant and

non-consultant led outpatient visits (service code:257 Paediatric Dermatology; currency code: WF01A); [e]Non-elective excess bed days across all HRGs.

7.4.13 Adverse event costs

As discussed in Section 6.4.5, only one previous TA in adults (TA 350) considered the costs of hospitalisations due to adverse events in their cost-effectiveness analysis. The adverse events that were assumed to lead to relevant resource use consumption (i.e. those leading to hospitalisations) in this evaluation were a) Non-melanoma skin cancer (NMSC), b) malignancies other than NMSC and c) severe infections. The rates of adverse events as reported in the literature (for adalimumab, etanercept, ustekinumab and infliximab) and from trial data (for secukinumab) were applied to each treatment arm as per the rates of these events occurring.

The safety data from the clinical trials of biologic drugs for the treatment of severe to moderate psoriasis (Sections 4.3.4, 4.4.4 and 4.5.4) suggested that there was little difference in the short- and long-term rates of adverse events between trial arms, with the potential exception of etanercept for which a higher rate of infections (not statistically significant) was observed compared to placebo. However, the trial data included a small number of observations for each treatment and a limited follow-up period (52 weeks for adalimumab to 312 weeks for etanercept). Observational studies in children and young people with psoriasis [75, 76](section 4.6) did not report any increase in infections or serious adverse events (SAEs) associated with the use of biological therapies.

Given the paucity of robust evidence on the incidence of adverse events in children and young people with moderate to severe psoriasis, the costs of these were not included in the base case analysis. However, scenario analyses were conducted to explore the impact on cost-effectiveness results by including the costs associated with hospitalisations due to serious infections serious infections and malignancies (both NMSC and other). The rates of adverse events were sourced from TA 350 and supplemented with data from Dixon et al (2006) [159] for methotrexate, while the unit costs were taken from the NHS reference cost schedule 2014-15. [158] Table 69 summarises the averse event rates applied in the model, alongside the respective unit costs.

Table 69 Adverse event rates applied in the model

Adverse events rates (rate/patient year)	Adalimumab	Etanercept	Ustekinumab	Methotrexate	Unit cost (£)
Non-melanoma skin cancer	0.0097	0.0354	0.0065	-	2,160.37[a]
Non NMSC malignancies	0.006	0.00043	0.0016	-	4,974.76[b]
Severe infections	0.0519	0.0513	0.01	0.0414	2,679.66[c]

[a]Activity weighted average of Intermediate Skin Procedures (currency codes JC42A and JC43B for ages below 12 years old and 13 and over) for non-elective admissions, excess bed days; [b]Activity weighted average of Intermediate Skin Procedures (currency codes JC42A and JC43B for ages below 12 years old and 13 and over) and Malignant Lymphoma (currency codes SA31A-E), for non-elective admissions, excess bed days; [c]Activity weighted average of Pneumonia (currency codes DZ14F-J, DZ23H-N, DZ11K-V), Skin Disorders (JS07A-D), Infections of Bones or Joints(currency code HD25D-H), and Kidney or Urinary Tract Infections (currency codes LA04H-S) for non-elective admissions, excess bed days.

The cost of adverse events associated with biological therapies and methotrexate is applied in the model to individuals while on treatment. Individuals treated with BSC are assumed not to develop adverse events.

7.4.14 Analytic methods

7.4.14.1 Base-case analysis

The expected costs and QALYs of the interventions and comparators are determined for each population, and the relative cost-effectiveness is established using standard decision rules and reported using incremental cost-effectiveness ratios (ICERs) as appropriate. The ICER examines the additional cost that one treatment option incurs over another and compares this with the additional health benefits to give the additional cost of the treatment for each additional QALY gained. When more than two treatment options are being compared, the ICERs are calculated using the following process:

- The treatment options are ranked in terms of mean QALYs (from the least effective to the most effective);
- If a treatment option is more costly and less effective than any other option, then this treatment is said to be dominated and is excluded from the calculation of the ICERs;

- The ICERs are calculated for each successive alternative, from the least effective to the most effective. If the ICER for a given treatment option is higher than that of any more effective option, then this treatment option is ruled out on the basis of extended dominance;
- Finally, the ICERs are recalculated, excluding any treatment options that are ruled out by principles of dominance or extended dominance.

The resulting ICERs provide the basis for establishing which treatment appears optimal based on cost-effectiveness considerations. Guidance from NICE suggests that an incremental cost per additional QALY of around £20,000-£30,000 is considered to represent an appropriate threshold of the health opportunity costs to the NHS.

The ICER comparing all interventions and comparators relates to a situation where the decision maker can only choose one of the treatment options. However, as indicated previously, if an individual patient does not respond to or tolerate one of the biological therapies an alternative one is usually tried. This means that treatments are usually trialled on an individual basis until an effective option is found in children and young people. The ICERs comparing each intervention with BSC (after systemic therapy) or methotrexate (before systemic therapy) is also presented. This is used to indicate the optimum ordering of treatments in terms of their cost-effectiveness. The most cost-effective order in which to give the therapies based on total expected costs and QALYs associated with each treatment option is dependent on the cost-effectiveness threshold.

Probabilistic sensitivity analysis is used to represent uncertainty in the cost-effectiveness results. The effectiveness data are entered as simulated posterior distributions from the Markov Chain Monte Carlo analysis to reflect uncertainty in the mean estimates. Monte Carlo simulation is used to propagate the uncertainty in the input parameters over 10,000 draws, from which mean costs and QALYs are then obtained by averaging over the 10,000 simulations. The probability that a treatment is first in the sequence is also estimated.

Differences in the marketing authorisation of the interventions by age and positioning of adalimumab before non-biological systemic therapy means that the comparative cost-effectiveness of the interventions needs to be evaluated by age and before or after use of systemics. The relevant comparator also depends on the position of the intervention in the pathway. Before systemic therapy, methotrexate is the relevant comparator (as the current standard of care), whereas after systemic therapy BSC represents the most relevant comparator. Three base-case populations are presented:

(i) Children and young people aged 4-17 years with adalimumab compared to methotrexate, i.e. as a second-line therapy in individuals who are inadequately controlled by, or intolerant to, topical therapy and phototherapies;

(ii) Children and young people aged 6-11 years with adalimumab and etanercept compared to BSC, and each other, i.e. as a third-line therapy in individuals who are inadequately controlled by, or intolerant to, systemic therapies or phototherapies;

(iii) Children and young people aged 12-17 years with adalimumab, etanercept and ustekinumab compared to BSC, and each other, i.e. as a third-line therapy in individuals who are inadequately controlled by, or intolerant to, systemic therapies or phototherapies.

Table 70 summarises the input parameters used in the base-case analysis.

Table 70 Summary of parameters in the model

Parameter	Mean	SE	Source
Baseline age (years)	4, 6 or 12	-	According to license for each comparator
Discount rate (per year)	3.5%	-	NICE methods guideline
Time horizon (years)	14, 12 or 6	-	Assumption: Until individuals reach 18 years
Duration of treatment trial period (weeks)			
Adalimumab	16	-	License definition of timing for treatment response assessment
Etanercept	12	-	
Ustekinumab	16	-	
Methotrexate	16	-	Response assessment in study M04-717
Treatment response - adalimumab		Simulated posterior distribution from the Bayesian network meta-analysis	NMA (Section 5.4.3.4)
Probability of PASI 50	91.5%		
Probability of PASI 75	79.0%		
Probability of PASI 90	54.6%		
Treatment response - etanercept			
Probability of PASI 50	75.2%		
Probability of PASI 75	54.4%		
Probability of PASI 90	27.9%		

Parameter	Mean	SE	Source
Treatment response - ustekinumab			
Probability of PASI 50	93.4%		
Probability of PASI 75	82.4%		
Probability of PASI 90	59.4%		
Treatment response - methotrexate			
Probability of PASI 50	70.8%		
Probability of PASI 75	49.2%		
Probability of PASI 90	23.9%		
Treatment response - BSC			
Probability of PASI 50	26.5%		
Probability of PASI 75	11.5%		
Probability of PASI 90	2.9%		
Withdrawal rate (annual)	0.20	SE=mean/4	Assumption based on adult data
Mortality rate	Age varying	-	Life table data for England & Wales 2013-15 [138]
Baseline utility	0.8596	-	CADMUS trial PedsQL data [141] mapped into EQ-5D using the algorithm by Khan et al, 2014 [140]
Utility Increment for PASI<50	0.0036	-	
Utility Increment for PASI50-75	0.0255	-	
Utility Increment for PASI50-90	0.0340	-	
Utility Increment for PASI>=90	0.0810	-	
Drug acquisition resource use and costs			
Adalimumab administrations in 'Trial Period'	9	-	According to license
Etanercept administrations in 'Trial Period'	12	-	
Ustekinumab administrations in 'Trial Period'	2	-	
Methotrexate administrations in 'Trial Period'	16	-	
Adalimumab administrations per cycle in 'Continued use'	2	-	
Etanercept administrations per cycle in 'Continued use'	4	-	

Parameter	Mean	SE	Source
Ustekinumab administrations per cycle in 'Continued use'	0.33	-	
Methotrexate administrations per cycle in 'Continued use' and 'BSC'	4	-	
Ciclosporin administrations per cycle in 'BSC'	28	-	
Proportion of patients on methotrexate in 'BSC'	61%	-	Assumption
Proportion of patients on ciclosporin in 'BSC'	29%	-	
Dosage of methotrexate (per Kg)	0.4 mg	-	Same as in M04-717 trial; de Jager et al (2010) [152]
Dosage of ciclosporin (per Kg)	5 mg	-	Clinical opinion; Mahé et al, (2001) ; Pereira et al (2006). [153, 154]
Adalimumab cost per dose	£352.14	-	MIMS [150]
Etanercept cost per dose (< 10 years old)	£89.38	-	MIMS [150]
Etanercept cost per dose (≥ 10 years old)	£178.75	-	MIMS [150]
Ustekinumab cost per dose	£2,147	-	MIMS [150]
Methotrexate cost per mg	£ 0.71	-	BNF [151]
Ciclosporin cost per mg	£ 0.02	-	BNF [151]
Drug administration costs			
Self-administration instruction (hours)	3	-	Assumption
Cost of hospital nurse Band 5 time (per hour)	£43	-	PSSRU 2015 [144]
Monitoring frequency			
FBC, LFT, U&E and physician visits for adalimumab, etanercept, ustekinumab and methotrexate in 'Trial Period'	2	-	Assumption based on adult data
FBC, LFT, U&E and physician visits for adalimumab, etanercept, ustekinumab and methotrexate per annum in 'Continued Use'	4	-	
FBC, LFT, U&E and physician visits for ciclosporin and methotrexate per annum in 'BSC'	4	-	
GFR for ciclosporin per annum in 'BSC'	1	-	
Monitoring test costs			

Parameter	Mean	SE	Source
FBC	£3.05	-	TA 103 [88, 89]
LFT	£0.77	-	
U&E	£1.41	-	
GFR	£195.07	-	NHS reference costs 2014-15 [158]
Physician monitoring visit	£119.99	-	
Palliative care resource use and costs in BSC		-	
NBUVB sessions per cycle	3.84	-	Assumption based on CG 153 (adults)
Day centre care visits	5	-	
Outpatient visits	0.5	-	
NBUVB cost per sessions	£95.53	-	NHS reference costs 2014/-15 [158]
Day centre care cost per visit	£472.55	-	
Outpatient cost per visit	£119.99	-	

7.4.14.2 Scenario analysis

A number of alternative scenarios are considered in which the assumptions used as part of the base-case analysis are varied. These analyses are undertaken to assess the robustness of the base-case results to variation in the assumptions and sources of the data used to populate the model. Table 71 summarises the alternative scenarios considered. For each element, the position in the base-case analysis is outlined, alongside the alternative assumptions applied. The cost-effectiveness of the interventions is considered under each of the scenarios for each of the licensed populations.

Table 71 Details of the key elements of the base-case analysis and the variation used in the scenario analysis

Scenario	Element	Position in base-case analysis	Variation in scenario analysis
Intervention and comparators			
1	Off-label use of biologics outside of age constraints	Adalimumab licensed for age 4+ years; Etanercept licensed for age 6+ years; Ustekinumab licensed for age 12+ years	Adalimumab, etanercept and ustekinumab for age 4+ years
Model time horizon			
2	Time horizon of model	14 years, 12 years and 6 years for populations 1 to 3, respectively (i.e. until individuals reach 18 years old)	Common time horizon of 14 years
Treatment effectiveness estimates			
3a	Direct trial evidence for treatment effects in children and young people	NMA using full network of evidence in children, young people and adults	M04-717 used to inform ADA vs. MTX; 20030211 used to inform ETA vs. BSC; CADMUS used to inform UST vs. BSC
3b	Indirect treatment comparison in children and young people		Indirect treatment comparison used to inform ETA vs. UST vs. BSC
3c	NMA using minimum evidence from the adult population		NMA using minimum evidence from the adult population (CHAMPION study) to link the trials in children and young people
3d	PASI response assessment	PASI 75	PASI 50
Health-related quality of life utility values			

4a	EQ-5D utility estimates from adults	PedsQL data mapped onto EQ-5D-Y	EQ-5D values from TA 103; TA 146; TA 180
4b	Utility estimates for BSC	Utility gains for BSC weighted by PASI response associated with placebo from NMA	Utility in BSC equal to baseline value (i.e. no utility gain associated with BSC)
Best supportive care costs			
5	Hospitalisations for BSC	No inpatient stay included for children and young people	6.49 days per annum based on Fonia et al (2010) in adults; 26.6 days per annum based on CG 153 in adults
Adverse events costs			
6	Costs associated with adverse events	Not included	Costs of severe infections included; Costs of severe infections and malignancies included
Treatment withdrawal rates			
7	Withdrawal rates from treatment	20% per annum	10% per annum; 30% per annum
Biosimilars			
8	Biosimlar for etanercept	Unit cost of etanercept	Unit cost of Benepali 50 mg (biosimilar)

7.5 Results

7.5.1 Results of the base-case cost-effectiveness analysis

Table 72 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy. Adalimumab is more costly (additional cost of £27,084) but also more effective than methotrexate (incremental gain in QALYs of 0.088). The resulting ICER is £308,329 per QALY gained. The small incremental gain in QALYs for adalimumab compared with methotrexate is a result of the modest utility increments in EQ-5D-Y for the different PASI response categories (<50, 50-75, 75-90, ≥90). The average proportion of individuals achieving PASI 75 response is 79% for adalimumab compared to 49% for methotrexate but the utility gain for individuals achieving a PASI 75–90 and PASI ≥90 response are very small at 0.0340 and 0.0810, respectively. Therefore, the difference in effectiveness translates into a small utility gain while on treatment with adalimumab compared to methotrexate. The difference in total costs for adalimumab compared to methotrexate is driven by the difference in treatment costs of adalimumab of £704.28 per 4-week cycle in the model (i.e. £352.14 per dose every 2 weeks) compared to methotrexate costs of approximately £60 per 4-week cycle. The difference in treatment costs is partly offset by the greater efficacy associated with adalimumab which results in lower costs associated with BSC (i.e. less time spent in BSC) for non-responders compared to higher costs on BSC with methotrexate, but this offset is not sufficient to outweigh the difference in treatment costs. The probability that adalimumab is cost-effective at a threshold of £30,000 per additional QALY is zero.

Table 72 Base-case probabilistic results for adalimumab as an alternative to systemic therapy

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						
MTX	34,914	9.939	-	-	-	MTX
ADA	61,999	10.027	27,084	0.088	308,329	

ADA , adalimumab; MTX, methotrexate.

Table 73 presents the cost-effectiveness results for the interventions after failed systemic therapy by age group. The difference in age group reflects the fact that ustekinumab does not have marketing authorisation for use in children and young people below 12 years of age. For the younger age group of 6-11 years, adalimumab is the most effective treatment (8.890 QALYs), followed by etanercept (8.813 QALYs) and BSC (8.710 QALYs). In terms of costs, adalimumab is the most costly treatment (£57,251), followed by etanercept (£43,808) and BSC (£36,406). Based on a fully incremental analysis, the ICER of etanercept compared to BSC is £71,903 per additional QALY, while the ICER of adalimumab compared to etanercept is £174,519 per additional QALY. The individual pairwise ICERs for etanercept and adalimumab compared to BSC are £71,903 and £115,825 per additional QALY, respectively.

For children and young people aged 12-17 years, ustekinumab is the most effective treatment (4.960 QALYs), followed by adalimumab (4.950 QALYs), etanercept (4.887 QALYs) and BSC (4.804 QALYs). In terms of costs, ustekinumab is the most costly treatment (£39,975), followed by adalimumab (£37,852), etanercept (£33,199) and BSC (£21,749). Based on a fully incremental analysis, etanercept is extendedly dominated by adalimumab (i.e. etanercept produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy of adalimumab, observed by a higher ICER for etanercept than that of adalimumab), the ICER of adalimumab compared to BSC is £110,430 per additional QALY, and the ICER of ustekinumab compared to adalimumab is £201,507 per additional QALY. The individual pairwise ICERs for etanercept, adalimumab and ustekinumab compared to BSC are £137,059, £110,430 and £116,568 per additional QALY, respectively.

Table 73 Base-case probabilistic results for interventions after failed systemic therapy

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	43,808	8.813	7,402	0.103	71,903	71,903	
ADA	57,251	8.890	13,444	0.077	174,519	115,825	
Children and young people aged 12-17 years							

BSC	21,749	4.804	-	-	-	-	BSC
ETA	33,199	4.887	11,450	0.084	ED ADA	137,059	
ADA	37,852	4.950	16,103	0.146	110,430	110,430	
UST	39,975	4.960	2,123	0.011	201,507	116,568	

ADA , adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

There are two important differences to note between the two age populations. Firstly, the reduction in total costs and QALYs for the interventions in the age group of 12-17 years is an artefact of the difference in model time horizon used in each analysis (i.e. 12 years for age group 6-11 years and 6 years for age group 12-17 years). The time horizon of the model extends until individuals reach 18 years of age, at which point it is assumed that separate NICE recommendations for the interventions in adults apply. A separate scenario analysis is presented below which considers a common time horizon of 14 years for both age populations, which is sufficient to capture differences in costs and effects between the interventions. Secondly, the total costs of etanercept are proportionally greater in the age group 12-17 years compared to the costs of etanercept for ages 6-11 years. This is due to the higher drug acquisition costs of etanercept once individuals reach 10 years old, i.e. etanercept costs £715 per 4-week cycle in the model (i.e. £178.75 per 50 mg dose each week) for age 10 years and older, whereas etanercept costs £357.50 per 4-week cycle in the model (i.e. £89.38 per 25 mg dose each week) for children younger than 10 years.

For children and young people aged 6-11 years, adalimumab is the most effective treatment but the incremental gain in QALYs compared to etanercept is relatively small because the utility gains in EQ-5D-Y associated with higher PASI response rates are small. Therefore, the benefits of achieving a greater PASI response do not translate into a large improvement in health outcomes. The benefit of more individuals achieving a higher PASI response rate manifests itself in lower costs associated with less time spent in BSC. The average proportion of individuals achieving PASI 75 response is 79% for adalimumab and 54% for etanercept. The higher efficacy associated with adalimumab compared to etanercept, which results in fewer individuals accumulating the costs associated with BSC (approximately £284 per 4-week cycle), is not sufficient to offset the additional treatment costs for adalimumab, which are £704.28 per 4-week cycle (i.e. £352.14 per dose every 2 weeks) compared to £357.50 per 4-week cycle for etanercept in children under 10 years and £715 per 4-week cycle for age 10 years and older (note that although the costs for etanercept increase at age 10 years, there are fewer

individuals receiving treatment because the starting age in the model is 6 years and the treatment withdrawal rate is assumed to be 20% per annum).

For children and young people aged 12-17 years, ustekinumab is the most effective treatment but again the incremental gain in QALYs compared to the alternative interventions is relatively small due to the small magnitude of utility gains for the different PASI response categories in the population of children and young people compared to adults (see Section 7.4.7). The drug acquisition costs of etanercept in young people aged 12 years and older are greater than those of adalimumab (£715 for etanercept compared to £704.28 for adalimumab per 4-week cycle), while the efficacy for adalimumab is greater than etanercept, which reduces the time on BSC for treatment with adalimumab. As a result, it might be expected that the total costs of adalimumab are lower than etanercept; however, the improved efficacy for adalimumab also extends the time that individuals receive the intervention and therefore the overall costs for adalimumab increase. Despite this, the incremental costs of etanercept relative to BSC are greater for each additional gain in QALYs compared to the incremental costs of adalimumab relative to BSC for each QALY gain. As a result, adalimumab extendedly dominates etanercept, which rules out etanercept as a potential cost-effective treatment option.

Ustekinumab has the highest average proportion of individuals achieving a PASI 75 response rate of 82% compared to 79% for adalimumab and 54% for etanercept, but also has the highest total costs. The higher total costs for ustekinumab compared to adalimumab are due to marginally higher drug acquisition costs associated with ustekinumab of £715.67 per 4-week cycle (i.e. £2,147 per dose with each dose given at 12 weekly intervals) compared to £704.28 per 4-week cycle (i.e. £352.14 per dose at fortnightly intervals) for adalimumab and a greater cost of ustekinumab during the induction period (i.e. a cost of £2,147 per dose given at baseline, 4 weeks and 16 weeks) compared to adalimumab in the induction period (i.e. a cost of £352.14 per dose given at baseline, 1 week and then every 2 weeks up to week 16). The higher efficacy associated with ustekinumab compared to adalimumab with an average of 3% more individuals achieving PASI 75 response results in a reduction in costs associated with individuals remaining off BSC for longer for ustekinumab, but this reduction is not sufficient to offset the additional treatment costs associated with ustekinumab.

The pairwise ICERs for each of the interventions compared to BSC indicate the ICER at which the particular therapy might enter a sequence. Under base-case assumptions, these ICERs are very high, ranging from £110,430 (adalimumab) to £137,059 (etanercept) per additional QALY in children and

young people aged 12-17 years. The optimal treatment option is BSC up until the threshold reaches £111,000 per QALY gained, when adalimumab would then enter as the first treatment in sequence. The fact that BSC is the only form of management listed until the threshold reaches £111,000 per QALY suggests that, under base-case assumptions, none of the biological therapies are sufficiently cost-effective to enter the sequence until this threshold is used. The probability that any of the biologics are cost-effective at a threshold of £30,000 per additional QALY is zero.

7.5.2 Cost-effectiveness results for alternative scenarios

7.5.2.1 Intervention and comparators

Scenario 1: Off-label use of biologics outside of age constraints and position in pathway

As discussed in Section 7.2, the biologic interventions differ in their marketing authorisation by age and positioning of treatment in the pathway. Adalimumab is licensed for the youngest age of 4 years and older and is the only biological treatment positioned as a second-line therapy in individuals who are inadequately controlled by, or intolerant to, topical therapy and phototherapies, i.e. as an alternative to systemic therapy. This makes the comparison of adalimumab with etanercept and ustekinumab more problematic since the latter interventions are licensed as third-line therapies in individuals who are inadequately controlled by, or intolerant to, systemic therapies or phototherapies and for ages 6 years and older in the case of etanercept and 12 years and older for ustekinumab. In this scenario, the off-label use of the biologics outside of their age constraints and positioning in the management pathway is considered.

In the absence of clinical effectiveness evidence in a systemic-naïve population, the same efficacy estimates as the base-case analysis is used in this scenario. Therefore, the only difference between this scenario and the base-case assumptions is the comparator, which is methotrexate in the analysis that considers biologics as an alternative to systemic therapy, and the time horizon of the model, which extends to 14 years because the starting age in the model is now 4 years.

Table 74 presents the cost-effectiveness results for the interventions as an alternative to systemic therapy for all ages (4-17 years). Ustekinumab is the most effective treatment, followed by adalimumab, etanercept and methotrexate, since the efficacy of the treatments follow in this order. In terms of costs, ustekinumab is the most costly treatment, followed by adalimumab, etanercept and

methotrexate. The reason for this ordering is the same as the base-case results where ustekinumab costs £715.67 per 4-week cycle compared to adalimumab at £704.28, etanercept at £357.50 for <10 years and £715 for ≥10 years, and methotrexate at approximately £60 per cycle, but the reduction in costs associated with improved efficacy (i.e. less time spent on BSC) is not sufficient to offset the additional treatment costs. Based on a fully incremental analysis, the incremental costs of etanercept and adalimumab relative to methotrexate are greater for each additional gain in QALYs compared to the incremental costs of ustekinumab relative to methotrexate for each QALY gain. Therefore, etanercept and adalimumab are extendedly dominated by ustekinumab. The ICER of ustekinumab compared to methotrexate is very high at £293,117 per QALY gained. As a result, the optimal treatment option in a systemic-naïve population is methotrexate.

Table 74 Scenario 1 results for interventions as an alternative to systemic therapy: Off-label use of biologics outside of age constraints and position in pathway

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years							
MTX	34,914	9.939	-	-	-	-	MTX
ETA	46,767	9.948	11,853	0.009	ED ADA	1,319,539	
ADA	61,999	10.027	27,084	0.088	ED UST	308,329	
UST	64,426	10.040	29,512	0.101	293,117	293,117	

ADA , adalimumab; BSC, best supportive care; ETA, etanercept; MTX, methotrexate; UST, ustekinumab.

Table 75 presents the cost-effectiveness results for the interventions after failed systemic therapy for all ages (4-17 years). The only difference between this scenario and the base-case analysis is the starting age used in the model of 4 years. The total absolute costs and QALYs are greater compared to the base-case due to a longer model time horizon of 14 years. The ordering of the treatments in terms of costs and QALYs follows that of the base-case with ustekinumab the most effective but more costly treatment, followed by adalimumab, etanercept and BSC. Based on a fully incremental analysis, adalimumab is extendedly dominated by ustekinumab. Compared to the base-case population of ages 12-17 years, etanercept is no longer extendedly dominated because there are more

individuals receiving a lower dose of etanercept at the cost of a 25 mg vial rather than a 50 mg vial. The ICERs are lower than the base-case analysis, but the optimal treatment option remains as BSC. BSC is the optimal option until the threshold reaches £60,000 per QALY gained, when etanercept would then enter as the first treatment in sequence.

Table 75 Scenario 1 results for interventions after failed systemic therapy: Off-label use of biologics outside of age constraints

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years							
BSC	40,478	9.843	-	-	-	-	BSC
ETA	46,767	9.948	6,289	0.105	59,924	59,924	
ADA	61,999	10.027	15,231	0.079	ED UST	117,080	
UST	64,426	10.040	23,948	0.013	121,779	121,779	

ADA , adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.2 Model time horizon

Scenario 2: Time horizon of model

The time horizon of the model was chosen to reflect the fact that once individuals reach 18 years of age separate NICE recommendations for the use of the interventions in adults apply. In order to incorporate these recommendations, evidence on the efficacy of the treatments in biologic experienced patients (i.e. effectiveness estimates conditional on prior biologic therapy) would be required. This would involve modelling the sequential use of therapies, with every possible potential treatment sequence considered based on current recommendations in adults. As well as being outside the scope of this appraisal, this would represent a significant challenge for two reasons; firstly, there is very limited evidence on the efficacy of biologics when used in sequence, i.e. in biologic experienced patients; and secondly, current NICE recommendations for the use of biologic therapies in moderate to severe psoriasis in adults have been informed by a series of STAs rather than an MTA that establishes the optimal sequence of treatments in adults.

Furthermore, the differences in marketing authorisation of the interventions by age inevitably means that the time horizon of the model will differ according to age group. In this scenario, the impact of the time horizon is assessed by considering a common time horizon of 14 years for all age groups, but with the same starting age for each group as used in the base-case analysis. The time horizon of 14 years is sufficient to capture differences in costs and effects between the interventions under comparison because all individuals on each treatment in the model have moved to BSC by 14 years. This time horizon is also greater than 10 years as used in previous TAs in adults.

The base-case results for adalimumab as an alternative to systemic therapy already considers a time horizon of 14 years because the starting age is 4 years. Therefore, Table 76 presents the cost-effectiveness results for the interventions after failed systemic therapy for a common time horizon of 14 years. By extending the time horizon, the total costs and QALYs for the interventions are greater compared to the base-case results, but the relative cost-effectiveness of the interventions remain the same, i.e. the ICERs for each intervention relative to the next best treatment option or BSC are similar to those observed in the base-case. Therefore, the model time horizon used in the base-case analysis is sufficient to capture the differences between the interventions in terms of costs and QALYs.

Table 76 Scenario 2 results for interventions after failed systemic therapy: Common time horizon of 14 years

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	41,413	9.842	-	-	-	-	BSC
ETA	49,109	9.948	7,696	0.105	73,153	73,153	
ADA	62,723	10.027	13,614	0.079	172,000	115,592	
Children and young people aged 12-17 years							
BSC	44,010	9.836	-	-	-	-	BSC
ETA	58,286	9.942	14,275	0.105	ED ADA	135,354	
ADA	64,204	10.021	20,194	0.184	109,531	109,531	
UST	66,503	10.033	2,299	0.012	188,715	114,439	

ADA , adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.3 Treatment effectiveness estimates

Scenario 3a: Direct trial evidence for treatment effects in children and young people

As discussed in Section 5, a NMA was used in the base-case analysis to connect the evidence from the adalimumab trial (M04-717) in children and young people to the evidence from the etanercept (20030211) and ustekinumab (CADMUS) trials by drawing strength from the wider network of evidence in adults. In this scenario, the relative cost-effectiveness of adalimumab compared to methotrexate, and etanercept and ustekinumab compared to BSC, is considered using the direct efficacy estimates derived from their corresponding trials. The limitation of this approach is that it does not allow the relative cost-effectiveness of all three biologics to be assessed in the same analysis. However, it may give an indication of how much influence the wider network of evidence has on the individual pairwise comparisons.

Table 77 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy using the efficacy estimates from the M04-717 trial alone. The incremental costs (£20,256) and QALYs (0.037) for adalimumab compared to methotrexate are lower than the base-case incremental costs (£27,084) and QALYs (0.088). The PASI 75 response rate is 58% for adalimumab and 32% for methotrexate from trial M04-717 compared to 79% and 49%, respectively, from the NMA. The NMA estimates higher absolute values for PASI 75, but the incremental difference between adalimumab and methotrexate is of a similar magnitude in the NMA (30% difference in PASI 75) and M04-717 (26% difference in PASI 75). This smaller difference in relative effectiveness between adalimumab and methotrexate from M04-717 means that the incremental costs for each additional gain in QALYs is greater for adalimumab compared to methotrexate. The resulting ICER increases from £308,329 per additional QALY in the base-case analysis to £549,899 per additional QALY with the direct trial evidence.

Table 77 Scenario 3a results for adalimumab as an alternative to systemic therapy: Direct trial evidence for treatment effects in children and young people

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)

Children and young people aged 4-17 years						
MTX	36,601	9.919	-	-	-	MTX
ADA	56,857	9.956	20,256	0.037	549,899	

ADA , adalimumab; MTX, methotrexate.

Table 78 presents the cost-effectiveness results for the interventions after failed systemic therapy using the efficacy estimates from study 20030211 (etanercept) and CADMUS (ustekinumab). The total costs and QALYs for etanercept and ustekinumab compared with BSC are very similar to the base-case results. This is because the PASI 75 response rates estimated from the NMA for etanercept (54%), ustekinumab (82%) and placebo (11.5%) are very similar to the corresponding response rates from the individual trials (81% ustekinumab vs. 11% placebo, CADMUS; 57% etanercept vs. 11.4% placebo, study 20030211). As a result, the pairwise ICERs for etanercept and ustekinumab compared to BSC are similar to the base-case analysis: ICER for etanercept vs. BSC increases from £71,903 per QALY in base-case analysis to £75,350 per QALY using direct trial evidence, while the ICER for ustekinumab vs. BSC increases marginally from £116,568 per QALY in base-case analysis to £116,982 per QALY using direct trial evidence.

Table 78 Scenario 3a results for interventions after failed systemic therapy: Direct trial evidence for treatment effects in children and young people

	Mean costs (£)	Mean QALYs	Incremental costs vs. BSC (£)	Incremental QALYs vs. BSC	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years						
BSC	36,406	8.720	-	-	-	BSC
ETA	44,108	8.822	7,701	0.102	75,350	
Children and young people aged 12-17 years						
BSC	21,749	4.814	-	-	-	BSC
UST	39,622	4.966	17,873	0.153	116,982	

ADA , adalimumab; BSC, best supportive care; ETA, etanercept; UST, ustekinumab.

Scenario 3b: Indirect treatment comparison estimates in children and young people

In this scenario, the relative cost-effectiveness of etanercept and ustekinumab compared to BSC is considered using the indirect treatment comparison estimates from study 20030211 and CADMUS, with placebo used as a common comparator. The limitation of this approach is that it does not allow the relative cost-effectiveness of etanercept and ustekinumab to be compared with adalimumab due to the absence of a placebo arm in M04-717.

Table 79 presents the cost-effectiveness results for the interventions after failed systemic therapy using efficacy estimates from an indirect treatment comparison of etanercept from study 20030211 and ustekinumab from CADMUS. The total costs and QALYs for etanercept, ustekinumab and BSC are similar to the base-case analysis. This is expected since the efficacy estimates from the individual trials for these interventions are similar to those estimated in the NMA. Etanercept is extendedly dominated by ustekinumab since the incremental costs of etanercept relative to BSC are greater for each additional gain in QALYs compared to the incremental costs of ustekinumab relative to BSC for each QALY gain. This occurs because ustekinumab has better efficacy (78% PASI 75 response) compared to etanercept (57% PASI 75 response), which results in improved health outcomes for ustekinumab. Interestingly, the total costs for ustekinumab are greater than etanercept despite the fact that the drug acquisation costs are similar between the two treatments in children and young people aged 12-17 years. This arises because although the improved efficacy reduces the time spent on BSC, it also means that a greater proportion of time is spent on a cost-ineffective treatment option. The ICER of ustekinumab compared to BSC is £119,092 per QALY gained. As a result, the optimal treatment option is BSC unless the cost-effectiveness threshold reaches £120,000 per additional QALY.

Table 79 Scenario 3b results for interventions after failed systemic therapy: Indirect treatment comparison estimates in children and young people

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 12-17 years							
BSC	21,749	4.809	-	-	-	-	BSC
ETA	33,662	4.901	11,913	0.092	ED UST	128,903	

UST	39,105	4.955	17,356	0.146	119,092	119,092	

ADA , adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

Scenario 3c: Treatment effects from NMA using minimum evidence from adult population

In Section 5 the disconnected network of evidence in children and young people was connected in the first instance by bringing together the minimum amount of evidence required from the adult population in order to link the adalimumab trial with the other paediatric trials. The CHAMPION study in adults, which was a three-arm trial comparing adalimumab, methotrexate and placebo, represented the best way to connect adalimumab to etanercept and ustekinumab using the least amount of evidence borrowed from the adult population. In this scenario, the relative cost-effectiveness of the interventions are considered in the base-case populations using the treatment effects estimated from the minimum network of evidence.

Table 80 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy using the NMA with minimum links to adult evidence. The incremental costs for adalimumab compared to methotrexate of £18,422 are lower than the base-case analysis of £27,084. This is due to a larger difference in PASI 75 response rates between adalimumab and methotrexate in the minimum NMA (approximately 40% difference) compared to the full network of evidence (approximately 30% difference). Although there is a higher efficacy difference between adalimumab and methotrexate in this scenario, the health outcomes also depend on the utility associated with BSC, which is based on the proportion of individuals in the different PASI response categories for the placebo arm in the NMA. In the minimum NMA, the PASI response rates for placebo are greater than the full network. Therefore, the gain in utility associated with better efficacy on adalimumab is offset by a higher gain in utility associated with BSC. As a result, the incremental QALYs for adalimumab compared to methotrexate are very similar to the base-case analysis. The corresponding ICER for adalimumab vs. methotrexate is reduced from the base-case of £308,329 to £211,259 per additional QALY.

Table 80 Scenario 3c results for adalimumab as an alternative to systemic therapy: Treatment effects from NMA using minimum evidence from adult population

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						
MTX	38,177	9.879	-	-	-	MTX
ADA	56,599	9.966	18,422	0.087	211,259	

ADA , adalimumab; MTX, methotrexate.

Table 81 presents the cost-effectiveness results for the interventions after failed systemic therapy using the NMA with minimum links to adult evidence. The incremental costs and QALYs for etanercept and ustekinumab compared to BSC are similar to the base-case analysis, but the incremental costs and QALYs for adalimumab are reduced in both age groups. This is because the difference in PASI 75 response rates between the interventions and BSC in the minimum NMA compared to the full NMA are similar for etanercept (44% vs. 43%) and ustekinumab (66% vs. 71%) but much smaller for adalimumab (44% vs. 68%). As a result, adalimumab is less cost-effective in children and young people aged 6-11 years (ICER vs. BSC increases from base-case of £115,825 to £137,329 per additional QALY) and is extendedly dominated by ustekinumab in the age group of 12-17 years. The ICER for etanercept is reduced by £3,400 in children aged 6-11 years, but etanercept is also extendedly dominated by ustekinumab in ages 12-17 years. The ICER for ustekinumab vs. BSC increases slightly from the base-case value of £116,568 to £118,515 per QALY gained using the minimum NMA.

Table 81 Scenario 3c results for interventions after failed systemic therapy: Treatment effects from NMA using minimum evidence from adult population

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							

BSC	36,406	8.717	-	-	-	-	BSC
ETA	44,063	8.828	7,657	0.112	68,485	68,485	
ADA	52,067	8.831	8,004	0.002	3,587,196	137,329	
Children and young people aged 12-17 years							
BSC	21,749	4.807	-	-	-	-	BSC
ETA	33,598	4.898	11,849	0.091	ED UST	130,389	
ADA	33,977	4.899	380	0.001	ED UST	132,682	
UST	39,264	4.955	17,515	0.148	118,515	118,515	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

Scenario 3d: PASI response assessment

In this scenario, PASI 50 is considered as the primary efficacy endpoint for response assessment at the end of the trial period instead of PASI 75 as used in the base-case analysis.

Table 82 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy using PASI 50. The incremental costs and QALYs for adalimumab compared to methotrexate increase because there is a smaller difference in PASI 50 response rates between the interventions (91.5% ADA vs. 71% MTX) compared to PASI 75 response rates (79% ADA vs. 49% MTX). As a result, the ICER increases from £308,329 to £353,148 per QALY gained.

Table 82 Scenario 3d results for adalimumab as an alternative to systemic therapy: PASI 50 response assessment

	Mean costs (£)	**Mean QALYs**	**Incremental costs vs. MTX (£)**	**Incremental QALYs vs. MTX**	**ICER vs. MTX (£/QALY)**	**Optimal treatment (£30,000 threshold)**
Children and young people aged 4-17 years						
MTX	32,765	9.932	-	-	-	MTX
ADA	65,008	10.023	32,243	0.091	353,148	

ADA, adalimumab; MTX, methotrexate.

Table 83 presents the cost-effectiveness results for the interventions after failed systemic therapy using PASI 50. The incremental cost per additional QALY gained is greater for all interventions compared to the base-case analysis. This is because the total costs have increased (a greater proportion of individuals continue treatment as responders) but total QALYs have decreased across the interventions. The difference in PASI 50 response rates between the interventions and BSC is similar to the difference observed in PASI 75 response rates. The decrease in QALYs is due to a proportionally smaller utility gain associated with PASI 50-75 response category compared to PASI 75-90 and PASI ≥90 response categories. BSC remains the optimal treatment option and the probability that any of the biologics are cost-effective at a threshold of £30,000 per additional QALY is zero.

Table 83 Scenario 3d results for interventions after failed systemic therapy: PASI 50 response assessment

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	46,396	8.807	9,990	0.097	103,388	103,388	
ADA	60,091	8.886	13,695	0.079	172,967	134,724	
Children and young people aged 12-17 years							
BSC	21,749	4.804	-	-	-	-	BSC
ETA	36,930	4.882	15,180	0.078	ED ADA	193,536	
ADA	40,024	4.947	18,275	0.143	127,783	127,783	
UST	41,833	4.957	1,809	0.010	131,128	131,128	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.4 Health-related quality of life utility values

Scenario 4a: EQ-5D utility estimates from adults

The HRQoL utility values in children and young people are subject to considerable uncertainty. EQ-5D-Y values mapped from PedsQL data from the CADMUS trial (ustekinumab) at baseline and 12

weeks follow-up were used to estimate utility gains from baseline associated with different PASI response categories (<50, 50-75, 75-90, ≥90). The utility values associated with treatment were then based on the proportion of individuals in the different PASI response categories from the NMA and the associated utility gain for each PASI category. As discussed in Section 7.4.6.3, the estimated EQ-5D-Y utility gains from the PedsQL data were of a much smaller magnitude compared to the EQ-5D values used in previous TAs in adults. It was also noted that the gains in CDLQI by PASI response category were of a smaller magnitude compared to DLQI values reported in adults. It is not clear whether these smaller utility increments observed in children and young people is a reflection of less impact of severe psoriasis on quality of life in a paediatric population or a result of small sample sizes and limited data in this population.

In this scenario, EQ-5D utility values from the adult population are used to inform the gains in utility associated with PASI response in children and young people. Utility values from TA 103 (etanercept) are used in this scenario; however, the implications of using alternative adult utility values from TA 146 (adalimumab) and TA 180 (ustekinumab) are also considered (see Table 62, Section 7.4.6.3 for comparison of utility values in children and young people and adults).

Table 84 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy using utility estimates from an adult population. The total QALYs for the interventions are lower than those of the base-case analysis, but this is due to the use of a lower baseline utility value in this scenario to prevent the utility values rising above 1.0. Note that changing the baseline utility value used in the model does not significantly affect the cost-effectiveness results because the model is driven by the incremental changes in utility score from baseline. The incremental QALYs for adalimumab compared to methotrexate of 0.150 are significantly higher than those of the base-case of 0.088. As a result, the ICER for adalimumab reduces from £308,329 to £180,773 per additional QALY. The implications of using adult utility values from TA 180 and TA 146 are even more pronounced, where the incremental gain in QALYs for adalimumab compared to methotrexate are 0.204 and 0.260, respectively, resulting in corresponding ICERs of £132,616 and £104,010 per additional QALY (see Appendix 12.13 for results based on utility estimates from TA180).

Table 84 Scenario 4a results for adalimumab as an alternative to systemic therapy: EQ-5D utility estimates from adults

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Utility estimates sourced from TA103						
Children and young people aged 4-17 years						
MTX	34,931	9.116	-	-	-	MTX
ADA	62,043	9.266	27,112	0.150	180,773	
Utility estimates sourced from TA146						
Children and young people aged 4-17 years						
MTX	34,919	9.229	-	-	-	MTX
ADA	62,000	9.489	27,081	0.260	104,010	

ADA, adalimumab; MTX, methotrexate.

Table 85presents the cost-effectiveness results for the interventions after failed systemic therapy using utility estimates from an adult population. The incremental QALYs for the interventions compared to BSC are substantially greater than those of the base-case. Ustekinumab is the most effective intervention, followed by adalimumab, etanercept and BSC, and the incremental gain in QALYs from moving from one intervention to the next is greater than the base-case results. As a result, all the ICERs are substantially lower than the base-case, falling by 55 – 61%. Etanercept has the largest reduction in the ICER, and at a threshold of £30,000 per additional QALY etanercept becomes the optimal treatment in the age group 6-11 years. In the older age group 12-17 years, etanercept is extendedly dominated by adalimumab due to the higher drug acquisition costs associated with young people requiring more than a 25 mg dose. In children and young people aged 12-17 years, the optimal treatment option remains BSC up until a threshold of £51,000 per QALY gained, when adalimumab would then enter as the first treatment in sequence. At a threshold of £60,000 per QALY, adalimumab represents the only cost-effective treatment option based on a fully incremental analysis, whereas all the biologics would be considered cost-effective based on a pairwise comparison with BSC.

The implications of using adult utility values from TA 180 and TA 146 are even more pronounced compared to TA 103 due to greater utility gains in the PASI 75-90 and ≥90 categories. The ICERs for children and young people aged 6-11 years are £22,578 (TA 146) and £21,546 (TA 180) for etanercept vs. BSC and £37,125 (TA 146) and £39,682 (TA 180) for adalimumab vs. BSC. The lowest ICERs for children and young people aged 12-17 years are £33,517 for adalimumab vs. BSC, £35,612 for ustekinumab vs. BSC and £39,247 for etanercept vs. BSC.

Table 85 Scenario 4a results for interventions after failed systemic therapy: EQ-5D utility estimates from adults

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Utility estimates sourced from TA103							
Children and young people aged 6-11 years							
BSC	36,406	7.844	-	-	-	-	ETA
ETA	43,798	8.102	7,392	0.257	28,740	28,740	
ADA	57,257	8.237	13,459	0.135	99,419	53,112	
Utility estimates sourced from TA146							
Children and young people aged 6-11 years							
BSC	36,406	7.890	-	-	-	-	ETA
ETA	43,829	8.219	7,423	0.329	22,578	22,578	
ADA	57,215	8.450	13,386	0.232	57,762	37,125	
Utility estimates sourced from TA103							
Children and young people aged 12-17 years							
BSC	21,749	4.326	-	-	-	-	BSC
ETA	33,181	4.535	11,432	0.209	ED ADA	54,717	
ADA	37,844	4.644	16,095	0.318	50,578	50,578	
UST	39,968	4.661	2,124	0.016	131,702	54,491	
Utility estimates sourced from TA146							
Children and young people aged 12-17 years							
BSC	21,749	4.326	-	-	-	-	BSC

ETA	33,195	4.618	11,446	0.292	ED ADA	39,247	
ADA	37,873	4.807	16,124	0.481	33,517	33,517	
UST	39,928	4.837	2,055	0.029	69,895	35,612	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

Scenario 4b: Utility estimates for best supportive care

The base-case analysis assumes that the utility associated with BSC is based on the proportion of individuals in the different PASI response categories for placebo of the NMA. In this scenario, the utility for BSC is set equal to the baseline value, i.e. there is no utility gain associated with BSC.

Table 86 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy assuming no utility benefit associated with BSC. For the comparison of adalimumab and methotrexate, the assumption of no utility benefit on BSC only affects the utility of non-responders. The total QALYs for both interventions are reduced and the incremental QALYs for adalimumab compared to methotrexate increase from 0.088 (base-case) to 0.102 due to higher efficacy for adalimumab, which reduces the time spent in BSC.

Table 86 Scenario 4b results for interventions as an alternative to systemic therapy: Utility in BSC equal to baseline

	Mean costs (£)	**Mean QALYs**	**Incremental costs vs. MTX (£)**	**Incremental QALYs vs. MTX**	**ICER vs. MTX (£/QALY)**	**Optimal treatment (£30,000 threshold)**
Children and young people aged 4-17 years						
MTX	34,925	9.833	-	-	-	MTX
ADA	62,010	9.935	27,085	0.102	266,161	

ADA, adalimumab; MTX, methotrexate.

Table 87 presents the cost-effectiveness results for the interventions after failed systemic therapy assuming no utility benefit associated with BSC. This assumption reduces the total QALYs for the comparator of BSC and the utility of non-responders. As a result, the incremental QALYs for the

interventions compared to BSC increases, and the incremental gain in QALYs for the interventions relative to the next best option (e.g. ustekinumab is the most effective treatment, followed by adalimumab and etanercept) also increases since less time is spent on BSC. Consequently, the ICERs for the interventions are reduced compared to the base-case values.

Table 87 Scenario 4b results for interventions after failed systemic therapy: Utility in BSC equal to baseline

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	8.593	-	-	-	-	BSC
ETA	43,785	8.724	7,378	0.131	56,430	56,430	
ADA	57,208	8.812	13,423	0.089	151,299	94,780	
Children and young people aged 12-17 years							
BSC	21,749	4.739	-	-	-	-	BSC
ETA	33,193	4.846	11,444	0.106	ED ADA	107,462	
ADA	37,844	4.917	16,095	0.178	90,292	90,292	
UST	39,969	4.929	2,124	0.012	180,232	95,871	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.5 Costs associated with best supportive care

Scenario 5a: Number of hospitalisations per annum for BSC

The resource use associated with BSC, in particular the number of hospitalisations per annum, was identified as an area of high uncertainty and a key driver of cost-effectiveness in previous TAs in adults. Two main sources have been referred to in previous appraisals: (i) resource use estimates used in NICE CG 153, which estimated an average of 26.6 inpatient days per year for individuals whose psoriasis has not responded to treatment; and (ii) resource use estimates based on Fonia et al (2010), which equates to 6.49 days of hospitalisation per annum. During previous NICE appraisals, the clinical experts considered that both sources are likely to overestimate the actual number of hospital

days and resource use associated with BSC. This is in part due to the populations considered in CG 153 and Fonia et al, (2010) where CG 153 considers a high-need population with very severe psoriasis, while Fonia et al describes care in a tertiary care centre known for treating the most severely affected individuals. The clinical experts, in recent appraisals, also noted that the number of individuals hospitalised for severe psoriasis has fallen over time and is continuing to fall. They also indicated that BSC is mostly given to individuals during their outpatient visits. As a result, the resource use associated with BSC is an area of considerable uncertainty and both sources of data have a number of shortcomings, even in the adult population.

In the base-case analysis for children and young people, it is assumed that there are no hospitalisations for psoriasis in this population. This was informed by clinical opinion where our clinical advisor suggested that hospitalisations in children and young people are very rare, partly due to the fact that this population has not yet developed co-morbidities which often complicate more severe cases of psoriasis in adults. In this scenario, the implications of assuming no inpatient stay in children and young people is explored by using an estimate of 6.49 hospitalisations per annum based on Fonia et al, and 26.6 hospitalisations per annum based on CG 153 in adults.

Table 88 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy assuming hospitalisations for BSC. For the comparison of adalimumab and methotrexate, the total costs for both interventions are increased, but the incremental costs for adalimumab compared to methotrexate decrease due to the higher efficacy associated with adalimumab which reduces the time spent in BSC. The resulting ICER decreases from £308,329 to £281,029 for 6.49 inpatient days per annum and £202,571 per additional QALY for 26.6 inpatient days per annum.

Table 88 Scenario 5a results for interventions as an alternative to systemic therapy: Number of hospitalisations per annum for BSC

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
6.49 hospitalisation days per annum for BSC based on Fonia et al (2010) in adults						
Children and young people aged 4-17 years						
MTX	52,280	9.939	-	-	-	MTX
ADA	77,153	10.027	24,873	0.089	281,029	

26.6 hospitalisation days per annum for BSC based on CG 153 in adults						
Children and young people aged 4-17 years						
MTX	106,053	9.939	-	-	-	MTX
ADA	123,929	10.027	17,876	0.088	202,571	

ADA, adalimumab; MTX, methotrexate.

Table 89 presents the cost-effectiveness results for the interventions after failed systemic therapy assuming hospitalisations for BSC. Under this assumption, the costs of BSC increase by £147.67 and £605.25 per 4-week cycle for 6.49 and 26.6 inpatient days per annum, respectively. As a result, the total costs associated with the comparator of BSC increase and the costs for non-responders increase. For children and young people aged 6-11 years, the reduction in incremental costs for etanercept vs. BSC is sufficient to make etanercept the optimal treatment option at a threshold of £30,000 per QALY with 6.49 inpatient days per annum. When the number of hospitalisations per annum are increased to 26.6 days in this age group, etanercept becomes the least costly treatment option and BSC becomes dominated by etanercept (i.e. BSC costs more than etanercept but produces fewer QALYs). In this same age group, adalimumab only enters as a cost-effective option if the threshold increases to £70,000 per QALY gained.

For children and young people aged 12-17 years, etanercept is dominated by adalimumab. The ICER for adalimumab compared to BSC is £74,501 per QALY when 6.49 inpatient days per annum are assumed. When the number of hospitalisations are increased to 26.6 days adalimumab becomes the the least costly treatment option and the most cost-effective option at a threshold of £30,000 per QALY. The ICER for ustekinumab compared to adalimumab is £118,665 per QALY with 26.6 inpatient days per annum.

Table 89 Scenario 4b results for interventions after failed systemic therapy: Utility in BSC equal to baseline

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
6.49 hospitalisation days per annum for BSC based on Fonia et al (2010) in adults							
Children and young people aged 6-11 years							

BSC	55,597	8.710	-	-	-	-	ETA
ETA	58,500	8.813	2,903	0.103	28,286	28,286	
ADA	70,016	8.891	11,516	0.078	148,586	80,046	
Children and young people aged 12-17 years							
BSC	32,333	4.804	-	-	-	-	BSC
ETA	40,099	4.887	7,766	0.083	ED ADA	93,102	
ADA	43,188	4.950	10,855	0.146	74,501	74,501	
UST	45,064	4.960	1,875	0.010	186,634	81,735	
26.6 hospitalisation days per annum for BSC based on CG 153 in adults							
Children and young people aged 6-11 years							
BSC	115,063	8.710	5,550	-0.180	Dominated	-	ETA
ETA	104,113	8.813	-	-	-	Dominant	
ADA	109,512	8.891	5,399	0.077	69,797	Dominant	
Children and young people aged 12-17 years							
BSC	65,129	4.804	4,119	-0.156	Dominated	-	ADA
ETA	61,537	4.887	1,777	-0.062	Dominated	Dominant	
ADA	59,760	4.950	-	-	-	Dominant	
UST	61,010	4.960	1,250	0.011	118,665	Dominant	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.6 Costs associated with adverse events

Scenario 6: Costs of severe infections and malignancies

In the absence of robust evidence on the incidence of adverse events in children and young people, the base-case analysis assumed that there are no adverse events associated with treatment. In this scenario, the costs associated with serious adverse events including non-melanoma skin cancer, malignancies other than non-melanoma skin cancer and severe infections are included. These events are expected to be very rare.

Table 90 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy with costs of adverse events included. The incremental costs for adalimumab have increased by a very small amount of £400. The resulting impact on the ICER is minor, increasing it from £308,329 to £311,067 per QALY gained.

Table 90 Scenario 6 results for interventions as an alternative to systemic therapy: Costs of severe infections and malignancies included

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						
MTX	35,176	9.939	-	-	-	MTX
ADA	62,694	10.027	27,518	0.088	311,067	

ADA, adalimumab; MTX, methotrexate.

Table 91 presents the cost-effectiveness results for the interventions after failed systemic therapy with costs of adverse events included. As expected, the incremental costs for the interventions relative to BSC increase, but the resulting impact on the ICER results for all interventions is very minor.

Table 91 Scenario 6 results for interventions after failed systemic therapy: Costs of severe infections and malignancies included

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	44,310	8.813	7,904	0.103	76,810	76,810	
ADA	57,911	8.891	13,601	0.077	176,012	119,357	
Children and young people aged 12-17 years							
BSC	21,749	4.804	-	-	-	-	BSC
ETA	33,584	4.887	11,835	0.083	ED ADA	142,041	

ADA	38,382	4.950	16,633	0.146	113,974	113,974	
UST	40,063	4.960	1,682	0.010	169,254	117,497	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.7 Treatment withdrawal rates

Scenario 7: Withdrawal rates from treatment

In the base-case analysis discontinuation from treatment is modelled as an all-cause withdrawal probability of 20% per annum, which is applied to all interventions. This withdrawal rate has been used in all previous TAs in adults and is consistent with long-term survival rates of biologics from the BADBIR audit. In the absence of alternative data in children and young people, this scenario considers two separate withdrawal rates of 10% and 30% per annum.

Table 92 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy for treatment withdrawal rates of 10% and 30% per annum. The lower withdrawal rate implies that individuals spend longer on treatment before moving to BSC, while the higher withdrawal rate means that individuals spend less time on treatment and more time on BSC. The total costs for adalimumab increase for the 10% rate and decrease for the 30% rate, while the total costs for methotrexate decrease for the 10% rate and increase for the 30% rate. This opposite effect between the treatments arises because the drug acquisition costs of adalimumab (£704.28 per 4-week cycle) are proportionally greater than the costs of BSC (approximately £284 per 4-week cycle) compared to the drug acquisition costs of methotrexate (approximately £60 per 4-week cycle) relative to costs of BSC. As a result, the withdrawal rate has less impact on the total costs of methotrexate compared to adalimumab. The incremental costs for adalimumab vs. methotrexate are £40,781 and £19,692 for 10% and 30% annual withdrawal rate, respectively, compared to the base-case incremental costs of £27,084. In terms of health outcomes, the more time spent on treatment the higher the utility gains. Therefore, the QALYs increase with the lower withdrawal rate and decrease with the higher rate. The resulting ICERs for adalimumab are £298,846 and £318,188 per additional QALY for 10% and 30% annual withdrawal rates, respectively, compared to the base-case value of £308,329 per additional QALY.

Table 92 Scenario 7 results for interventions as an alternative to systemic therapy: Treatment withdrawal rates of 10% and 30% per annum

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						
Withdrawal rate of 10% per annum						
MTX	32,274	9.990	-	-	-	MTX
ADA	73,055	10.126	40,781	0.136	298,846	
Withdrawal rate of 30% per annum						
MTX	36,364	9.912	-	-	-	MTX
ADA	56,057	9.974	19,692	0.062	318,188	

ADA, adalimumab; MTX, methotrexate.

Table 93 presents the cost-effectiveness results for the interventions after failed systemic therapy for treatment withdrawal rates of 10% and 30% per annum. The total costs for all the interventions increase for the 10% rate and decrease for the 30% rate due to the accumulation of higher drug acquisition costs while on treatment for longer. This increase in costs is counterbalanced by an increase in utility gains while on treatment. The resulting impact on the ICERs are minimal. BSC remains the optimal treatment option at a threshold of £30,000 per QALY gained.

Table 93 Scenario 7 results for interventions after failed systemic therapy: Treatment withdrawal rate of 10% and 30% per annum

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Withdrawal rate of 10% per annum							
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	49,361	8.864	12,955	0.154	84,138	84,138	
ADA	66,830	8.977	17,469	0.113	154,817	114,029	

Children and young people aged 12-17 years							
BSC	21,749	4.804	-	-	-	-	BSC
ETA	36,194	4.911	14,445	0.107	ED ADA	135,131	
ADA	42,002	4.989	20,253	0.185	109,399	109,399	
UST	44,400	5.002	2,398	0.013	182,511	114,244	
Withdrawal rate of 30% per annum							
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	40,978	8.784	4,572	0.074	61,924	61,924	
ADA	51,745	8.841	10,766	0.056	190,888	117,774	
Children and young people aged 12-17 years							
BSC	21,749	4.804	-	-	-	-	BSC
ETA	30,952	4.870	9,203	0.066	ED ADA	139,568	
ADA	34,732	4.920	3,780	0.050	75,289	111,784	
UST	36,599	4.928	1,867	0.008	230,608	119,527	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.8 Biosimilars

Scenario 8: Reduction in the cost of etanercept

The biosimilar of etanercept, Benapali 50 mg, does not have marketing authorisation for use in children and young people. In this scenario, the drug acquisition cost of etanercept is reduced by approximately 10% to match the cost of Benapali in adults.

Table 94 presents the cost-effectiveness results for the interventions after failed systemic therapy for a 10% reduction in the acquisition cost of etanercept. For children and young people aged 6-11 years, the incremental cost for etanercept relative to BSC is reduced by £580, which reduces the ICER from £71,903 to £66,240 per additional QALY. For children and young people aged 12-17 years, the incremental cost for etanercept relative to BSC is reduced by £1,480, which is greater than that

observed in the younger age group because it is assumed that the 10% reduction in the drug acquisition cost of etanercept only applies to children ≥10 years who require 50 mg of etanercept. The implications of the cost reduction has a very minor impact on the cost-effectiveness results.

Table 94 Scenario 8 results for interventions after failed systemic therapy: Reduction in the cost of etanercept to match unit cost of Benepali

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	43,225	8.813	6,819	0.103	66,240	66,240	
ADA	57,272	8.891	14,047	0.077	181,897	115,815	
Children and young people aged 12-17 years							
BSC	21,749	4.804	-	-	-	-	BSC
ETA	31,719	4.887	9,970	0.083	ED ADA	119,501	
ADA	37,826	4.949	16,077	0.146	110,437	110,437	
UST	39,908	4.960	2,082	0.010	205,422	116,619	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.6 Discussion of the cost-effectiveness results and alternative scenarios

The results of the base-case analysis suggest that adalimumab is not a cost-effective treatment option when positioned in the pathway as an alternative to systemic therapy, with an ICER of £308,329 per QALY gained compared to methotrexate. When positioned after systemic therapy, the ICER for adalimumab compared to BSC is £115,825 per QALY for ages 6-11 years and £110,430 per QALY for ages 12-17 years. At a threshold of £30,000 per QALY gained, etanercept is not a cost-effective option for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to systemic therapies or phototherapies. The ICER for etanercept compared to BSC is £71,903 per QALY for ages 6-11 years and is extendedly dominated by adalimumab for ages 12-17

years. Ustekinumab is the most effective treatment in children and young people aged 12-17 years but it is also the most costly treatment. Based on a fully incremental analysis, the ICER for ustekinumab compared to adalimumab is £201,507 per QALY, while the ICER for ustekinumab compared to BSC is £116,568 per QALY. The base-case results suggest that BSC is the only cost-effective form of management for the treatment of severe plaque psoriasis unless the threshold reaches at least £111,000 per additional QALY. The probability that any of the biologics are cost-effective at a threshold of £30,000 per QALY is zero.

The lack of cost-effectiveness appears to result from very modest QALY gains associated with treatment. The small incremental difference in health benefits between the treatments is a result of relatively small utility gains in EQ-5D-Y associated with higher PASI response rates. As a consequence, the benefits of achieving a greater PASI response do not translate into large improvements in health outcomes. The acquisition costs of the treatments are also not substantially different: ustekinumab costs £715.67 per 4-week cycle (i.e. £2,147 per dose with each dose given at 12 weekly intervals) compared to £704.28 per 4-week cycle (i.e. £352.14 per dose given every 2 weeks) for adalimumab and £715.00/£357.50 per 4-week cycle (i.e. £178.75 per 50 mg / £89.38 per 25 mg dose given each week) for etanercept depending on patient weight.

A number of scenarios were used to explore the impact of alternative assumptions on the cost-effectiveness of the biological treatments. Table 95 and Table 96 summarise the cost-effectiveness results for the scenario analyses as an alternative to systemic therapy and after failed systemic therapy, respectively.

Table 95 Summary of the cost-effectiveness results for adalimumab as an alternative to systemic therapy: base-case results and alternative scenarios

	Analysis	ICER ADA vs. MTX (£/QALY)
Children and young people aged 4-17 years	**Base-case**	**308,329**
	Scenario 1: Off-label use of biologics outside age constraints	-
	Scenario 2: Common time horizon of 14 years	-
	Scenario 3a: Direct trial evidence estimates of effect	549,899
	Scenario 3b: Indirect treatment comparison estimates	-
	Scenario 3c: NMA using minimum evidence from adult population	211,259

	Scenario 3d: PASI 50 response assessment	353,148
	Scenario 4a: EQ-5D utility estimates from adults TA 103	180,773
	EQ-5D utility estimates from adults TA 146	104,010
	Scenario 4b: Utility in BSC equal to baseline value	266,161
	Scenario 5: Hospitalisations of 6.49 days per annum	281,029
	Hospitalisations of 26.6 days per annum	202,571
	Scenario 6: Costs associated with adverse events	311,067
	Scenario 7: Treatment withdrawal rate of 10% per annum	298,846
	Treatment withdrawal rate of 30% per annum	318,188
	Scenario 8: Unit cost of biosimilar for etanercept	-

-, scenario is not applicable; ADA, adalimumab; MTX, methotrexate.

Table 96 Summary of the pairwise cost-effectiveness results for interventions after failed systemic therapy: base-case results and alternative scenarios

	Analysis	**ICER (£/QALY)**		
		ADA vs. BSC	**ETA vs. BSC**	**UST vs. BSC**
	Base-case	**117,080**	**-**	**-**
	Scenario 1: Off-label use of biologics outside age constraints	117,080	59,924	121,779
Children and young people aged 6-11 years	**Base-case**	**115,825**	**71,903**	-
	Scenario 1: Off-label use of biologics outside age constraints	-	-	-
	Scenario 2: Common time horizon of 14 years	115,592	73,153	-
	Scenario 3a: Direct trial evidence estimates of effect	-	75,350	-
	Scenario 3b: Indirect treatment comparison estimates	-	-	-
	Scenario 3c: NMA using minimum evidence from adult population	137,329	68,485	-
	Scenario 3d: PASI 50 response assessment	134,724	103,388	-
	Scenario 4a: EQ-5D utility estimates from adults TA 103	53,112	28,740	-
	EQ-5D utility estimates from adults TA 146	37,125	22,578	
	Scenario 4b: Utility in BSC equal to baseline value	94,780	56,430	-
	Scenario 5: Hospitalisations of 6.49 days per annum	80,046	28,286	-
	Hospitalisations of 26.6 days per annum	Dominant	Dominant	
	Scenario 6: Costs associated with adverse events	119,357	76,810	-

	Scenario 7: Treatment withdrawal rate of 10% per annum	114,029	84,138	-
	Treatment withdrawal rate of 30% per annum	117,774	61,924	
	Scenario 8: Unit cost of biosimilar for etanercept	115,815	66,240	-
Children and young people aged 12-17 years	**Base-case**	**110,430**	**137,059**	**116,568**
	Scenario 1: Off-label use of biologics outside age constraints	-	-	-
	Scenario 2: Common time horizon of 14 years	109,531	135,354	114,439
	Scenario 3a: Direct trial evidence estimates of effect	-	-	116,982
	Scenario 3b: Indirect treatment comparison estimates	-	128,903	119,092
	Scenario 3c: NMA using minimum evidence from adult population	132,682	130,389	118,515
	Scenario 3d: PASI 50 response assessment	127,783	193,536	131,128
	Scenario 4a: EQ-5D utility estimates from adults TA 103	50,578	54,717	54,491
	EQ-5D utility estimates from adults TA 146	33,517	39,247	35,612
	Scenario 4b: Utility in BSC equal to baseline value	90,292	107,462	95,871
	Scenario 5: Hospitalisations of 6.49 days per annum	74,501	93,102	81,735
	Hospitalisations of 26.6 days per annum	Dominant	Dominant	Dominant
	Scenario 6: Costs associated with adverse events	113,974	142,041	117,497
	Scenario 7: Treatment withdrawal rate of 10% per annum	109,399	135,131	114,244
	Treatment withdrawal rate of 30% per annum	111,784	139,568	119,527
	Scenario 8: Unit cost of biosimilar for etanercept	110,437	119,501	116,619

-, scenario is not applicable; ADA, adalimumab; MTX, methotrexate; ETA, etanercept; UST, ustekinumab.

The scenarios which have the most impact on the cost-effectiveness results are: (i) utility estimates from an adult population (scenario 4a); (ii) no health benefits associated with BSC (scenario 4b); and (iii) hospitalisations associated with BSC (scenario 5).

The gains in utility in the adult population for the different PASI response categories are of an order of magnitude up to 6.6 times greater than the utility gains estimated in children and young people. It is unclear whether this difference reflects a lower impact of severe psoriasis on health-related quality of life in children and young people or simply reflects the limited data available in this population and the significant uncertainty surrounding quality of life estimates for a paediatric psoriasis population. The use of utility values from an adult population brings the ICER of etanercept compared to BSC under a threshold of £30,000 per QALY gained in children and young people aged 6-11 years. The

ICERs for ustekinumab and adalimumab with adult utility data are reduced significantly but remain above £30,000 per QALY threshold, even with the most favourable estimates from TA 146. Under the assumption of no health benefits associated with treatment on BSC, the ICERs are reduced by up to £30,000 from the base-case value but remain quite high with the lowest ICER of £56,430 per QALY gained for etanercept compared to BSC.

The number of hospitalisations associated with BSC is a key driver of the cost-effectiveness of the biological interventions. This was also identified as a key consideration in previous TAs of adults. Based on clinical opinion, the base-case analysis assumed that hospitalisations for severe psoriasis are very rare in children and young people. If the average number of hospitalisations per annum is considered to be as much as 6.49 days based on Fonia et al (2010), the ICERs for the interventions reduce significantly; however, the only ICER which falls below £30,000 is for the use of etanercept compared to BSC in children and young people aged 6-11 years. If the average number of hospitalisations per annum is increased significantly to 26.6 days per annum based on the very high need population described in CG 153, the biological treatments compared to BSC are all considered cost-effective in individuals who have failed systemic therapy. However, recent appraisals in adults have considered the estimate of 26.6 days per annum to be too high.

The combined impact of the most optimistic utility estimates in adults (TA 146), 6.49 inpatient days per annum and no health benefits for BSC are presented in Table 97 and Table 98 for the use of the interventions before and after systemic therapy. The combined impact of the utility gains from an adult population and an assumption of 6.49 hospitalisations per annum is sufficient to reduce the pairwise ICERs for the interventions compared to BSC to below a threshold of £30,000 per additional QALY, while the additional assumption of no health benefits on BSC reduces the ICERs further to below a threshold of £20,000 per additional QALY. Based on a fully incremental analysis, etanercept is the optimal treatment for children and young people aged 6-11 years, while adalimumab is the optimal treatment for ages 12-17 years.

Table 97 Combined impact of alternative assumptions on the cost-effectiveness of adalimumab as an alternative to systemic therapy

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						

Adult utility data (TA 146) + 6.49 hospitalisations per annum						
MTX	52,273	9.229	-	-	-	MTX
ADA	77,106	9.489	24,834	0.260	95,527	
Adult utility data (TA 146) + 6.49 hospitalisations per annum + no health benefits for BSC						
MTX	52,291	8.351	-	-	-	MTX
ADA	77,136	8.727	24,845	0.376	66,126	

ADA, adalimumab; MTX, methotrexate.

Table 98 Combined impact of alternative assumptions on the cost-effectiveness of the interventions after failed systemic therapy

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
Adult utility data (TA 146) + 6.49 hospitalisations per annum							
BSC	55,597	7.890	-	-	-	-	ETA
ETA	58,515	8.218	2,917	0.328	8,897	8,897	
ADA	69,982	8.451	11,467	0.233	49,274	25,657	
Adult utility data (TA 146) + 6.49 hospitalisations per annum + no health benefits for BSC							
BSC	55,597	6.918	-	-	-	-	ETA
ETA	58,506	7.474	2,909	0.557	5,227	5,227	
ADA	70,021	7.809	11,515	0.334	34,438	16,190	
Children and young people aged 12-17 years							
Adult utility data (TA 146) + 6.49 hospitalisations per annum							
BSC	32,333	4.351	-	-	-	-	ADA
ETA	40,102	4.618	7,769	0.266	ED ADA	29,177	
ADA	43,193	4.807	10,860	0.455	23,861	23,861	
UST	45,087	4.837	1,894	0.031	61,722	26,253	
Adult utility data (TA 146) + 6.49 hospitalisations per annum + no health benefits for BSC							

BSC	32,333	3.815	-	-	-		ADA
ETA	40,100	4.269	7,767	0.454	ED ADA	17,108	
ADA	43,194	4.537	10,861	0.722	15,040	15,040	
UST	45,099	4.579	1,905	0.042	45,818	16,716	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

8 Assessment of factors relevant to the NHS and other parties

The potential extra cost to the NHS of providing adalimumab, etanercept or ustekinumab to children and young people with moderate to severe plaque psoriasis is largely uncertain, given the paucity of evidence on the health care resource use specific to this population and the uncertainties on the effectiveness evidence base. The resource use associated with BSC in terms of the expected number of hospitalisations per annum was identified as a key area of uncertainty, similarly to previous TAs of psoriasis in adults. Reducing uncertainty at this level, would allow a more accurate assessment of the the potential impact on the consumption of NHS resources of providing biologic treatment to children and young people with moderate to severe plaque psoriasis.

9 Discussion

9.1 Statement of principal findings

One multicentre RCT (M04-717) found that adalimumab at the licenced dose of 0.8mg/kg (up to 40mg) lead to significantly greater responses than methotrexate for the outcomes of PASI 50 and PASI 75, but not PASI 90 at 16 weeks. PGA 0/1 response rates were non-significantly higher for adalimumab 0.8mg/kg than methotrexate. The benefits of half-dose adalimumab were not statistically greater than those for methotrexate. Evidence on quality of life was inconsistent across different measures, possibly due to baseline imbalance on PedsQL. In children and young people, adalimumab did not appear to be associated with an increase in adverse effects relative to methotrexate over 16 weeks, though the possibility of rare adverse events cannot be entirely excluded. The trial did not provide evidence for children aged 4 to 6 years of age. [redacted]

One multicentre RCT (20030211) found etanercept to be significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50, 75 and 90, and PGA 0/1 response rates at 12 weeks. Improvements in health-related quality of life were larger for etanercept than placebo, but only reached statistical significance when measured by CDLQI. Adverse events rates were mostly similar in etanercept and placebo groups at 12 weeks with no serious adverse events observed for either treatment. However, a higher observed rate of infections among participants receiving etanercept was of borderline statistical significance. Relatively few young children (9% aged under 8 years; 4.3% aged under 6 years) were included in study. Up to six years open-label follow-up (20050111) found that the proportion of PASI and PGA responders were stable over time, though only 36% of participants were available at the latest follow-up point. The proportion of participant withdrawing due to lack of efficacy is unknown. Through 264 weeks of follow-up, withdrawals due to adverse events were infrequent, and no deaths or malignancies were observed.

One multicentre trial (CADMUS) in children 12 to 17 years of age found both the standard dosage and half dosage of ustekinumab were significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50, 75 and 90 and PGA 0/1 responses at 12 weeks. Both ustekinumab dosages also lead to significantly greater improvements in health-related quality of life

(CDLQI and PedsQL). Among participants originally allocated to ustekinumab, PASI and PGA effects observed at 12 weeks appeared to be largely sustained at 52 weeks, with few withdrawals due to lack of efficacy. There were no notable adverse effects associated with ustekinumab, though the number of observations was small and longest the follow-up time was just 60 weeks. Few participants withdrew due to adverse effects.

No statistically significant differences were identified in PASI response outcomes across different age groups within the trials. Therefore, in order to establish the relative efficacy of the interventions the analyses assumed that treatment effects were exchangeable across ages in the population of children and young people. Based on an indirect treatment comparison of PASI response outcomes at 12 weeks from study 20030211 and CADMUS, using the placebo arms of the trials as a common comparator, ustekinumab is a more effective treatment option compared to etanercept. The lack of a common comparator arm between the adalimumab trial (M04-717) and study 20030211 and CADMUS meant that it was not possible to draw conclusions about the relative efficacy of adalimumab, etanercept and ustekinumab based on the three trials in children and young people alone. In order to fill this evidence gap for the economic analysis it was necessary to draw strength from a wider evidence base of trials examining the efficacy of the interventions in adults. This wider network of evidence was used to facilitate an indirect comparison of adalimumab with etanercept and ustekinumab by examining the relationships that exist between the different interventions and study populations (i.e. children and young people and adults) and drawing conclusions for each population based on the full network of evidence. Adjustments were also made for differences in placebo response rates across the trials. The network meta-analysis results – adjusted for differences in population and placebo response rates – demonstrated that ustekinumab is the most effective intervention, followed by adalimumab, etanercept and methotrexate in children and young people. These rankings also matched those of the adult population. The absolute PASI response outcomes were estimated to be higher in children and young people compared to adults, due to higher placebo response rates in study 20030211 and CADMUS, but the relative effectiveness of the interventions were similar across the two populations.

The cost-effectiveness of adalimumab, etanercept and ustekinumab was evaluated by comparing the additional costs of the interventions to each other and to either, methotrexate or BSC depending on the position of the intervention in the pathway, with the additional health benefits, over a time horizon sufficient to capture differences in costs and effects. Health outcomes were expressed in QALYs and all costs were considered from the perspective of the NHS & PSS. Due to differences in the

marketing authorisation of the interventions by age and positioning of adalimumab before non-biologic systemic therapy, cost-effectiveness estimates were presented for three base-case populations: (i) children and young people aged 4-17 years with adalimumab compared to methotrexate; (ii) children and young people aged 6-11 years with adalimumab and etanercept compared to BSC; and (iii) children and young people aged 12-17 years with adalimumab, etanercept and ustekinumab compared to BSC.

The paucity of clinical and economic evidence to inform the evaluation of cost-effectiveness in children and young people resulted in a number of strong assumptions and uncertainties in the analysis. These assumptions arose from the need to extrapolate data from the adult population to inform the population of children and young people. A number of alternative scenarios were considered in order to examine the impact of these assumptions on the cost-effectiveness results. The base-case cost-effectiveness results indicated that adalimumab was not a cost-effective treatment option when positioned in the treatment pathway as an alternative to systemic therapy. When positioned after systemic therapy, the ICER for adalimumab compared to BSC was more favourable, but it still remained well above conventional NICE thresholds of cost-effectiveness. Etanercept was also not considered a cost-effective option after systemic therapy for ages 6-11 years and was extendedly dominated by adalimumab for ages 12-17 years. Ustekinumab was the most effective treatment in children and young people aged 12-17 years but it was also the most costly treatment. The ICERs for ustekinumab compared to adalimumab and BSC were above £100,000 per QALY gained. Based on base-case assumptions, the probability that any of the biological treatments would be considered cost-effective at the higher end of the NICE threshold of £30,000 per QALY was zero.

The lack of cost-effectiveness of the biologics compared to BSC was due to very modest QALY gains associated with improvements in PASI response outcomes. The difference in total costs between the interventions was driven by the time spent on BSC (non-responders). The acquisition costs of the biologics were not significantly different. The key drivers of cost-effectiveness were the utility estimates, the health benefits associated with BSC, and the number of hospitalisations on BSC. Extrapolating utility estimates from the adult population to the population of children and young people reduced the ICERs by over 50% because the gains in utility associated with different PASI response outcomes were up to 6.6 times greater than the estimated utility gains from mapping PedsQL data from CADMUS onto EQ-5D-Y. The choice of EQ-5D utility values from other previous TAs in adults also had a significant impact. The base-case analysis included the possibility that psoriasis can improve with BSC and used the response rates for placebo from the NMA to inform this. When this

assumption was altered to assume that there were no health benefits from BSC, the ICERs were reduced by £20,000 - £30,000 per additional QALY. The resource use associated with BSC in terms of the expected number of hospitalisations per annum had a major impact on the cost-effectiveness results, reducing the ICERs compared to BSC considerably with the more days of hospitalisations assumed. This was also identified as a key area of uncertainty in previous TAs of psoriasis in adults.

9.2 Strengths and limitations of the assessment

Strengths

The reviews of clinical and cost-effectiveness were based on comprehensive searches of the literature, which were supplemented by data from multiple additional sources, including EMEA and FDA documents and clinical study reports, allowing the inclusion of unpublished studies and data.

The clinical effectiveness review presented here focused directly on evidence relating to children and young people with plaque psoriasis, resulting in just four relevant studies for the three biologics of interest. Consequently, the total number of included participants and average length of follow-up (for adalimumab and ustekinumab) was limited. However, this provides the best evidence of efficacy and short- to medium-term safety of adalimumab, etanercept and ustekinumab directly relevant to the decision problem.

A key strength of this evaluation was the fact that it went beyond the scope of the appraisal by bringing together evidence from the adult population in order to support an economic evaluation in children and young people. The review of cost-effectiveness evidence in this population, and the absence of economic models from the companies, highlighted the challenges involved in evaluating the cost-effectiveness of biological interventions in children and young people with plaque psoriasis. The fundamental challenge was the limited clinical evidence base for short- and long-term outcomes. Therefore, any estimation was going to be subject to a number of uncertainties. Clinical opinion suggests that the management and approach to care of treatment appears to mirror that used in adults. Therefore, in the absence of evidence, it seemed reasonable to extrapolate data from the adult population to inform the economic model in children and young people. This approach was also supported by the companies.

A major strength of the network meta-analysis was the fact that it brought together clinical evidence from the adult population in order to allow the evidence from the M04-717 trial to be connected with the other paediatric trials, while making an adjustment for any differences in PASI outcomes by population. This enabled the relative effectiveness of adalimumab, etanercept and ustekinumab to be estimated in children and young people by using what is already known about the relative effectiveness of the interventions in adults.

The economic model represents the first attempt at evaluating the cost-effectiveness of biological treatments in children and young people. This model used the same approach as the most widely accepted York model, which has been used in previous TAs in adults. This ensures consistency in the approaches undertaken for both populations. The main changes have been the availability of new evidence, including evidence in a paediatric population, health-related quality of life outcomes specific to a paediatric population, and resource use and cost estimates. The analysis also attempted to reflect differences between the interventions in terms of their marketing authorisation by age and positioning of treatment before and after systemic therapy.

Limitations

The flow of participants through the etanercept studies was complex, with data spread across a number of publications and regulatory data sources. No CSR data were available to investigate this in further detail. Similarly, the lack of a CSR meant that some details of study conduct required for a complete risk of bias assessment were unavailable. Wherever possible, we avoided making assumptions and presented the most complete data as reported.

In the absence of sufficient clinical evidence and economic data in children and young people, a simplified modelling approach was undertaken. This simplified approach involved modelling a single line of therapy before receiving BSC. However, plaque psoriasis is a lifelong chronic condition where if the condition no longer responds to a biological treatment, individuals are usually offered another biological treatment; a pattern which is likely to be repeated over an individual's lifetime. This means that treatments are usually trialled on an individual basis until an effective option is found. If individuals do not respond to multiple biological interventions, then the only remaining option is BSC. This approach to treatment is expected to be similar for children and young people and adults. However, much more caution is usually exercised in the younger population due to the limited availability of licensed treatment options. Therefore, the modelling approach undertaken is likely to be a simplification of reality. This simplification was necessary due to an absence of evidence on the

sequential use of biologics in children and young people, where treatment response would need to be conditioned on prior biological treatments received. The modelling of sequential treatments also requires every potential treatment permutation to be considered. This has already presented a significant issue in the most recent TAs for adults which did consider more than one line of therapy (TA 368 for apremilast and the appraisal of ixekizumab which is currently out for consultation), where the modelled sequences did not reflect current clinical practice. Any attempt at treatment sequencing in the population of children and young people would be highly uncertain; this is not only because of the lack of data but also due to the further complication of differences between the biological treatments in terms of marketing authorisation by age, severity and positioning in the treatment pathway. Furthermore, if a cost-effectiveness analysis identifies the optimal treatment sequence in children and young people, this is less likely to be helpful to clinical practice as that particular sequence may not be suitable for all (or any) individuals. For example, treatment in this population is usually tailored to the child or young person due to needle phobia or the presence of psoriatic arthritis.

9.3 Uncertainties

Evidence on the efficacy and safety of adalimumab, etanercept and ustekinumab in younger children is mostly absent from the included RCTs. The ustekinumab trial (CADMUS) restricted inclusion to participants aged over 12 years. No subjects below the age of 6 received the licenced dose of adalimumab (0.8 mg/kg), with the majority of participants in the adalimumab trial being 9-18 years of age. Similarly, only 19 children (9%) included in the trial evaluating etanercept were under the age of 8 years.

It has not been possible to define moderate or severe psoriasis in children and young people. The definition varies across the three trials in this population, with ustekinumab licensed for moderate to severe psoriasis, while etanercept and adalimumab are licensed for severe psoriasis. Previous TAs in adults has defined severe psoriasis as a PASI score of 10 or more and a DLQI of more than 10. The trial populations for etanercept and ustekinumab included children or young people with a baseline PASI score of 12 or more (mean score was around 18-21), a 10% or greater of body surface area affected (for at least 6 months in the case of ustekinumab), and a Physician Global Assessment score of at least 3. The trial population for adalimumab included a baseline PASI score of 20 or more, involvement of 20% or greater of body surface area affected or very thick lesions and 10% or greater

body surface area affected, a Physician Global Assessment score of at least 4, or a baseline PASI score of 10 or more (mean score was 18.3 in trial) and a number of other characteristics such as active psoriatic arthritis or CDLQI of more than 10. There does not appear to be a standard routine assessment because the tools of PASI and CDLQI have not been validated in this population.

The paucity of clinical and economic evidence to inform the cost-effectiveness of biological treatments in a population of children and young people has led to a number of uncertainties. The most significant of these is the health-related quality of life gains associated with treatment. The incremental health benefits between the biological treatments are very sensitive to the utility gains associated with PASI response outcomes. In the base-case analysis these gains were estimated based on a mapping of PedsQL data from the ustekinumab trial onto EQ-5D-Y values. The PedsQL data were based on a very small sample size. In the absence of any other data, this represented the only method available to estimate EQ-5D values in this population. However, the PedsQL or CDLQI instruments have not been validated for the assessment of disease severity in a population of children and young people with psoriasis and PedsQL does not appear to be used routinely in clinical practice. Furthermore, these instruments are not specific to psoriasis and therefore may not capture all the important impacts of the condition, such as anxiety, depression, schooling and social interactions with friends. The PedsQL data from the ustekinumab trial is also based on a population aged 12-17 years; therefore it is unlikely to reflect the same quality of life outcomes in younger children. For example, very young children may not have developed a certain level of self-awareness, which means that any quality of life instrument in young children is unlikely to be accurate. Quality of life outcomes in children and young people can be lower due to the fear of subcutaneous injections rather than the severity of the condition itself.

The cost-effectiveness results are also very sensitive to the benefits and resource use associated with BSC. The number of hospitalisations per annum in children and young people is an area of considerable uncertainty. Extrapolating the data on hospitalisations from adults to this population is also subject to uncertainty due to a number of shortcomings that exist among all sources of data on resource use for BSC. Given these uncertainties the results from the base-case cost-effectiveness analysis should be considered alongside the results of the separate scenarios.

10 Conclusions

Etanercept and ustekinumab, within their licenced indications, lead to significantly greater improvements in psoriasis symptoms than placebo at 12 weeks' follow-up. Quality of life benefits were also observed. While these effects appear to persist beyond 12 weeks, their magnitude and persistence is less certain.

Adalimumab at the licenced dose of 0.8mg/kg (up to 40mg) leads to significantly greater improvements in psoriasis symptoms than methotrexate for some, but not all measures at 16 weeks. Observed quality of life benefits were inconsistent across different measures.

With the exception of a non-significantly higher observed rate of infections among participants receiving etanercept, there was little evidence of short-term adverse events. However, the relatively small number of observations and limited length of follow-up across trials cannot exclude the possibility of rare events being undetected.

The absence of head-to-head comparisons of the three drugs meant that these treatments would have to be compared indirectly. In addition, the lack of a common comparator meant that a wider network of data from adults with psoriasis needed to be used to connect the network. This further increased uncertainty about the relative effects of these treatments and further diminished the relative contribution of data from children to the analysis.

Based on the economic assessment, the majority of ICERs for the use of biologics in children and young people are in excess of NICE's usual range of cost-effectiveness and are reduced significantly only when combined assumptions that align with those for the management of psoriasis in adults are adopted.

10.1 Implications for service provision

- While two biologics are licenced for younger children with plaque psoriasis (adalimumab from age four years, etanercept from six years) the existing randomised trials include very few young children, with just four children under the age of six having received biologic treatment (etanercept in all cases). Consequently, evidence of the effectiveness and safety of these treatments in younger children has been generalised from observations in older children and young people.

10.2 Suggested research priorities

- Adequately powered randomised trials are needed to inform the effectiveness of biological treatments in biologic-experienced populations of children and young people, i.e. treatment response rates conditional on prior treatment are required.
- In particular, further evidence is needed to inform the clinical effectiveness and safety of adalimumab and etanercept in younger children
- Further research is needed to establish the impact of biological therapies on improving the health-related quality of life of children and young people. Future trials should consider collecting direct estimates of EQ-5D-Y.
- There is a need for PASI and other tools such as CDLQI to be validated for disease severity assessment in a population of children and young people.
- With the introduction of biological treatments in the population of children and young people continued collection of data through biologic registries for < 18 years is warranted in order to investigate safety, patterns of treatment switching, and long-term withdrawal rates.
- Resource use and costs associated with best supportive care is an area of further research.

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223. Christiansen JV, Holm P, Moller R, Reymann F, Schmidt H. Etretinate (tigason) and betamethasone valerate (celeston valerate) in the treatment of psoriasis. A double-blind, randomized, multicenter trial. *Dermatologica* 1982;**165**:204-7.
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225. Wyeth. *Study evaluating the safety of Enbrel (etanercept)*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2008. URL: https://ClinicalTrials.gov/show/NCT00683384 (accessed 24 May 2016).
226. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013;**33**:607-17. http://dx.doi.org/10.1177/0272989x12458724
227. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: Inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013;**33**:641-56. http://dx.doi.org/10.1177/0272989X12455847

12 Appendices

12.1 Search strategy for clinical effectiveness searches

The following searches were carried out to identify:

- RCTs of adalimumab, etanercept and ustekinumab for children and young people with plaque psoriasis

Database search strategies

MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R))

via Ovid http://ovidsp.ovid.com/

1946 to present

Searched on: 24th May 2016

Records retrieved: 334

The search was updated on 30th September 2016 and retrieved 347 records.

1 Psoriasis/ (29080)

2 (psorias$ or psoriat$).ti,ab. (36767)

3 parapsoriasis.ti,ab. (525)

4 (pustul$ adj2 palm$).ti,ab. (785)

5 1 or 2 or 3 or 4 (42607)

6 Adalimumab/ (3349)

7 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (5219)

8 (adfrar or exemptia or MSB11022 or MSB 11022 or GP2017 or GP 2017 or GP2015 or GP 2015 or M923 or "M 923" or ABP501 or ABP 501).af. (19)

9 Etanercept/ (4651)

10 (etanercept or enbrel or 185243-69-0).af. (6612)

11 (benepali or brenzys or SB4 or CHS-0214 or CHS0214).af. (107)

12 Ustekinumab/ (414)

13 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (796)

14 or/6-13 (10289)

15 5 and 14 (2651)

16 exp Child/ (1665584)

17 exp Infant/ (1007205)

18 Adolescent/ (1731066)

19 (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 teenage$ or toddler$ or youth or youths or young people or young person$).ti,ab. (1671736)

20 16 or 17 or 18 or 19 (3484944)

21 15 and 20 (334)

Key:

/ = indexing term (MeSH heading)

exp = exploded indexing term (MeSH heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = terms in any field

adj = terms next to each other (order specified)

adj2 = terms within two words of each other (any order)

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Issue 4 of 12, April 2016

Searched on: 24th May 2016

Records retrieved: 32

The strategy below was used to search CENTRAL and CDSR.

The search was updated on 30th September 2016 and retrieved 39 records from CENTRAL.

#1 MeSH descriptor: [Psoriasis] this term only 1891

#2 (psorias* or psoriat*):ti,ab,kw 4321

#3 parapsoriasis:ti,ab,kw 3

#4 (pustul* near/2 palm*):ti,ab,kw 72

#5 #1 or #2 or #3 or #4 4353

#6 MeSH descriptor: [Adalimumab] this term only 239

#7 (adalimumab or humira or D2E7 or (D2 next E7) or "331731-18-1") 1088

#8 (adfrar or exemptia or MSB11022 or "MSB 11022" or GP2017 or "GP 2017" or GP2015 or "GP 2015" or M923 or "M 923" or ABP501 or "ABP 501") 2

#9 MeSH descriptor: [Etanercept] this term only 383

#10 (etanercept or enbrel or "185243-69-0") 1162

#11 (benepali or brenzys or SB4 or CHS-0214 or CHS0214) 2

#12 MeSH descriptor: [Ustekinumab] this term only 49

#13 (ustekinumab or stelara or "CNTO1275" or "CNTO-1275" or "815610-63-0") 194

#14 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 2054

#15 #5 and #14 614

#16 MeSH descriptor: [Child] explode all trees 173

#17 MeSH descriptor: [Infant] explode all trees 14329

#18 MeSH descriptor: [Adolescent] this term only 85135

#19 (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 teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") 193089

#20 #16 or #17 or #18 or #19 193089

#21 #15 and #20 50

NB: Results at line #21 are the total results for all databases within the Cochrane Library.

Key:

MeSH descriptor = indexing term (MeSH heading)

* = truncation

ti,ab,kw = terms in either title or abstract or keyword fields

near/2 = terms within two words of each other (any order)

next = terms are next to each other

" " = phrase search

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Issue 5 of 12, May 2016

Searched on: 24th May 2016

Records retrieved: 10

See above under CENTRAL for search strategy used.

The search was updated on 30th September 2016 and retrieved 10 records.

Cumulative Index to Nursing & Allied Health (CINAHL Plus)

via EBSCO https://www.ebscohost.com/

Inception to 23rd May 2016

Searched on: 24th May 2016

Records retrieved: 69

The search was updated on 30th September 2016 and retrieved 77 records.

S19	S14 AND S18	69
S18	S15 OR S16 OR S17	815,757
S17	TX 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 teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons"	815,757
S16	(MH "Adolescence+")	355,038
S15	(MH "Child+")	459,154
S14	S5 AND S13	532
S13	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	2,252
S12	TX ustekinumab or stelara or CNTO1275 or "CNTO-1275" or "815610-63-0"	157
S11	TX benepali or brenzys or SB4 or "CHS-0214" or CHS0214	3
S10	TX etanercept or enbrel or "185243-69-0"	1,528
S9	(MH "Etanercept")	701
S8	TX adfrar or exemptia or MSB11022 or "MSB 11022" or GP2017 or "GP 2017" or GP2015 or "GP 2015" or M923 or "M 923" or ABP501 or "ABP 501"	4
S7	TX (adalimumab or humira or D2E7 or "D2-E7" or "D2 E7" or "331731-18-1")	933
S6	(MH "Adalimumab")	124
S5	S1 OR S2 OR S3 OR S4	5,573
S4	TI (pustul* N2 palm*) OR AB (pustul* N2 palm*)	50

S3	TI parapsoriasis OR AB parapsoriasis	11
S2	TI (psorias* or psoriat*) OR AB (psorias* or psoriat*)	4,364
S1	(MH "Psoriasis")	3,589

Key:

MH = indexing term (CINAHL heading)

* = truncation

TI = terms in the title

AB = terms in the abstract

TX = all text - search of all the database's searchable fields

" " = phrase search

N2 = terms within two words of each other (any order)

Database of Abstracts of Reviews of Effects (DARE)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 24th May 2016

Records retrieved: 4

This search strategy was not updated as DARE closed at the end of March 2015.

1	MeSH DESCRIPTOR Psoriasis	202
2	(psorias* or psoriat*)	311
3	(parapsoriasis)	1
4	(pustul* NEAR2 palm*)	2
5	(palm* NEAR2 pustul*)	3
6	#1 OR #2 OR #3 OR #4 OR #5	311
7	MeSH DESCRIPTOR Adalimumab	112
8	(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1")	240
9	MeSH DESCRIPTOR Etanercept	99
10	(etanercept or enbrel or "185243-69-0")	246
11	MeSH DESCRIPTOR Ustekinumab	16
12	(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0")	32

13	(adfrar or exemptia or MSB11022 or "MSB 11022" or GP2017 or "MSB-11022" or "GP 2017" or "GP-2017" or GP2015 or "GP 2015" or "GP-2015" or M923 or "M 923" or "M-923" OR ABP501 or "ABP 501" or "ABP-501")	0
14	(benepali or brenzys or SB4 or CHS-0214 or CHS0214)	0
15	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	355
16	MeSH DESCRIPTOR child EXPLODE ALL TREES	4890
17	MeSH DESCRIPTOR infant EXPLODE ALL TREES	2947
18	MeSH DESCRIPTOR adolescent	4584
19	(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 teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons")	13284
20	#16 OR #17 OR #18 OR #19	13284
21	#6 AND #15 AND #20	11
22	(#6 AND #15 AND #20) IN DARE	4
23	(#6 AND #15 AND #20) IN HTA	7
24	(#6 AND #15 AND #20) IN NHSEED	0

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

" " = phrase search

NEAR2 = terms within two words of each other (order specified)

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2016 May 20

Searched on: 23rd May 2016

Records retrieved: 771

The search was updated on 30th September 2016 and retrieved 826 records.

1 exp psoriasis/ (57775)

2 (psorias$ or psoriat$).ti,ab. (53835)

3 parapsoriasis.ti,ab. (571)

4 (pustul$ adj2 palm$).ti,ab. (1042)

5 1 or 2 or 3 or 4 (70014)

6 adalimumab/ (20228)

7 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (20663)

8 (adfrar or exemptia or MSB11022 or MSB 11022 or GP2017 or GP 2017 or GP2015 or GP 2015 or M923 or "M 923" or ABP501 or ABP 501).af. (49)

9 etanercept/ (22718)

10 (etanercept or enbrel or 185243-69-0).af. (23579)

11 (benepali or brenzys or SB4 or CHS-0214 or CHS0214).af. (85)

12 ustekinumab/ (2696)

13 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (2813)

14 or/6-13 (34307)

15 5 and 14 (8172)

16 exp child/ (2315907)

17 exp adolescent/ (1350949)

18 juvenile/ (26103)

19 (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 teenage$ or toddler$ or youth or youths or young people or young person$).ti,ab. (2067003)

20 16 or 17 or 18 or 19 (3558532)

21 15 and 20 (771)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = all fields

adj2 = terms within two words of each other (any order)

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 24th May 2016

Searched on: 24th May 2016

Records retrieved: 7

See above under DARE for search strategy used.

The search was updated on 30th September 2016 and retrieved 7 records.

PubMed

http://www.ncbi.nlm.nih.gov/pubmed/

Searched on: 24th May 2016

Records retrieved: 333

The search was updated on 30th September 2016 and retrieved 347 records.

((((((((((((((("Adalimumab"[Mesh:noexp]) OR ((adalimumab OR humira OR D2E7 OR "D2 E7" OR "D2-E7" OR "331731-18-1"))) OR ((adfrar OR exemptia))) OR (("MSB11022" OR "MSB 11022" OR "MSB 11022"))) OR "Etanercept"[Mesh:noexp]) OR ((etanercept OR enbrel OR "185243-69-0"))) OR ((benepali OR brenzys))) OR (("SB4" OR "CHS-0214" OR "CHS0214"))) OR "Ustekinumab"[Mesh:noexp]) OR ((ustekinumab OR stelara OR CNTO1275 OR "CNTO-1275" OR "815610-63-0"))) OR ("M923"[All Fields] OR "M 923"[All Fields] OR "M-923"[All Fields])) OR (("ABP501") OR "ABP 501") OR "ABP-501")) OR (("GP2017") OR "GP-2017") OR "GP 2017")) OR (("GP2015"[All Fields] OR "GP-2015"[All Fields] OR "GP 2015"[All Fields]))))) AND ((((("Psoriasis"[Mesh:noexp]) OR ((psorias*[Title/Abstract] OR psoriat*[Title/Abstract]))) OR parapsoriasis[Title/Abstract]) OR ((pustul*[Title/Abstract] AND palm*[Title/Abstract])))))) AND ((((("Child"[Mesh]) OR "Infant"[Mesh]) OR "Adolescent"[Mesh]) OR ((adolescen*[Title/Abstract] OR baby[Title/Abstract] OR babies[Title/Abstract] OR child[Title/Abstract] OR children[Title/Abstract] OR boy[Title/Abstract] OR boys[Title/Abstract] OR girl[Title/Abstract] OR girls[Title/Abstract] OR infant*[Title/Abstract] OR infanc*[Title/Abstract] OR juvenile*[Title/Abstract] OR paediatric[Title/Abstract] OR pediatric[Title/Abstract] OR preschooler*[Title/Abstract] OR schoolboy*[Title/Abstract] OR schoolgirl*[Title/Abstract] OR schoolchild*[Title/Abstract] OR teens[Title/Abstract] OR teenage*[Title/Abstract] OR toddler*[Title/Abstract] OR youth[Title/Abstract] OR youths[Title/Abstract] OR "young people"[Title/Abstract] OR "young person"[Title/Abstract] OR "young persons"[Title/Abstract])))

Key:

[Mesh] = exploded indexing term (MeSH heading)

[Mesh:noexp] = indexing term (MeSH heading) not exploded

* = truncation

" " = phrase search

[Title/Abstract]) = terms in either title or abstract fields

Science Citation Index

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1900 – 20th May 2016

Searched on: 23rd May 2016

Records retrieved: 256

The search was updated on 30th September 2016 and retrieved 272 records.

# 13	256	#12 AND #11 *Indexes=SCI-EXPANDED Timespan=All years*
# 12	1,516,336	TS=(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 teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") *Indexes=SCI-EXPANDED Timespan=All years*
# 11	3,490	#10 AND #4 *Indexes=SCI-EXPANDED Timespan=All years*
# 10	13,549	#9 OR #8 OR #7 OR #6 OR #5 *Indexes=SCI-EXPANDED Timespan=All years*
# 9	1,006	TS=(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0") *Indexes=SCI-EXPANDED Timespan=All years*
# 8	145	TS=(benepali or brenzys or SB4 or CHS-0214 or CHS0214) *Indexes=SCI-EXPANDED Timespan=All years*
# 7	8,405	TS=(etanercept or enbrel or "185243-69-0") *Indexes=SCI-EXPANDED Timespan=All years*
# 6	12	TS=(adfrar or exemptia or MSB11022 or "MSB 11022" or GP2017 or "GP 2017" or GP2015 or "GP 2015" or M923 or "M 923" or ABP501 or "ABP 501") *Indexes=SCI-EXPANDED Timespan=All years*
# 5	6,376	TS=(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1") *Indexes=SCI-EXPANDED Timespan=All years*

# 4	46,577	#3 OR #2 OR #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 3	806	TS=(pustul* NEAR/2 palm*) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	480	TS=parapsoriasis *Indexes=SCI-EXPANDED Timespan=All years*
# 1	45,734	TS=(psorias* or psoriat*) *Indexes=SCI-EXPANDED Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

On-going, unpublished or grey literature search strategies

ClinicalTrials.gov

https://clinicaltrials.gov/

Searched on: 24th May 2016

Records retrieved: 23

Searches were carried out as per the search strings below. A total of 28 studies were found, which came down to 23 after deduplication of results.

The search was updated on 15th September 2016 – see under network meta-analysis Search 2. Update searches for the biosimilar drugs (lines 2, 3, 4, 6) was carried out on 30th September 2016 but did not identify any further studies.

1. **6 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1)

2. **no studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (adfrar OR exemptia)

3. **no studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (MSB11022 OR "MSB 11022" OR MSB-11022 OR GP2017 OR "GP 2017" OR GP-2017 OR GP2015 OR "GP 2015" OR GP-2015)

4. **no studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (M923 OR "M 923" OR M-923 OR ABP501 OR "ABP 501" OR ABP-501)

5. **15 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (etanercept OR enbrel OR 185243-69-0)

6. **no studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (benepali OR brenzys OR SB4 OR CHS-0214 OR CHS0214)

7. **7 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0)

Conference Proceedings Citation Index: Science

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1990 – 20th May 2016

Searched on: 23rd May 2016

Records retrieved: 21

The search was updated on 30th September 2016 and retrieved 21 records.

# 13	21	#12 AND #11 *Indexes=CPCI-S Timespan=All years*
# 12	148,800	TS=(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 teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") *Indexes=CPCI-S Timespan=All years*

# 11	633	#10 AND #4 *Indexes=CPCI-S Timespan=All years*
# 10	2,726	#9 OR #8 OR #7 OR #6 OR #5 *Indexes=CPCI-S Timespan=All years*
# 9	179	TS=(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0") *Indexes=CPCI-S Timespan=All years*
# 8	30	TS=(benepali or brenzys or SB4 or CHS-0214 or CHS0214) *Indexes=CPCI-S Timespan=All years*
# 7	1,341	TS=(etanercept or enbrel or "185243-69-0") *Indexes=CPCI-S Timespan=All years*
# 6	6	TS=(adfrar or exemptia or MSB11022 or "MSB 11022" or GP2017 or "GP 2017" or GP2015 or "GP 2015" or M923 or "M 923" or ABP501 or "ABP 501") *Indexes=CPCI-S Timespan=All years*
# 5	1,351	TS=(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1") *Indexes=CPCI-S Timespan=All years*
# 4	6,375	#3 OR #2 OR #1 *Indexes=CPCI-S Timespan=All years*
# 3	68	TS=(pustul* NEAR/2 palm*) *Indexes=CPCI-S Timespan=All years*
# 2	18	TS=parapsoriasis *Indexes=CPCI-S Timespan=All years*
# 1	6,317	TS=(psorias* or psoriat*) *Indexes=CPCI-S Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/ctr-search/search

Searched on: 24th May 2016

Records retrieved: 10

The search was updated on 19th September 2016 – see under network meta-analysis Search 2. Update searches for the biosimilar drugs (lines 2, 3, 4, 6) was carried out on 30th September 2016 but did not identify any further studies.

1. 2 result(s) found for: (Psoriasis OR psoriatic) AND (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

2. 0 result(s) found for: (Psoriasis OR psoriatic) AND (adfrar OR exemptia). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

3. 1 result(s) found for: (Psoriasis OR psoriatic) AND (MSB11022 OR "MSB 11022" OR MSB-11022 OR GP2017 OR "GP 2017" OR GP-2017 OR GP2015 OR "GP 2015" OR GP-2015) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

4. 0 result(s) found for: (Psoriasis OR psoriatic) AND (M923 OR "M 923" OR M-923 OR ABP501 OR "ABP 501" OR ABP-501). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

5. 5 result(s) found for: (Psoriasis OR psoriatic) AND (etanercept OR enbrel OR 185243-69-0) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

6. 0 result(s) found for: (Psoriasis OR psoriatic) AND (benepali OR brenzys OR SB4 OR CHS-0214 OR CHS0214). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

7. 2 result(s) found for: (Psoriasis OR psoriatic) AND (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

PROSPERO

http://www.crd.york.ac.uk/PROSPERO/

Searched on: 24th May 2016

Records retrieved: 32

Search: Psoriasis in all fields.

The search was updated on 30th September 2016 and retrieved 13 new records, added since the previous search on 24th May 2016.

WHO International Clinical Trials Registry Platform

http://www.who.int/ictrp/search/en/

Searched on: 24th May 2016

Records retrieved: 32

The search was updated on 19th September 2016 – see under network meta-analysis Search 2. Update searches for the biosimilar drugs (lines 2, 3, 4, 6) was carried out on 30th September 2016 but did not identify any further studies.

1. Condition: (psoriasis OR psoriatic) AND Intervention: (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1) limited to clinical trials in children (birth to 18 years)

8 trials found.

2. Condition: (psoriasis OR psoriatic) AND Intervention: (adfrar OR exemptia) limited to clinical trials in children (birth to 18 years)

0 trials

3. Condition: (psoriasis OR psoriatic) AND Intervention: (MSB11022 OR “MSB 11022” OR MSB-11022 OR GP2017 OR “GP 2017” OR GP-2017 OR GP2015 OR “GP 2015” OR GP-2015) limited to clinical trials in children (birth to 18 years)

0 trials

4. Condition: (psoriasis OR psoriatic) AND Intervention: (M923 OR "M 923" OR M-923 OR ABP501 OR “ABP 501” OR ABP-501) limited to clinical trials in children (birth to 18 years)

0 trials

5. Condition: (psoriasis OR psoriatic) AND Intervention: (etanercept OR enbrel OR 185243-69-0) limited to clinical trials in children (birth to 18 years)

15 trials found

6. Condition: (psoriasis OR psoriatic) AND Intervention: (benepali OR brenzys OR SB4 OR CHS-0214 OR CHS0214) limited to clinical trials in children (birth to 18 years)

2 trials found

7. Condition: (psoriasis OR psoriatic) AND Intervention: (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0) limited to clinical trials in children (birth to 18 years)

7 trials found

Guideline searches

The following resources were searched for relevant guidelines on 25th May 2016. The same searches were repeated on 30th September 2016 with 1 further guideline identified from NHS Evidence.

National Guideline Clearinghouse

http://www.guideline.gov/

Searched on: 25th May 2016 (update search on 30th September 2016)

Records retrieved: 4

Keyword: psorias* or psoriat*
Age of Target Population: Infant, Newborn (to 1 month), Infant (1 to 23 months), Child (2 to 12 years), Adolescent (13 to 18 years)

10 results were browsed and 4 were identified as potentially relevant.

NICE Clinical Knowledge Summaries (CKS)

http://cks.nice.org.uk/

Searched on: 25th May 2016 (update search on 30th September 2016)

Records retrieved: 1

The topics section was browsed and 1 CKS for psoriasis identified.

NHS Evidence

https://www.evidence.nhs.uk/

Searched on: 25th May 2016 (update search on 30th September 2016)

Records retrieved: 22

((intitle:psorias* OR intags: psorias* OR inurl:psorias*) AND (child* or infant* or adolescen*))

Results filtered by type of information = guidance. Results scanned for relevance, 22 documents identified.

NICE Evidence summaries: new medicines

https://www.nice.org.uk/about/what-we-do/our-programmes/nice-advice/evidence-summaries-new-medicines

Searched on: 24th May 2016 (update search on 30th September 2016)

Records retrieved: 0

Browsed 63 titles of published evidence summaries – no relevant summaries found.

NICE website

https://www.nice.org.uk/

Searched on: 25th May 2016 (update search on 30th September 2016)

Records retrieved: 4

Browsed psoriasis topic page https://www.nice.org.uk/guidance/conditions-and-diseases/skin-conditions/psoriasis – 4 relevant documents identified.

Network meta-analysis searches

The following searches were carried out to identify:

1. RCTs of systemic non-biological (acitretin, methotrexate, cyclosporine) and biological therapies (infliximab, secukinumab) in children and young people with plaque psoriasis

2. RCTs of adalimumab, etanercept, ustekinumab, acitretin, methotrexate, cyclosporine, infliximab or secukinumab in adults with plaque psoriasis

Search 1

RCTs of systemic non-biological (acitretin, methotrexate, cyclosporine) and biological therapies (infliximab, secukinumab) in children and young people with plaque psoriasis

Database search strategies

MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R))

via Ovid http://ovidsp.ovid.com/

1946 to present

Searched on: 31st May 2016

Records retrieved: 760

The search was updated on 30th September 2016 and retrieved 784 records.

1 Psoriasis/ (29106)

2 (psorias$ or psoriat$).ti,ab. (36848)

3 parapsoriasis.ti,ab. (525)

4 (pustul$ adj2 palm$).ti,ab. (787)

5 or/1-4 (42692)

6 Acitretin/ (922)

7 (acitretin$ or etretin or neotigason or soriatane or 55079-83-9).af. (2571)

8 Methotrexate/ (33972)

9 (methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or 15475-56-6 or 59-05-2 or 7413-34-5).af. (48192)

10 exp Cyclosporins/ (37382)

11 (cyclosporin$ or ciclosporin$ or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or 59865-13-3 or 63798-73-2).af. (55065)

12 Infliximab/ (7830)

13 (infliximab or remicade or 170277-31-3).af. (11015)

14 (inflectra or remsima or CT-P13).af. (63)

15 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (193)

16 or/6-15 (111288)

17 5 and 16 (5655)

18 exp Child/ (1666387)

19 exp Infant/ (1007661)

20 Adolescent/ (1732216)

21 (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 teenage$ or toddler$ or youth or youths or young people or young person$).ti,ab. (1674732)

22 or/18-21 (3488828)

23 17 and 22 (761)

24 exp animals/ not humans/ (4247320)

25 23 not 24 (760)

Key:

/ = indexing term (MeSH heading)

exp = exploded indexing term (MeSH heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = terms in any field

adj2 = terms within two words of each other (any order)

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Issue 5 of 12, May 2016

Searched on: 31st May 2016

Records retrieved: 70

The strategy below was used to search CENTRAL and CDSR.

The search was updated on 30th September 2016 and retrieved 79 records from CENTRAL.

#1 MeSH descriptor: [Psoriasis] this term only 1891

#2 (psorias* or psoriat*):ti,ab,kw 4328

#3 parapsoriasis:ti,ab,kw 3

#4 (pustul* near/2 palm*):ti,ab,kw 73

#5 #1 or #2 or #3 or #4 4360

#6 MeSH descriptor: [Acitretin] this term only 66

#7 (acitretin* or etretin or neotigason or soriatane or "55079-83-9") 162

#8 MeSH descriptor: [Methotrexate] this term only 3050

#9 (methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5") 7671

#10 MeSH descriptor: [Cyclosporins] explode all trees 2699

#11 (cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2") 6059

#12 MeSH descriptor: [Infliximab] this term only 433

#13 (infliximab or remicade or "170277-31-3") 1347

#14 (inflectra or remsima or "CT-P13") 17

#15 (secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6") 153

#16 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 14174

#17 #5 and #16 822

#18 MeSH descriptor: [Child] explode all trees 178

#19 MeSH descriptor: [Infant] explode all trees 14343

#20 MeSH descriptor: [Adolescent] this term only 85203

#21 (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 teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") 193591

#22 #18 or #19 or #20 or #21 193591

#23 #17 and #22 89

#24 #17 and #22 in Cochrane Reviews (Reviews and Protocols) 15

#25 #17 and #22 in Trials 70

Key:

MeSH descriptor = indexing term (MeSH heading)

* = truncation

ti,ab,kw = terms in either title or abstract or keyword fields

near/2 = terms within two words of each other (any order)

" " = phrase search

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Issue 5 of 12, May 2016

Searched on: 31st May 2016

Records retrieved: 15

See above under CENTRAL for search strategy used.

The search was updated on 30th September 2016 and retrieved 15 records from CDSR.

Cumulative Index to Nursing & Allied Health (CINAHL Plus)

via EBSCO https://www.ebscohost.com/

Inception to 30th May 2016

Searched on: 31st May 2016

Records retrieved: 68

The search was updated on 30th September 2016 and retrieved 74 records.

S22	S17 AND S21	68
S21	S18 OR S19 OR S20	816,943
S20	TX 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 teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons"	816,943
S19	(MH "Adolescence+")	355,343
S18	(MH "Child+")	459,529
S17	S5 AND S16	718
S16	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	9,936
S15	TX (secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6")	73
S14	TX (inflectra or remsima or "CT-P13")	34
S13	TX (infliximab or remicade or "170277-31-3")	2,106
S12	(MH "Infliximab")	1,001

S11	TX (cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2")	2,710
S10	(MH "Cyclosporins") OR (MH "Cyclosporine")	1,875
S9	TX methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5")	5,106
S8	(MH "Methotrexate")	3,692
S7	TX acitretin* or etretin or neotigason or soriatane or "55079-83-9"	90
S6	(MH "Retinoids")	662
S5	S1 OR S2 OR S3 OR S4	5,585
S4	TI (pustul* N2 palm*) OR AB (pustul* N2 palm*)	50
S3	TI parapsoriasis OR AB parapsoriasis	11
S2	TI (psorias* or psoriat*) OR AB (psorias* or psoriat*)	4,375
S1	(MH "Psoriasis")	3,599

Key:

MH = indexing term (CINAHL heading)

* = truncation

TI = terms in the title

AB = terms in the abstract

TX = all text - search of all the database's searchable fields

" " = phrase search

N2 = terms within two words of each other (any order)

Database of Abstracts of Reviews of Effects (DARE)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 31st May 2016

Records retrieved: 6

This search strategy was not updated as DARE closed at the end of March 2015.

1	MeSH DESCRIPTOR Psoriasis	202
2	(psorias* or psoriat*)	311

3	(parapsoriasis)	1
4	(pustul* NEAR2 palm*)	2
5	(palm* NEAR2 pustul*)	3
6	#1 OR #2 OR #3 OR #4 OR #5	311
7	MeSH DESCRIPTOR Acitretin	7
8	(acitretin* or etretin or neotigason or soriatane or "55079-83-9")	25
9	MeSH DESCRIPTOR Methotrexate	176
10	(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5")	452
11	MeSH DESCRIPTOR Cyclosporins EXPLODE ALL TREES	109
12	(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2")	279
13	MeSH DESCRIPTOR Infliximab	163
14	(infliximab or remicade or "170277-31-3")	349
15	(inflectra or remsima or "CT-P13")	5
16	(secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6")	11
17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	921
18	#6 AND #17	118
19	MeSH DESCRIPTOR child EXPLODE ALL TREES	4890
20	MeSH DESCRIPTOR infant EXPLODE ALL TREES	2947
21	MeSH DESCRIPTOR adolescent	4585
22	(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*)	13225
23	(schoolboy* or schoolgirl* or schoolchild* or teens or teenage*)	148
24	(toddler* or youth or youths or "young people" or "young person" or "young persons")	614
25	#19 OR #20 OR #21 OR #22 OR #23 OR #24	13340
26	#18 AND #25	7
27	(#18 AND #25) IN DARE	6
28	(#18 AND #25) IN HTA	1
29	(#18 AND #25) IN NHSEED	0

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

" " = phrase search

NEAR2 = terms within two words of each other (order specified)

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2016 May 27

Searched on: 31st May 2016

Records retrieved: 1467

The search was updated on 30th September 2016 and retrieved 1564 records.

1 exp psoriasis/ (57814)

2 (psorias$ or psoriat$).ti,ab. (53874)

3 parapsoriasis.ti,ab. (571)

4 (pustul$ adj2 palm$).ti,ab. (1043)

5 1 or 2 or 3 or 4 (70062)

6 etretin/ (4892)

7 (acitretin$ or etretin or neotigason or soriatane or 55079-83-9).af. (5033)

8 methotrexate/ (146811)

9 (methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or 15475-56-6 or 59-05-2 or 7413-34-5).af. (152425)

10 cyclosporin derivative/ (1950)

11 cyclosporin/ (70557)

12 cyclosporin A/ (65595)

13 (cyclosporin$ or ciclosporin$ or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or 59865-13-3 or 63798-73-2).af. (139555)

14 infliximab/ (35519)

15 (infliximab or remicade or 170277-31-3).af. (36260)

16 (inflectra or remsima or CT-P13).af. (157)

17 secukinumab/ (768)

18 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (849)

19 or/6-18 (289812)

20 5 and 19 (15485)

21 exp child/ (2317206)

22 exp adolescent/ (1351704)

23 juvenile/ (26120)

24 (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 teenage$ or toddler$ or youth or youths or young people or young person$).ti,ab. (2068480)

25 or/21-24 (3560620)

26 20 and 25 (1468)

27 (animal/ or nonhuman/) not exp human/ (5037476)

28 26 not 27 (1467)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = all fields

adj2 = terms within two words of each other (any order)

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st May 2016

Searched on: 31st May 2016

Records retrieved: 1

See above under DARE for search strategy used.

The search was updated on 30th September 2016 and retrieved 1 record.

PubMed

http://www.ncbi.nlm.nih.gov/pubmed/

Searched on: 31st May 2016

Records retrieved: 698

The search was updated on 30th September 2016 and retrieved 715 records.

Search ((((((((((("Acitretin"[Mesh:NoExp]) OR ((acitretin* OR etretin OR neotigason OR soriatane OR "55079-83-9"))) OR "Methotrexate"[Mesh:NoExp]) OR ((methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR "15475-56-6" OR "59-05-2" OR "7413-34-5"))) OR "Cyclosporins"[Mesh]) OR ((cyclosporin$ OR ciclosporin$ OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR "59865-13-3" OR "63798-73-2"))) OR "Infliximab"[Mesh:NoExp]) OR ((infliximab OR remicade OR "170277-31-3"))) OR ((inflectra OR remsima OR CT-P13))) OR ((secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR "1229022-83-6")))) AND ((((("Psoriasis"[Mesh:NoExp]) OR ((psorias*[Title/Abstract] OR psoriat*[Title/Abstract]))) OR parapsoriasis[Title/Abstract]) OR ((pustul*[Title/Abstract] AND palm*[Title/Abstract])))))) AND ((((("Child"[Mesh]) OR "Infant"[Mesh]) OR "Adolescent"[Mesh:NoExp]) OR ((adolescen*[Title/Abstract] OR baby[Title/Abstract] OR babies[Title/Abstract] OR child[Title/Abstract] OR children[Title/Abstract] OR boy[Title/Abstract] OR boys[Title/Abstract] OR girl[Title/Abstract] OR girls[Title/Abstract] OR infant*[Title/Abstract] OR infanc*[Title/Abstract] OR juvenile*[Title/Abstract] OR paediatric[Title/Abstract] OR pediatric[Title/Abstract] OR preschooler*[Title/Abstract] OR schoolboy*[Title/Abstract] OR schoolgirl*[Title/Abstract] OR schoolchild*[Title/Abstract] OR teens[Title/Abstract] OR teenage*[Title/Abstract] OR toddler*[Title/Abstract] OR youth[Title/Abstract] OR youths[Title/Abstract] OR “young people”[Title/Abstract] OR “young person”[Title/Abstract] OR “young persons”[Title/Abstract])))

Key:

[Mesh] = exploded indexing term (MeSH heading)

[Mesh:NoExp] = indexing term (MeSH heading) not exploded

* = truncation

" " = phrase search

[Title/Abstract]) = terms in either title or abstract fields

Science Citation Index

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1900 – 30th May 2016

Searched on: 31st May 2016

Records retrieved: 402

The search was updated on 30th September 2016 and retrieved 420 records.

# 14	402	#13 AND #12 *Indexes=SCI-EXPANDED Timespan=All years*
# 13	1,529,440	TS=(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 teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") *Indexes=SCI-EXPANDED Timespan=All years*
# 12	6,098	#11 AND #4 *Indexes=SCI-EXPANDED Timespan=All years*
# 11	122,506	#10 OR #9 OR #8 OR #7 OR #6 OR #5 *Indexes=SCI-EXPANDED Timespan=All years*
# 10	329	TS=(secukinumab or Cosentyx or AIN457 or AIN-457 or "1229022-83-6") *Indexes=SCI-EXPANDED Timespan=All years*
# 9	78	TS=(inflectra or remsima or CT-P13) *Indexes=SCI-EXPANDED Timespan=All years*
# 8	16,040	TS=(infliximab or remicade or "170277-31-3") *Indexes=SCI-EXPANDED Timespan=All years*
# 7	67,052	TS=(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2") *Indexes=SCI-EXPANDED Timespan=All years*
# 6	44,388	TS=(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5") *Indexes=SCI-EXPANDED Timespan=All years*
# 5	1,259	TS=(acitretin* or etretin or neotigason or soriatane or "55079-83-9") *Indexes=SCI-EXPANDED Timespan=All years*
# 4	46,956	#3 OR #2 OR #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 3	808	TS=(pustul* NEAR/2 palm*) *Indexes=SCI-EXPANDED Timespan=All years*

# 2	480	TS=parapsoriasis *Indexes=SCI-EXPANDED Timespan=All years*
# 1	46,113	TS=(psorias* or psoriat*) *Indexes=SCI-EXPANDED Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

On-going, unpublished or grey literature search strategies

ClinicalTrials.gov

https://clinicaltrials.gov/

Searched on: 31st May 2016

Records retrieved: 20

Searches were carried out as per the search strings below. A total of 47 studies were found, which came down to 20 after deduplication of results.

The search was updated on 15th September 2016 – see under network meta-analysis Search 2.

1. **3 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (acitretin OR etretin OR neotigason OR soriatane OR 55079-83-9)

2. **9 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal)

3. **9 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5)

4. **7 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (cyclosporin OR ciclosporin OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin)

5. **7 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2)

6. **9 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (infliximab OR remicade OR 170277-31-3)

7. **no studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (inflectra OR remsima OR CT-P13)

8. **3 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6)

Conference Proceedings Citation Index: Science

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1990 – 30th May 2016

Searched on: 31st May 2016

Records retrieved: 16

The search was updated on 30th September 2016 and retrieved 16 records.

# 14	16	#13 AND #12 *Indexes=CPCI-S Timespan=All years*
# 13	149,897	TS=(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 teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") *Indexes=CPCI-S Timespan=All years*

# 12	592	#11 AND #4 *Indexes=CPCI-S Timespan=All years*
# 11	15,410	#10 OR #9 OR #8 OR #7 OR #6 OR #5 *Indexes=CPCI-S Timespan=All years*
# 10	76	TS=(secukinumab or Cosentyx or AIN457 or AIN-457 or "1229022-83-6") *Indexes=CPCI-S Timespan=All years*
# 9	8	TS=(inflectra or remsima or CT-P13) *Indexes=CPCI-S Timespan=All years*
# 8	2,781	TS=(infliximab or remicade or "170277-31-3") *Indexes=CPCI-S Timespan=All years*
# 7	8,929	TS=(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2") *Indexes=CPCI-S Timespan=All years*
# 6	4,027	TS=(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5") *Indexes=CPCI-S Timespan=All years*
# 5	129	TS=(acitretin* or etretin or neotigason or soriatane or "55079-83-9") *Indexes=CPCI-S Timespan=All years*
# 4	6,417	#3 OR #2 OR #1 *Indexes=CPCI-S Timespan=All years*
# 3	68	TS=(pustul* NEAR/2 palm*) *Indexes=CPCI-S Timespan=All years*
# 2	18	TS=parapsoriasis *Indexes=CPCI-S Timespan=All years*
# 1	6,359	TS=(psorias* or psoriat*) *Indexes=CPCI-S Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/ctr-search/search

Searched on: 31st May 2016

Records retrieved: 7

The search was updated on 19th September 2016 – see under network meta-analysis Search 2.

1. 0 result(s) found for: (Psoriasis OR psoriatic) AND (acitretin* OR etretin OR neotigason OR soriatane OR 55079-83-9). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

2. 5 result(s) found for: (Psoriasis OR psoriatic) AND (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5)). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

3. 0 trials found for: (Psoriasis OR psoriatic) AND (cyclosporin* OR ciclosporin* OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

4. 1 result(s) found for: (Psoriasis OR psoriatic) AND (infliximab OR remicade OR 170277-31-3) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

5. 0 results(s) found for: (Psoriasis OR psoriatic) AND (inflectra OR remsima OR CT-P13) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

6. 1 result(s) found for: (Psoriasis OR psoriatic) AND (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

Key:

* = truncation

WHO International Clinical Trials Registry Platform

http://www.who.int/ictrp/search/en/

Searched on: 30th May 2016

Records retrieved: 25

The search was updated on 19th September 2016 – see network meta-analysis Search 2.

1. Condition: (psoriasis OR psoriatic) AND Intervention: (acitretin* OR etretin OR neotigason OR soriatane OR 55079-83-9) limited to clinical trials in children (birth to 18 years)

0 trials found.

2. Condition: (psoriasis OR psoriatic) AND Intervention: (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5) limited to clinical trials in children (birth to 18 years)

5 trials found.

3. Condition: (psoriasis OR psoriatic) AND Intervention: (cyclosporin* OR ciclosporin* OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2) limited to clinical trials in children (birth to 18 years)

2 trials found.

4. Condition: (psoriasis OR psoriatic) AND Intervention: (infliximab OR remicade OR 170277-31-3) limited to clinical trials in children (birth to 18 years)

5 trials found

5. Condition: (psoriasis OR psoriatic) AND Intervention: (inflectra OR remsima OR CT-P13) limited to clinical trials in children (birth to 18 years)

1 trial found

6. Condition: (psoriasis OR psoriatic) AND Intervention: (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6) limited to clinical trials in children (birth to 18 years)

12 trials found

Search 2

RCTs of adalimumab, etanercept, ustekinumab, acitretin, methotrexate, cyclosporine, infliximab or secukinumab in adults with plaque psoriasis

Database search strategies

MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R))

via Ovid http://ovidsp.ovid.com/

1946 to present

Searched on: 14th September 2016

Records retrieved: 274

The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in Ovid MEDLINE: sensitivity-maximizing version was used to limit retrieval to RCTs (lines 26-35).[1]

1 Psoriasis/ (29604)

2 (psorias$ or psoriat$).ti,ab. (37897)

3 parapsoriasis.ti,ab. (529)

4 (pustul$ adj2 palm$).ti,ab. (804)

5 1 or 2 or 3 or 4 (43797)

6 Adalimumab/ (3560)

7 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (5547)

8 Etanercept/ (4829)

9 (etanercept or enbrel or 185243-69-0).af. (6906)

10 Ustekinumab/ (449)

11 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (859)

12 or/6-11 (10712)

13 Acitretin/ (944)

14 (acitretin$ or etretin or neotigason or soriatane or 55079-83-9).af. (2610)

15 Methotrexate/ (34625)

16 (methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or 15475-56-6 or 59-05-2 or 7413-34-5).af. (49306)

17 exp Cyclosporins/ (37792)

18 (cyclosporin$ or ciclosporin$ or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or 59865-13-3 or 63798-73-2).af. (55843)

19 Infliximab/ (8112)

20 (infliximab or remicade or 170277-31-3).af. (11419)

21 (inflectra or remsima or CT-P13).af. (78)

22 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (236)

23 or/13-22 (113486)

24 5 and 12 (2777)

25 5 and 23 (5831)

26 randomized controlled trial.pt. (430970)

27 controlled clinical trial.pt. (91709)

28 randomized.ab. (370512)

29 placebo.ab. (179018)

30 clinical trials as topic.sh. (179518)

31 randomly.ab. (263747)

32 trial.ti. (162078)

33 26 or 27 or 28 or 29 or 30 or 31 or 32 (1067990)

34 exp animals/ not humans.sh. (4316367)

35 33 not 34 (984770)

36 24 and 35 (611)

37 25 and 35 (851)

38 36 or 37 (1163)

39 (2014$ or 2015$ or 2016$).ed,dc. (3860024)

40 38 and 39 (274)

Key:

/ = indexing term (MeSH heading)

exp = exploded indexing term (MeSH heading)

$ = truncation

ti,ab = terms in either title or abstract fields

adj2 = terms within two words of each other (any order)

af = terms in any field

sh = subject heading

ed = entry date field

dc = date record created field

pt = publication type

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Issue 8 of 12, August 2016

Searched on: 14th September 2016

Records retrieved: 280

The strategy below was used to search CENTRAL and CDSR.

#1	MeSH descriptor: [Psoriasis] this term only	1903
#2	(psorias* or psoriat*):ti,ab,kw	4457
#3	parapsoriasis:ti,ab,kw	3
#4	(pustul* near/2 palm*):ti,ab,kw	75
#5	#1 or #2 or #3 or #4	4489
#6	MeSH descriptor: [Adalimumab] this term only	253
#7	(adalimumab or humira or D2E7 or (D2 next E7) or "331731-18-1")	1167
#8	MeSH descriptor: [Etanercept] this term only	391
#9	(etanercept or enbrel or "185243-69-0")	1216
#10	MeSH descriptor: [Ustekinumab] this term only	50
#11	(ustekinumab or stelara or "CNTO1275" or "CNTO-1275" or "815610-63-0")	207
#12	#6 or #7 or #8 or #9 or #10 or #11	2186

#13 MeSH descriptor: [Acitretin] this term only 66

#14 acitretin* or etretin or neotigason or soriatane or "55079-83-9" 167

#15 MeSH descriptor: [Methotrexate] this term only 3087

#16 methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5" 7891

#17 MeSH descriptor: [Cyclosporins] explode all trees 2708

#18 cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2" 6124

#19 MeSH descriptor: [Infliximab] this term only 445

#20 infliximab or remicade or "170277-31-3" 1404

#21 inflectra or remsima or "CT-P13" 19

#22 secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6" 187

#23 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 14517

#24 #5 and #12 651

#25 #5 and #23 869

#26 #24 or #25 1271

#27 #24 or #25 Publication Year from 2014 to 2016 305

NB: Results at line #27 are the total results for this search including all databases within the Cochrane Library.

Key:

MeSH descriptor = indexing term (MeSH heading)

* = truncation

ti,ab,kw = terms in either title or abstract or keyword fields

near/2 = terms within two words of each other (any order)

" " = phrase search

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Issue 9 of 12, September 2016

Searched on: 14th September 2016

Records retrieved: 10

See above under CENTRAL for search strategy used.

Cumulative Index to Nursing & Allied Health (CINAHL Plus)

via EBSCO https://www.ebscohost.com/

Inception to 14th September 2016

Searched on: 14th September 2016

Records retrieved: 108

S43	S40 OR S42	108
S42	S38 AND S41	28
S41	(ZD "in process")	225,905
S40	S38 AND S39	80
S39	EM 2014-	914,196
S38	S25 AND S37	378
S37	S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36	1,073,032
S36	TX allocat* random*	5,244
S35	(MH "Quantitative Studies")	14,844
S34	(MH "Placebos")	9,797
S33	TX placebo*	39,440
S32	TX random* allocat*	5,244
S31	(MH "Random Assignment")	41,555
S30	TX randomi* control* trial*	109,672
S29	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	850,155

S28	TX clinic* n1 trial*	189,284
S27	PT Clinical trial	79,715
S26	(MH "Clinical Trials+")	202,495
S25	S12 OR S24	1,104
S24	S5 AND S23	746
S23	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22	10,196
S22	TX (secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6")	83
S21	TX (inflectra or remsima or "CT-P13")	37
S20	TX (infliximab or remicade or "170277-31-3")	2,163
S19	(MH "Infliximab")	1,013
S18	TX (cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2")	2,766
S17	(MH "Cyclosporins") OR (MH "Cyclosporine")	1,909
S16	TX methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5")	5,246
S15	(MH "Methotrexate")	3,761
S14	TX acitretin* or etretin or neotigason or soriatane or "55079-83-9"	95
S13	(MH "Retinoids")	672
S12	S5 AND S11	567
S11	S6 OR S7 OR S8 OR S9 OR S10	2,369
S10	TX ustekinumab or stelara or CNTO1275 or "CNTO-1275" or "815610-63-0"	176
S9	TX etanercept or enbrel or "185243-69-0"	1,590

S8	(MH "Etanercept")	708
S7	TX (adalimumab or humira or D2E7 or "D2-E7" or "D2 E7" or "331731-18-1")	1,003
S6	(MH "Adalimumab")	135
S5	S1 OR S2 OR S3 OR S4	5,815
S4	TI (pustul* N2 palm*) OR AB (pustul* N2 palm*)	52
S3	TI parapsoriasis OR AB parapsoriasis	11
S2	TI (psorias* or psoriat*) OR AB (psorias* or psoriat*)	4,590
S1	(MH "Psoriasis")	3,656

Key:

MH = indexing term (CINAHL heading)

* = truncation

TI = terms in the title

AB = terms in the abstract

TX = all text - search of all the database's searchable fields

" " = phrase search

N2 = terms within two words of each other (any order)

Database of Abstracts of Reviews of Effects (DARE)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 14th September 2016

Records retrieved: 15

1	MeSH DESCRIPTOR Psoriasis	203
2	(psorias* or psoriat*)	312
3	(parapsoriasis)	1
4	(pustul* NEAR2 palm*)	2
5	(palm* NEAR2 pustul*)	3

6	#1 OR #2 OR #3 OR #4 OR #5	312
7	MeSH DESCRIPTOR Adalimumab	113
8	(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1")	241
9	MeSH DESCRIPTOR Etanercept	99
10	(etanercept or enbrel or "185243-69-0")	246
11	MeSH DESCRIPTOR Ustekinumab	17
12	(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0")	33
13	#7 OR #8 OR #9 OR #10 OR #11 OR #12	357
14	#6 AND #13	111
15	MeSH DESCRIPTOR Acitretin	7
16	(acitretin* or etretin or neotigason or soriatane or "55079-83-9")	25
17	MeSH DESCRIPTOR Methotrexate	176
18	(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5")	453
19	MeSH DESCRIPTOR Cyclosporins EXPLODE ALL TREES	109
20	(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2")	279
21	MeSH DESCRIPTOR Infliximab	164
22	(infliximab or remicade or "170277-31-3")	350
23	(inflectra or remsima or "CT-P13")	5
24	(secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6")	11
25	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	923
26	#6 AND #25	119
27	#14 OR #26	155
28	(#14 OR #26) IN DARE, HTA FROM 2014 TO 2016	26

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

" " = phrase search

NEAR2 = terms within two words of each other (order specified)

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2016 September 13

Searched on: 14th September 2016

Records retrieved: 832

A search strategy developed by Lefebvre et al. to limit retrieval of studies to RCTs was used (see lines 29-45).[2]

1 exp psoriasis/ (59685)

2 (psorias$ or psoriat$).ti,ab. (55841)

3 parapsoriasis.ti,ab. (576)

4 (pustul$ adj2 palm$).ti,ab. (1072)

5 1 or 2 or 3 or 4 (72314)

6 adalimumab/ (21367)

7 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (21859)

8 etanercept/ (23491)

9 (etanercept or enbrel or 185243-69-0).af. (24393)

10 ustekinumab/ (2986)

11 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (3119)

12 or/6-11 (35874)

13 etretin/ (5060)

14 (acitretin$ or etretin or neotigason or soriatane or 55079-83-9).af. (5207)

15 methotrexate/ (149388)

16 (methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or 15475-56-6 or 59-05-2 or 7413-34-5).af. (155196)

17 cyclosporin derivative/ (1951)

18 cyclosporin/ (71661)

19 cyclosporin A/ (66255)

20 (cyclosporin$ or ciclosporin$ or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or 59865-13-3 or 63798-73-2).af. (141395)

21 infliximab/ (36969)

22 (infliximab or remicade or 170277-31-3).af. (37773)

23 (inflectra or remsima or CT-P13).af. (227)

24 secukinumab/ (909)

25 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (994)
26 or/13-25 (295191)
27 5 and 12 (8698)
28 5 and 26 (16051)
29 random$.ti,ab. (1123629)
30 factorial$.ti,ab. (28599)
31 crossover$.ti,ab. (59028)
32 cross-over$.ti,ab. (26272)
33 placebo$.ti,ab. (244396)
34 (doubl$ adj blind$).ti,ab. (172319)
35 (singl$ adj blind$).ti,ab. (18249)
36 assign$.ti,ab. (296256)
37 allocat$.ti,ab. (107971)
38 volunteer$.ti,ab. (211580)
39 Crossover Procedure/ (48681)
40 double blind procedure/ (134149)
41 Randomized Controlled Trial/ (420204)
42 single blind procedure/ (23202)
43 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (1760154)
44 (animal/ or nonhuman/) not exp human/ (5111869)
45 43 not 44 (1564985)
46 27 and 45 (1443)
47 28 and 45 (1756)
48 46 or 47 (2351)
49 (2014$ or 2015$ or 2016$).em. (4971904)
50 48 and 49 (832)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = all fields

adj2 = terms within two words of each other (any order)

em = entry date

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 14th September 2016

Searched on: 14th September 2016

Records retrieved: 11

See above under DARE for search strategy used.

PubMed

http://www.ncbi.nlm.nih.gov/pubmed/

Searched on: 14th September 2016

Records retrieved: 225

The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in PubMed sensitivity-maximizing version was used to limit retrieval to clinical trials.[1]

Search ((((((("Psoriasis"[Mesh:NoExp]) OR ((psorias*[Title/Abstract] OR psoriat*[Title/Abstract] OR parapsoriasis[Title/Abstract]))) OR ((pustul*[Title/Abstract] AND palm*[Title/Abstract])))) AND ((((((("Adalimumab"[Mesh:NoExp]) OR ((adalimumab OR humira OR D2E7 OR "D2 E7" OR "331731-18-1"))) OR "Etanercept"[Mesh:NoExp]) OR ((etanercept OR enbrel OR "185243-69-0"))) OR "Ustekinumab"[Mesh:NoExp]) OR ((ustekinumab OR stelara OR CNTO1275 OR "CNTO-1275" OR "815610-63-0")))) OR ((((((((((acitretin* OR etretin OR neotigason OR soriatane OR "55079-83-9"))) OR "Acitretin"[Mesh:NoExp]) OR "Methotrexate"[Mesh:NoExp]) OR ((methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR "15475-56-6" OR "59-05-2" OR "7413-34-5"))) OR "Cyclosporins"[Mesh]) OR ((cyclosporin$ OR ciclosporin$ OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR "59865-13-3" OR "63798-73-2"))) OR "Infliximab"[Mesh:NoExp]) OR ((infliximab OR remicade OR "170277-31-3"))) OR ((inflectra OR remsima OR CT-P13))) OR ((secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR "1229022-83-6")))))) AND (((((((((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR clinical trials as topic [mesh: noexp]) OR randomly [tiab]) OR trial [ti])) NOT ((animals [mh] NOT humans [mh]))) Filters: Publication date from 2014/01/01 to 2016/12/31

Key:

[Mesh] = exploded indexing term (MeSH heading)

[Mesh:NoExp] = indexing term (MeSH heading) not exploded

* = truncation

" " = phrase search

[Title/Abstract]) = terms in either title or abstract fields

[tiab] = terms in either title or abstract fields

[pt] = publication type

[mh] = exploded indexing term (MeSH heading)

Science Citation Index

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1900 – 13th September 2016

Searched on: 14th September 2016

Records retrieved: 820

# 28	820	#26 not #27 *Indexes=SCI-EXPANDED Timespan=2014-2016*
# 27	3,866,779	TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*) *Indexes=SCI-EXPANDED Timespan=All years*
# 26	3,492	#24 AND #18 *Indexes=SCI-EXPANDED Timespan=All years*
# 25	3,492	#24 AND #18 *Indexes=SCI-EXPANDED Timespan=All years*
# 24	5,910,291	#23 OR #22 OR #21 OR #20 OR #19 *Indexes=SCI-EXPANDED Timespan=All years*
# 23	5,038,629	TS=(placebo* or random* or control* or prospectiv* or volunteer*) *Indexes=SCI-EXPANDED Timespan=All years*
# 22	518,826	TS=(clinic* SAME trial*) *Indexes=SCI-EXPANDED Timespan=All years*
# 21	15,215	TS=(singl* SAME mask*) or TS=(doubl* SAME mask*) or TS=(trebl* SAME mask*) or TS=(tripl* SAME mask*)

		Indexes=SCI-EXPANDED Timespan=All years
# 20	218,910	TS=(singl* SAME blind*) or TS=(doubl* SAME blind*) or TS=(trebl* SAME blind*) or TS=(tripl* SAME blind*) *Indexes=SCI-EXPANDED Timespan=All years*
# 19	1,076,694	TS=(stud* SAME design*) *Indexes=SCI-EXPANDED Timespan=All years*
# 18	8,309	#17 OR #9 *Indexes=SCI-EXPANDED Timespan=All years*
# 17	6,234	#16 AND #4 *Indexes=SCI-EXPANDED Timespan=All years*
# 16	123,797	#15 OR #14 OR #13 OR #12 OR #11 OR #10 *Indexes=SCI-EXPANDED Timespan=All years*
# 15	374	TS=(secukinumab or Cosentyx or AIN457 or AIN-457 or "1229022-83-6") *Indexes=SCI-EXPANDED Timespan=All years*
# 14	99	TS=(inflectra or remsima or CT-P13) *Indexes=SCI-EXPANDED Timespan=All years*
# 13	16,441	TS=(infliximab or remicade or "170277-31-3") *Indexes=SCI-EXPANDED Timespan=All years*
# 12	67,409	TS=(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2") *Indexes=SCI-EXPANDED Timespan=All years*
# 11	44,932	TS=(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5") *Indexes=SCI-EXPANDED Timespan=All years*
# 10	1,288	TS=(acitretin* or etretin or neotigason or soriatane or "55079-83-9") *Indexes=SCI-EXPANDED Timespan=All years*
# 9	3,641	#8 AND #4 *Indexes=SCI-EXPANDED Timespan=All years*
# 8	13,940	#7 OR #6 OR #5

		Indexes=SCI-EXPANDED Timespan=All years
# 7	1,098	TS=(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0") *Indexes=SCI-EXPANDED Timespan=All years*
# 6	8,642	TS=(etanercept or enbrel or "185243-69-0") *Indexes=SCI-EXPANDED Timespan=All years*
# 5	6,703	TS=(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1") *Indexes=SCI-EXPANDED Timespan=All years*
# 4	47,963	#3 OR #2 OR #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 3	819	TS=(pustul* NEAR/2 palm*) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	482	TS=parapsoriasis *Indexes=SCI-EXPANDED Timespan=All years*
# 1	47,116	TS=(psorias* or psoriat*) *Indexes=SCI-EXPANDED Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

SAME = terms in the same record

On-going, unpublished or grey literature search strategies

ClinicalTrials.gov

https://clinicaltrials.gov/

Searched on: 15th September 2016

Records retrieved: 105

Searches were carried out as per the search strings below. A total of 171 studies were found, which came down to 105 after deduplication of results.

1. **26 studies found for**: (Psoriasis OR psoriatic) AND (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1) | Studies received from 01/01/2014 to 09/15/2016

2. **22 studies found for**: (Psoriasis OR psoriatic) AND (etanercept OR enbrel OR 185243-69-0) | Studies received from 01/01/2014 to 09/15/2016

3. **23 studies found for**: (Psoriasis OR psoriatic) AND (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0) | Studies received from 01/01/2014 to 09/15/2016

4. **5 studies found for**: (Psoriasis OR psoriatic) AND (acitretin OR etretin OR neotigason OR soriatane OR 55079-83-9) | Studies received from 01/01/2014 to 09/15/2016

5. **24 studies found for**: (Psoriasis OR psoriatic) AND (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal) | Studies received from 01/01/2014 to 09/15/2016

6. **24 studies found for**: (Psoriasis OR psoriatic) AND (trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5) | Studies received from 01/01/2014 to 09/15/2016

7. **4 studies found for**: (Psoriasis OR psoriatic) AND (cyclosporin OR ciclosporin OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin) | Studies received from 01/01/2014 to 09/15/2016

8. **4 studies found for**: (Psoriasis OR psoriatic) AND (sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2) | Studies received from 01/01/2014 to 09/15/2016

9. **6 studies found for**: (Psoriasis OR psoriatic) AND (infliximab OR remicade OR 170277-31-3) | Studies received from 01/01/2014 to 09/15/2016

10. **3 studies found for**: (Psoriasis OR psoriatic) AND (inflectra OR remsima OR CT-P13) | Studies received from 01/01/2014 to 09/15/2016

11. **30 studies found for**: (Psoriasis OR psoriatic) AND (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6) | Studies received from 01/01/2014 to 09/15/2016

Conference Proceedings Citation Index: Science

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1990 – 13th September 2016

Searched on: 14th September 2016

Records retrieved: 33

# 28	33	#26 not #27 *Indexes=CPCI-S Timespan=2014-2016*
# 27	306,516	TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*) *Indexes=CPCI-S Timespan=All years*
# 26	235	#24 AND #18 *Indexes=CPCI-S Timespan=All years*
# 25	235	#24 AND #18 *Indexes=CPCI-S Timespan=All years*
# 24	1,276,541	#23 OR #22 OR #21 OR #20 OR #19 *Indexes=CPCI-S Timespan=All years*
# 23	1,060,361	TS=(placebo* or random* or control* or prospectiv* or volunteer*) *Indexes=CPCI-S Timespan=All years*
# 22	41,861	TS=(clinic* SAME trial*) *Indexes=CPCI-S Timespan=All years*
# 21	5,279	TS=(singl* SAME mask*) or TS=(doubl* SAME mask*) or TS=(trebl* SAME mask*) or TS=(tripl* SAME mask*) *Indexes=CPCI-S Timespan=All years*
# 20	19,759	TS=(singl* SAME blind*) or TS=(doubl* SAME blind*) or TS=(trebl* SAME blind*) or TS=(tripl* SAME blind*) *Indexes=CPCI-S Timespan=All years*
# 19	257,226	TS=(stud* SAME design*) *Indexes=CPCI-S Timespan=All years*
# 18	1,159	#17 OR #9

		Indexes=CPCI-S Timespan=All years
# 17	599	#16 AND #4 *Indexes=CPCI-S Timespan=All years*
# 16	15,543	#15 OR #14 OR #13 OR #12 OR #11 OR #10 *Indexes=CPCI-S Timespan=All years*
# 15	83	TS=(secukinumab or Cosentyx or AIN457 or AIN-457 or "1229022-83-6") *Indexes=CPCI-S Timespan=All years*
# 14	10	TS=(inflectra or remsima or CT-P13) *Indexes=CPCI-S Timespan=All years*
# 13	2,799	TS=(infliximab or remicade or "170277-31-3") *Indexes=CPCI-S Timespan=All years*
# 12	8,983	TS=(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2") *Indexes=CPCI-S Timespan=All years*
# 11	4,083	TS=(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5") *Indexes=CPCI-S Timespan=All years*
# 10	133	TS=(acitretin* or etretin or neotigason or soriatane or "55079-83-9") *Indexes=CPCI-S Timespan=All years*
# 9	645	#8 AND #4 *Indexes=CPCI-S Timespan=All years*
# 8	2,720	#7 OR #6 OR #5 *Indexes=CPCI-S Timespan=All years*
# 7	185	TS=(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0") *Indexes=CPCI-S Timespan=All years*
# 6	1,356	TS=(etanercept or enbrel or "185243-69-0") *Indexes=CPCI-S Timespan=All years*
# 5	1,361	TS=(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1")

		Indexes=CPCI-S Timespan=All years
# 4	6,587	#3 OR #2 OR #1 *Indexes=CPCI-S Timespan=All years*
# 3	69	TS=(pustul* NEAR/2 palm*) *Indexes=CPCI-S Timespan=All years*
# 2	18	TS=parapsoriasis *Indexes=CPCI-S Timespan=All years*
# 1	6,529	TS=(psorias* or psoriat*) *Indexes=CPCI-S Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

SAME = terms in the same record

EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/ctr-search/search

Searched on: 19th September 2016

Records retrieved: 85

Date limits: 2014-01-01 to 2016-09-19

1. 17 result(s) found for: (Psoriasis OR psoriatic) AND (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1

2. 9 result(s) found for: (Psoriasis OR psoriatic) AND (etanercept OR enbrel OR 185243-69-0)

3. 11 result(s) found for: (Psoriasis OR psoriatic) AND (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0)

4. 1 result(s) found for: (Psoriasis OR psoriatic) AND (acitretin* OR etretin OR neotigason OR soriatane OR 55079-83-9)

5. 20 result(s) found for: (Psoriasis OR psoriatic) AND (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5)

6. 5 result(s) found for (Psoriasis OR psoriatic) AND (cyclosporin* OR ciclosporin* OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2)

7. 3 result(s) found for: (Psoriasis OR psoriatic) AND (infliximab OR remicade OR 170277-31-3)

8. 1 result(s) found for (Psoriasis OR psoriatic) AND (inflectra OR remsima OR CT-P13)

9. 18 result(s) found for: (Psoriasis OR psoriatic) AND (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6)

Key:

* = truncation

WHO International Clinical Trials Registry Platform

http://www.who.int/ictrp/search/en/

Searched on: 19th September 2016

Records retrieved: 188

Date limits: 01/01/2014 to 19/09/2016

1. Condition: (psoriasis OR psoriatic) AND Intervention: (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1)

41 trials found.

2. Condition: (psoriasis OR psoriatic) AND Intervention: (etanercept OR enbrel OR 185243-69-0)

26 trials found

3. Condition: (psoriasis OR psoriatic) AND Intervention: (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0)

25 trials found

4. Condition: (psoriasis OR psoriatic) AND Intervention: (acitretin* OR etretin OR neotigason OR soriatane OR 55079-83-9)

6 trials found

5. Condition: (psoriasis OR psoriatic) AND Intervention: (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5)

30 trials found

6. Condition: (psoriasis OR psoriatic) AND Intervention: (cyclosporin* OR ciclosporin* OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2)

4 trials found

7. Condition: (psoriasis OR psoriatic) AND Intervention: (infliximab OR remicade OR 170277-31-3)

7 trials found

8. Condition: (psoriasis OR psoriatic) AND Intervention: (inflectra OR remsima OR CT-P13)

2 trials found

9. Condition: (psoriasis OR psoriatic) AND Intervention: (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6)

47 trials found

12.2 Summary of included records

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
ADALIMUMAB				
M04-717 (NCT01251614)	RCT / Open-label extension	AbbVie, 2010	A Double Blind Study in Pediatric Participants With Chronic Plaque Psoriasis, Studying Adalimumab vs. Methotrexate[42]	Protocol
		Papp et al, 2013	Study design and baseline characteristics from a phase 3, randomized, double-blind study of adalimumab versus methotrexate treatment in pediatric patients with chronic plaque psoriasis[37]	Meeting abstract
		Papp et al, 2014	Baseline characteristics in pediatric patients with chronic plaque psoriasis from a phase 3, randomized, double-blind study of adalimumab versus methotrexate treatment[36]	Meeting abstract

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
		Papp et al, 2014	Study design and baseline characteristics from a phase 3, randomized, double-blind study of adalimumab versus methotrexate treatment in pediatric patients with chronic plaque psoriasis[41]	Meeting abstract
		Papp et al, 2015	Efficacy and safety of adalimumab versus methotrexate treatment in pediatric patients with severe chronic plaque psoriasis: Results from the 16-Week randomized, double-blind period of a phase 3 study[39]	Meeting abstract
		Phillip et al, 2015	Efficacy, safety of adalimumab versus methotrexate in pediatric patients with severe chronic plaque psoriasis: Results from the treatment withdrawal and double-blind retreatment periods of a phase 3 study[40]	Meeting abstract
		EMEA, 2015	Extension of indication variation assessment report. Procedure No. EMEA/H/C/000481/II/0134[43]	Regulatory documentation
		EMEA, 2015	Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006[44]	Regulatory documentation

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
		Papp et al 2016	Adalimumab long-term safety/efficacy results for pediatric patients with chronic plaque psoriasis from a phase 3, randomized study[38]	Meeting abstract
ETANERCEPT				
20030211 (NCT00078819)	RCT / open-label	Amgen, 2004	Etanercept (Enbrel®) in Psoriasis - Pediatrics[160]	Protocol
		Levy et al, 2005	Etanercept in children and adolescents with psoriasis[53]	Meeting abstract
		Siegfried et al, 2006	Etanercept in children and adolescents with psoriasis[54]	Meeting abstract
		Paller et al, 2007	A 12-week phase 3 study of efficacy and safety of etanercept therapy in children and adolescents with moderate to severe plaque psoriasis[55]	Meeting abstract
		Paller et al, 2008	Etanercept treatment for children and adolescents with plaque psoriasis[48]	Journal article

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
		Paller et al, 2008	Etanercept treatment in children and adolescents with plaque psoriasis[56]	Meeting abstract
		Langley et al, 2010	Patient-reported outcomes in pediatric patients with psoriasis undergoing etanercept treatment: 12-week results from a phase III randomized controlled trial[46]	Journal article
		Siegfried et al, 2010	Intermittent etanercept therapy in pediatric patients with psoriasis[161]	Journal article
		Paller et al, 2010	Subgroup analyses of etanercept in pediatric patients with psoriasis[49]	Research letter
		Landells et al, 2010	Efficacy and safety of etanercept in children and adolescents aged > or = 8 years with severe plaque psoriasis[50]	Journal article

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
		Paller et al, 2010	Interim results of a long-term safety and tolerability study of etanercept treatment in children and adolescents age 8 to 17 years with plaque psoriasis[57]	Meeting abstract
		FDA, 2008	Enbrel (etanercept) for the Treatment of Pediatric Plaque Psoriasis[60]	Regulatory documentation
		Amgen (via FDA), 2008	Background information for the dermatologic and ophthalmologic drugs advisory committee (DODAC) meeting, 18 June 2008[61]	Regulatory documentation
		EMEA, 2008	ASSESSMENT REPORT FOR ENBREL. International Nonproprietary Name: INN- etanercept. Procedure No. EMEA/H/C/262/II/94[62]	Regulatory documentation
		EMEA, 2011	ASSESSMENT REPORT FOR ENBREL. International Nonproprietary Name: Etanercept. Procedure No. Type II variation EMEA/H/C/262/II/134[63]	Regulatory documentation

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
20050111 (NCT00141921)	Observational study (long term extension of 20030211)	Amgen, 2005	An Open-Label Extension Study to Evaluate the Safety of Etanercept in Pediatric Participants With Plaque Psoriasis[65]	Protocol
		Amgen, 2012	An Open-Label Extension Study to Evaluate the Safety of Etanercept in Pediatric Participants With Plaque Psoriasis[64]	Protocol
		Paller et al, 2010	Long-term etanercept in pediatric patients with plaque psoriasis[51]	Journal article
		Paller et al, 2010	Safety and efficacy of etanercept treatment in children and adolescents with plaque psoriasis: 96-week results of open-label extension study[58]	Meeting abstract
		Paller et al, 2015	Long-term safety and efficacy of etanercept in children and adolescents with plaque psoriasis[52]	Journal article

Study ID (clinicaltrials.gov ID)	**Design**	**Author / Source, year**	**Title**	**Record type**
		Paller et al, 2016	Five-year open-label extension study of safety and efficacy of etanercept in children and adolescents with moderate to severe plaque psoriasis[59]	Meeting abstract
		EMEA, 2013	Enbrel: etanercept. Procedure No. EMEA/H/C/000262/A46/134. CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006[66]	Regulatory documentation
NCT01100034	Observational study	Pfizer, 2010	A Long-term, Prospective, Observational Cohort Study Of The Safety And Effectiveness Of Etanercept In The Treatment Of Paediatric Psoriasis Patients In A Naturalistic Setting: A Post-authorization Safety Study (Pass)[67]	Protocol
NCT01432249	Observational study	Pfizer, 2011	Post Marketing Surveillance To Observe Safety And Efficacy Of Enbrel In Pediatric Patients With Psoriasis[68]	Protocol

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
CAIN457A2310 (NCT02471144)	RCT	Novartis Pharmaceuticals, 2015	A Randomized, Double-blind, Placebo- and Active Controlled Multicenter Trial to Demonstrate Efficacy of Subcutaneous Secukinumab Compared to Placebo and Etanercept (in a Single-blinded Arm) After Twelve Weeks of Treatment, and to Assess the Safety, Tolerability, and Long-term Efficacy in Participants From 6 to Less Than 18 Years of Age With Severe Chronic Plaque Psoriasis[69]	Protocol
		Novartis Pharma Services AG, 2015	A randomized, double-blind, placebo- and active controlled multicenter trial to demonstrate efficacy of subcutaneous secukinumab compared to placebo and etanercept (in a single blinded arm) after twelve weeks of treatment, and to assess the safety, tolerability, and long-term efficacy in participants from 6 to less than 18 years of age with severe chronic plaque psoriasis[70]	Protocol
USTEKINUMAB				

Study ID (clinicaltrials.gov ID)	**Design**	**Author / Source, year**	**Title**	**Record type**
CNTO1275PSO3006/CADMUS (NCT01090427)	RCT / Open-label extension	Janssen Research & Development, 2010	A Study of the Safety and Efficacy of Ustekinumab in Adolescent Patients With Psoriasis (CADMUS)[73]	Protocol
		Landells et al 2015	Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study[71]	Journal article
		Landells et al 2015	Safety and efficacy of ustekinumab in adolescent patients with moderate to severe plaque psoriasis: Results through 1 year of the phase 3 CADMUS trial[72]	Meeting abstract
		EMEA, 2015	Assessment report: Stelara. International non-proprietary name: USTEKINUMAB. Procedure No. EMEA/H/C/000958/II/0042[74]	Regulatory documentation

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
CR108129 / CNTO1275PSO3013 / CADMUS Jr (NCT02698475)	Observational study	Janssen Research & Development, 2016	An Efficacy, Safety, and Pharmacokinetics Study of Subcutaneously Administered Ustekinumab in the Treatment of Moderate to Severe Chronic Plaque Psoriasis in Pediatric Participants Greater Than 6 to Less Than 12 Years of Age (CADMUS Jr)[162]	Protocol
	Observational study	Janssen-Cilag International, 2016	A phase 3 open-label study to assess the efficacy, safety, and pharmacokinetics of subcutaneously administered ustekinumab in the treatment of moderate to severe chronic plaque psoriasis in pediatric participants greater than 6 to less than 12 years of age[163]	Protocol
MULTIPLE BIOLOGIC/SYSTEMIC TREATMENTS				
Garber et al, 2015	Observational study	Garber et al, 2015	Systemic Treatment of Recalcitrant Pediatric Psoriasis: A Case Series and Literature Review[75]	Journal article
Klufas et al, 2016	Observational study	Klufas et al, 2016	Treatment of moderate to severe pediatric psoriasis: A retrospective case series[76]	Journal article

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
SYSTEMATIC REVIEWS				
PROSPERO2015:CRD42015025262	Systematic review	Chingcuanco, 2015	TNF-inhibitors: comparing the safety, efficacy and physicochemical profiles of biosimilars and innovators: PROSPERO2015:CRD42015025262[164]	Systematic review protocol
PROSPERO2015:CRD42015017538	Systematic review	Smith et al, 2015	In people with psoriasis (all types), what are the clinical effectiveness/efficacy, safety and tolerability of systemic biologics (adalimumab, etanercept, infliximab, secukinumab or ustekinumab) compared with each other, with methotrexate or with placebo?: PROSPERO2015:CRD42015017538[165]	Systematic review protocol
Sanclemente et al, 2015	Systematic review	Sanclemente et al, 2015	Anti-TNF agents for paediatric psoriasis[166]	Systematic review
de Jager et al, 2010	Systematic review	de Jager et al, 2010	Efficacy and safety of treatments for childhood psoriasis: a systematic literature review[152, 167]	Systematic review

12.3 List of excluded studies with reasons for exclusion

Author & Year	Record title	Reason for exclusion
Vencovsky et al, 2015	A phase III randomised, double-blind clinical study comparing SB4, an etanercept biosimilar, with etanercept reference product (Enbrel) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy (24-week results) [168]	1
Tarp et al, 2015	Comparative effectiveness associated with the use of biologics and small-molecules for psoriasis: protocol for a systematic review and meta-analysis [169]	1
Soliman et al, 2015	Combination therapy of methotrexate plus NBUVB phototherapy is more effective than methotrexate monotherapy in the treatment of chronic plaque psoriasis [170]	2
Ruano et al, 2015	Short-term effectiveness and safety of new biologic agents targeting IL-23/Th17 pathway for moderate to severe plaque psoriasis: a systematic review and network meta-analysis [171]	1
Puig et al, 2015	Long-term efficacy, safety and drug survival of ustekinumab in a Spanish cohort of patients with moderate to severe plaque psoriasis [172]	1
Lebwohl et at,2015	Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis [173]	1
Langley et al, 2015	Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up [174]	1
Kimball et al, 2015	OBSERVE-5: observational postmarketing safety surveillance registry of etanercept for the treatment of psoriasis final 5-year results [175]	1
Branisteanu et al, 2015	Adverse reactions of biological therapy for psoriasis [176]	2
Ali et al, 2015	A systematic review of the impact on quality of life of topical, systemic and biologic therapies for psoriasis [177]	1

Author & Year	Record title	Reason for exclusion
NIHR Horizon Scanning Centre, 2014	Adalimumab (Humira) for severe chronic plaque psoriasis in children and adolescents – second line [178]	4
Umezawa et al, 2013	Drug survival rates in patients with psoriasis after treatment with biologics [179]	2
Strohal et al, 2013	Etanercept provides an effective, safe and flexible short- and long-term treatment regimen for moderate-to-severe psoriasis: a systematic review of current evidence [180]	1
Park et al, 2013	A randomized, 'head-to-head' pilot study comparing the effects of etanercept monotherapy vs. etanercept and narrowband ultraviolet B (NB-UVB) phototherapy in obese psoriasis patients.	1
NIHR Horizon Scanning Centre, 2013	Ustekinumab (Stelara) for plaque psoriasis in adolescents [181]	4
Lopez-Ferrer et al, 2014	Adalimumab for the treatment of psoriasis in real life: a retrospective cohort of 119 patients at a single Spanish centre [182]	1
Lebwohl et al, 2013	A randomized study to evaluate the efficacy and safety of adding topical therapy to etanercept in patients with moderate to severe plaque psoriasis [183]	1
Janagond etal, 2013	Efficacy and safety of systemic methotrexate vs. acitretin in psoriasis patients with significant palmoplantar involvement: a prospective, randomized study [184]	2
Gisondi et al, 2013	Metabolic abnormalities associated with initiation of systemic treatment for psoriasis: evidence from the Italian Psocare Registry [185]	1
Da silva et al, 2013	Methotrexate for psoriasis [186]	5
Chen et al, 2013	Narrow-band ultraviolet B phototherapy versus broad-band ultraviolet B or psoralen-ultraviolet A photochemotherapy for psoriasis [187]	3
Burmester et al, 2013	Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease	1

Author & Year	Record title	Reason for exclusion
Balzola et al, 2013	Adalimumab: Long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease [188]	1
All Wales Medicines Strategy Group, 2013	Etanercept (Enbrel®) [189]	4
Strand et al, 2012	Comparison of health-related quality of life in rheumatoid arthritis, psoriatic arthritis and psoriasis and effects of etanercept treatment [190]	1
Lynde et al, 2012	A randomized study comparing the combination of nbUVB and etanercept to etanercept monotherapy in patients with psoriasis who do not exhibit an excellent response after 12 weeks of etanercept [191]	1
Kim et al, 2012	Comparative efficacy of biologics in psoriasis: a review [192]	1
Famenini et al, 2012	The Safety of Ustekinumab in Psoriasis [193]	1
Chiu et al, 2012	The effectiveness and safety of adalimumab in the treatment of non-reimbursed patients with mild-to-moderate psoriasis [194]	1
Burmester et al, 2012	Long-term safety of adalimumab in patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, and crohn's disease [195]	1
Young et al, 2011	The ACCEPT study: ustekinumab versus etanercept in moderate-to-severe psoriasis patients [196]	1
Ryan et al, 2011	Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials [197]	1
Lara-Corrales et al, 2011	Childhood psoriasis treatment: Evidence published over the last 5 years [198]	5
Brunasso et al, 2011	Tolerability and safety of biological therapies for psoriasis in daily clinical practice: a study of 103 Italian patients [199]	1

Author & Year	Record title	Reason for exclusion
Menter et al, 2010	Efficacy and safety of adalimumab across subgroups of patients with moderate to severe psoriasis [200]	1
Esposito et al, 2010	Continuous treatment of plaque-type psoriasis with etanercept: an observational long-term experience [201]	1
All Wales Medicines Strategy Group, 2010	Final appraisal report Etanercept (Enbrel®) [127]	5
National Horizon Scanning Centre, 2008	Etanercept (Enbrel) for moderate-to-severe plaque psoriasis in children and adolescents [202]	4
Flytstrom et al, 2008	Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial [110]	1
Romero-Mate et al, 2007	Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review [203]	1
Ranjan et al, 2007	Methotrexate versus hydroxycarbamide (hydroxyurea) as a weekly dose to treat moderate-to-severe chronic plaque psoriasis: a comparative study [204]	1
Krueger et al, 2006	Patients with psoriasis respond to continuous open-label etanercept treatment after initial incomplete response in a randomized, placebo-controlled trial [205]	1
Gordon et al, 2006	Efficacy of etanercept in an integrated multistudy database of patients with psoriasis [206]	1
Amornpinyokeit et al, 2006	8-Methoxypsoralen cream plus targeted narrowband ultraviolet B for psoriasis [207]	3
Bigby, 2004	A randomized controlled trial of methotrexate and cyclosporine in the treatment of psoriasis [208]	1
Heydendael et al, 2002	Cyclosporin trough levels: Is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels [209]	1
Faerber et al, 2001	Cyclosporine in severe psoriasis. Results of a meta-analysis in 579 patients [210]	1

Author & Year	Record title	Reason for exclusion
Ho et al, 1999	Intermittent short courses of cyclosporin (Neoral(R)) for psoriasis unresponsive to topical therapy: a 1-year multicentre, randomized study. The PISCES Study Group [211]	2
Zachariae et al, 1998	Conversion of psoriasis patients from the conventional formulation of cyclosporin A to a new microemulsion formulation: a randomized, open, multicentre assessment of safety and tolerability [212]	1
Koo, 1998	A randomized, double-blind study comparing the efficacy, safety and optimal dose of two formulations of cyclosporin, Neoral and Sandimmun, in patients with severe psoriasis. OLP302 Study Group [213]	1
Laburte et al, 1994	Efficacy and safety of oral cyclosporin A (CyA; Sandimmun) for long-term treatment of chronic severe plaque psoriasis [214]	1
_____1993	Cyclosporin versus etretinate: Italian multicenter comparative trial in severe plaque-form psoriasis. Italian Multicenter Study Group on Cyclosporin in Psoriasis [215]	1
Christophers et al, 1992	Cyclosporine in psoriasis: a multicenter dose-finding study in severe plaque psoriasis. The German Multicenter Study [216]	1
Tanew et al, 1991	Photochemotherapy for severe psoriasis without or in combination with acitretin: a randomized, double-blind comparison study [217]	1
Ruzicka et al, 1990	Efficiency of acitretin in combination with UV-B in the treatment of severe psoriasis [218]	1
Kragballe et al, 1989	A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis. Results of a Nordic multicentre study [219]	1
Takashima et al, 1988	Comparison of therapeutic efficacy of topical PUVA, oral etretinate, and combined PUVA and etretinate for the treatment of psoriasis and development of PUVA lentigines and antinuclear antibodies [220]	1
Geiger and Czarnetzki, 1988	Acitretin (Ro 10-1670, etretin): overall evaluation of clinical studies [221]	1

Author & Year	Record title	Reason for exclusion
Melis, 1984	[Treatment of plaque psoriasis with an aromatic retinoid (etretinate)] [222]	2
Christiansen et al, 1982	Etretinate (Tigason) and betamethasone valerate (Celeston valerate) in the treatment of psoriasis. A double-blind, randomized, multicenter trial [223]	2
	Ustekinumab Safety and Surveillance Program Using the Ingenix NHI Database [224]	1
	Study Evaluating the Safety of Enbrel (Etanercept) [225]	1

Key: 1= Not children and/or young people who have moderate to severe plaque psoriasis; 2= Mixed adults and children - unable to separate into subgroups; 3= Does not include data on adalimumab, etanercept, ustekinumab, methotrexate, cyclosporine, or acitretin; 4= Does not measure a clinical outcome (e.g. only pharmacokinetics); 5= Not an RCT, open label extension, or observational study (e.g. reject if a single case report).

12.4 Adalimumab risk of bias assessment for trial extension periods

	Period B		Period C		Period D	
	Judgement	**Justification**	**Judgement**	**Justification**	**Judgement**	**Justification**
Is the population based on a representative sample selected from a relevant population?	Unclear	Only responders in period A (RCT) entered the stage of the study	No	Not representative of patients receiving first biologic or switching biologic treatments: All participants had received adalimumab or methotrexate and experienced loss of disease control before being retreated	Yes	Participants from periods A, B, and C were included
Are the criteria for inclusion explicit?	Yes	Participants with a PASI 75 and PGA 0/1 response at the end of Period A	Yes	Participants from period B who had 16 weeks adalimumab of methotrexate and experienced loss of disease control were included	Yes	Participants from A,B and C who met entry criteria in period A were included
Were groups similar at baseline in terms of important confounding variables? If not, was the analysis adjusted to account for the imbalance?	N/A		Unclear	Insufficient demographic information. PASI 50 rates differ (p=0.06)	N/A	Non-comparative observational period.

Was knowledge of the allocated intervention to outcome assessors adequately prevented during the study?	Unclear	No information provided	Yes	Blinded re-treatment	N/A	Non-comparative observational period. Adalimumab dose was blinded for some participants, open-label for others.
Were losses to follow-up <20%?	Yes	53 of 54 patients entering group B completed follow-up	Yes	34 of 38 participants completed follow-up	Yes	90 of 108 participants completed follow-up
Were all patients accounted for at the end of study follow-up?	Yes		Yes		Yes	
Were reliable methods used to measure outcomes?	Yes	PGA worsening by at least two grades	Yes	Outcomes and methods were reported	Yes	Outcomes and methods were reported
Was the study sufficiently powered to detect treatment effect?	Unclear	No information was provided	Unclear	No information was provided	Unclear	No information was provided
Was study follow-up duration sufficient to detect long-term treatment effect?	Yes	Patients were followed-up for 36 weeks	Yes	As in Period A, participants were followed-up for 16 weeks	Yes	Participants were followed-up for 52 weeks in period D.

N/A= not applicable

12.5 Etanercept risk of bias assessment for trial extension periods

	Open-label treatment (24 weeks)		Withdrawal-retreatment period (12 weeks)		Long-term follow-up (264 weeks)	
	Judgement	**Justification**	**Judgement**	**Justification**	**Judgement**	**Justification**
Is the population based on a representative sample selected from a relevant population?	Yes	All patients entered to the randomisation stage were included	No	Only those who achieved PASI 50 at week 24 or PASI 75 at week 36 entered the study	Yes	182 of the 211 participants from the blinded period and completing the withdrawal-retreatment period entered this study
Are the criteria for inclusion explicit?	Yes	With the exception of 3 withdrawals, all patients entered the randomisation stage were included	Yes	Those who achieved PASI 50 at week 24 or PASI 75 at week 36 entered the study	Yes	All participants who completed the withdrawal-retreatment period were included
Were groups similar at baseline in terms of important confounding variables? If not, was the analysis adjusted to account for the imbalance?	N/A	All patients received the same treatment (etanercept), that is, no comparative efficacy analyses were planned.	Yes	Participants were similar in terms of age, sex, weight, height, PASI scores and BSA affected %.	N/A	The follow-up study did not aim for comparative analyses.

Was knowledge of the allocated intervention to outcome assessors adequately prevented during the study?	Unclear	Every patient was receiving etanercept	Unclear	Although the participants, caregiver, investigator and outcomes assessor were blinded during the blinding period, no information was available for this phase of the study.	Unclear	Although the participants, caregiver, investigator and outcomes assessor were blinded during the blinding period, no information was available for this phase of the study.
Were losses to follow-up <20%?	Yes	94.7% (197/208) of patients entered this stage were present at the end of this period	Yes	137/138 of participants completed the study.	No	115/182 of participants withdrew by the end of the study (week 264)
Were all patients accounted for at the end of study follow-up?	Yes	11 patients withdrew and 197 patients were present at the end of the study	Yes	137 completed and 1 lost to follow-up	Yes	Withdrawals and reasons (e.g. adverse events, lost to follow-up, withdrawal consent and protocol deviations) reported
Were reliable methods used to measure outcomes?	Yes	PASI scores and adverse events were recorded	Yes	PASI scores were reported	Yes	PASI scores and adverse events reported
Was the study sufficiently powered to detect treatment effect?	N/A	Power analysis was not done or needed for the study	Unclear	No power calculation was done or reported for this phase of the study.	Unclear	No power calculations were done or evidenced in the study reports.

Was study follow-up duration sufficient to detect long-term treatment effect?	Yes	Patients were followed up for 24 weeks	Unclear	The follow-up period was 12 weeks	Yes	The followed-up period was 5 years.

12.6 Ustekinumab risk of bias assessment for trial extension periods

	Placebo crossover and active treatment period (12-52 weeks)		**Follow-up period (52-60 weeks)**	
	Judgement	**Justification**	**Judgement**	**Justification**
Is the population based on a representative sample selected from a relevant population?	Yes	All participants from the initial blinded period were eligible to enter the crossover phase of the study	Yes	All participants who from previous phases were eligible for follow-up
Are the criteria for inclusion explicit?	Yes	All participants from the initial blinded period were eligible to enter the crossover phase of the study	Yes	All participants who from previous phases were eligible for follow-up
Were groups similar at baseline in terms of important confounding variables? If not, was the analysis adjusted to account for the imbalance?	N/A	This phase of the study did aim for comparative analysis.	N/A	This phase of the study did aim for comparative analysis.
Was knowledge of the allocated intervention to outcome assessors adequately prevented during the study?	Yes	The Sponsor, investigative study sites, and participants remained blinded to treatment assignment until the last participant enrolled completed the study	Yes	The Sponsor, investigative study sites, and participants remained blinded to treatment assignment until the last participant enrolled completed the Week 60 evaluations and the database was locked

Were losses to follow-up <20%?	Yes	Only 7/110 of the participants withdrew by the end of this phase.	Unclear	The total loss to follow-up or withdrawals at this phase of the study was not reported
Were all patients accounted for at the end of study follow-up?	Yes	Withdrawals and reasons (e.g. adverse events, death and lack of efficacy) were reported.	Unclear	The total loss to follow-up for this phase of the study was not reported
Were reliable methods used to measure outcomes?	Yes	PASI scores were reported	N/A	The follow-up only aimed at safety reports
Was the study sufficiently powered to detect treatment effect?	N/A	The follow-up period did not aim for comparative analyses	N/A	The follow-up period did not aim for comparative analyses
Was study follow-up duration sufficient to detect long-term treatment effect?	Yes	Participants were followed-up for 40 weeks.	No	Participants were followed-up for only 8 weeks.

12.7 Risk of bias assessment for observational multiple biologics studies

	Garber et al 2015		Klufas et al 2016	
	Judgement	**Justification**	**Judgement**	**Justification**
Is the population based on a representative sample selected from a relevant population?	Yes	All patients with the disease code ICD-9-CM 696.1 were considered in the study	Yes	All patients with the disease code ICD-9-CM 696.1 were considered in the study
Are the criteria for inclusion explicit?	Yes	Patients with S-MAPA ≥ 15 or otherwise documented moderate-to-severe psoriasis were included	Yes	Patients with moderate-to-severe psoriasis were included
Were groups similar at baseline in terms of important confounding variables? If not, was the analysis adjusted to account for the imbalance?	N/A	Not a comparative study	N/A	Not a comparative study
Was knowledge of the allocated intervention to outcome assessors adequately prevented during the study?	Unclear	No information provided	Unclear	No information provided
Were losses to follow-up <20%?	N/A	Retrospective analysis of health records	N/A	Retrospective analysis of health records
Were all patients accounted for at the end of study follow-up?	N/A	Retrospective analysis of health records	N/A	Retrospective analysis of health records

Were reliable methods used to measure outcomes?	Unclear	No information was provided	Unclear	No information was provided
Was the study sufficiently powered to detect treatment effect?	N/A	Not a comparative analysis	N/A	Not a comparative analysis
Was study follow-up duration sufficient to detect long-term treatment effect?	No	Mean duration of treatment was as short as 11 weeks in etanercept+MTX group.	No	Mean duration of treatment was as short as 3 weeks in Adalimumab+MTX group.

12.8 Evidence synthesis modelling, software and WinBUGS code

Bayesian NMA was conducted to pool trial results. NMA models were programmed in WinBUGS software (version 1.4.3) using a Bayesian statistical framework. WinBUGS is a Bayesian analysis software tool that, through the use of Gibbs sampling (a Markov Chain Monte Carlo method), evaluates posterior distributions for the parameters of interest given likelihood functions derived from data and prior probabilities. Fixed- and random-effects models were evaluated. Model selection was determined by model fit statistics (i.e., deviance information criterion and total residual deviance) to identify the best model choice. Treatment effects were expressed in relation to placebo. Uninformative priors were used throughout.

The Bayesian NMA for PASI utilised a framework of analysis that evaluated the probability of PASI responses in different categories of PASI thresholds 50/75/90 within a single model. The analyses followed the principles outlined in the NICE DSU. [81] This single synthesis multinomial model with a probit link is recommended by the NICE DSU [81] and assumes that there is an underlying continuous variable which has been categorised by specifying the cut-offs. It assumes also that the treatment effect is the same regardless of the different cut-offs in each trial. All PASI response models were run for 10,000 iterations after a burn-in of 20,000 on 2 chains. Synthesis model results provide pooled probabilities of achieving PASI 50, 75 and 90 for each treatment of interest, alongside a measure of uncertainty, i.e. 95% credibility intervals.

In brief, trials report r_{ikj}, the number of patients in arm k of trial i belonging to different, mutually exclusive categories j = 1, 2, 3, where these categories represent the different thresholds of PASI score (e.g., 50%, 75%, or 90% improvement). The responses for each arm k of trial i in category j follows a multinomial distribution as $r_{i,k,j=1,\ldots,J} \sim Multinomial\left(p_{i,k,j=1,\ldots,J}, n_{i,k}\right) with\ \sum_{j=1}^{J} p_{i,k,j} = 1$,which has been parameterised as a series of conditional binomial distributions, with parameters of interest the probabilities, p_{ikj}, that a patient in arm k (k = 1, 2,3) of trial i (i = 1,….., I) belongs to category j (j = 1,2,3). A probit link function was used, the inverse of the normal cumulative distribution function Φ, to define the p_{ikj} as a function of a set of threshold values, z_j. The threshold values (estimated within the model) are such that the probability that the standard normal (the probit score) will take a value less than or equal to z_1 will reflect the probability of obtaining a PASI response lower than 50%, that is, 1-PASI50. The probability that the standard normal will take a value less than or equal to z_2

will reflect the probability of obtaining a PASI response lower than 75%, that is, 1-PASI75, and analogously, evaluating Φ at z_3 will approximate 1- PASI90. Placebo and treatments are assumed to shift the mean of the distribution. This means that the pooled effect of taking the experimental treatment instead of the control is to change the probit score (or *Z* score) of the control arm, by $d_{i,1}$ standard deviations. Therefore, the model is written as $p_{ikj} = \Phi(\mu_i + z_j + \delta_{i,1k} I_{\{k \neq 1\}})$. The terms z_j as the differences on the standard normal scale between the response to category *j* and the response to category *j-1* in all the arms of trial *i*. Correlation structure induced by 3-arm trials was accounted for as a substantial proportion of the studies forming the evidence base had such characteristics.

We assumed that the baselines, μ_i, were trial-specific (i.e. unconstrained – except for model 1b) and were given non-informative prior. A non-informative prior was assign to the treatment effects parameter (δ_t). A uniform prior was assign to the parameter z_j.

Alternative assumptions were tested in two analyses. The first assumed a meta-regression for placebo effects (Model 2a). In a second analysis, we explored the impact on treatment effects of adjusting for age i.e. explicitly modelling children and young people and adult subgroups (Model 2b). Key assumptions for the models implemented for PASI responses and detailed coding of the models are presented in the table below. The preferred model was used to evaluate estimated probability of achieving PASI 50/75/90 responses on treatment *t* , using $T_{ajt} = 1 - \Phi(A + \delta_t + z_j)$ for adults, and $T_{cjt} = 1 - \Phi(A + \delta_t + z_j + B)$ for children and young people. Where A is the pooled baseline effect. The baseline effect, *A*, was estimated as, $A = \frac{\sum \mu_{i1}}{NS}$, where μ_{i1} is the baseline effects, where *i* is the studies and 1 = placebo; NS is the number of studies. And *B* is the common regression (slope) coefficient relating to the treatment by age interaction that is assumed identical for all treatments. This is a strong assumption but, due to only increasing the number of parameters in the model by one, is the least data demanding. Other interaction assumptions were tested (i.e. independent and exchangeable) [125] but the model was unable to appropriately estimate all parameters.

We adopted the WinBUG code presented in the DSU2 [226] for the analysis. Although, we identified that the model was not specifying the *z* score correctly in the liner predictor specification when the first category of the response data (in this case PASI50) was missing. A correction was made to incorporate the correct specification for the *z* score in the linear predictor specification.

Description of models and underlying assumptions for PASI response

Model 2	Model 2a	Model 2b
Likelihood $r_{ikj} \sim Binomial(p_{ikj}, n_{ikj})$ *Model* $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ $\delta_t \sim dnorm(d_t, \sigma^2)$ *Priors* $\sigma \sim dunif(0,2)$ $\mu_i \sim dnorm(0,0.000001)$ $z_j \sim dunif(0,5)$	*Likelihood* $r_{ikj} \sim Binomial(p_{ikj} n_{ikj})$ *Model* $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j + \beta(\mu_i - \overline{\mu})$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ $\delta_t \sim dnorm(d_t, \sigma^2)$ *Priors* $\sigma \sim dunif(0,2)$ $\mu_i \sim dnorm(0,0.0001)$ $\beta \sim dnorm(0,0.0001)$ $z_j \sim dunif(0,5)$	*Likelihood* $r_{ikj} \sim Binomial(p_{ikj} n_{ikj})$ *Model* $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j + \beta(\mu_i - \overline{\mu}) + \gamma \cdot x_i$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ $\delta_t \sim dnorm(d_t, \sigma^2)$ *Priors* $\sigma \sim dunif(0,2)$ $\mu_i \sim dnorm(0,0.0001)$ $\beta \sim dnorm(0,0.0001)$ $\gamma \sim dnorm(0,0.0001)$ $z_j \sim dunif(0,5)$
Assumptions • Unconstrained baselines • Independent treatment effects • Random effects between studies • Fixed effect for each of the *j-1* categories over all trials.	Assumptions • Unconstrained baselines • Independent treatment effects • Random effects between studies • Fixed effect for each of the *j-1* categories over all trials • Common interaction term between studies (placebo effect adjustment, β)	Assumptions • Unconstrained baselines • Independent treatment effects • Random effects between studies • Fixed effect for each of the *j-1* categories over all trials • Common interaction term between studies (placebo effect adjustment, β) • Common interaction term between studies (population adjustment, γ)

WinBUGS code of preferred model:

```
model {

   sw[1]<- 0
   for(i in 1:N) {
      p[i,1] <- 1
      for (j in 1:nc[i]-1) {
         r[i,j] ~ dbin(q[i,j],n[i,j])
         q[i,j] <- 1-(p[i,C[i,j+1]]/p[i,C[i,j]])
         z.index[i,j]<- C[i,j+1]-1
         theta[i,j] <- mu[s[i]] + delta[i]*(1-equals(t[i],b[i])) + z[z.index[i,j]] +
                       betaplac*(mu[s[i]]-mu_m)*(1-equals(t[i],1)) +
                       (beta[t[i]]-beta[t[1]]) * (1-equals(t[i],1)) * pop[i]
         rhat[i,j] <- q[i,j] * n[i,j]
         dv[i,j] <- 2 * (r[i,j]*(log(r[i,j])-log(rhat[i,j])) + (n[i,j]-r[i,j])*(log(n[i,j]-r[i,j]) - log(n[i,j]-rhat[i,j])))
         }
   dev[i] <- sum(dv[i,1:nc[i]-1])
```

```
   delta[i] ~ dnorm(md[i], prec)
   md[i] <- d[t[i]] - d[b[i]] + equals(m[i],3) * sw[i]

   for (j in 2:nc[i]) {
      p[i,C[i,j]] <- 1 - phi.adj[i,j]
      phi.adj[i,j] <- phi(theta[i,j-1])
      }
   }

   for(k in 2:N) {
      sw[k]<- (delta[k-1] - d[t[k-1]] + d[b[k-1]]) / 2
      }
   totresdev <- sum(dev[])
   z[1] <- 0
   for (j in 2:Cmax-1) {
      z.aux[j] ~ dunif(0,5)
      z[j] <- z[j-1] + z.aux[j]
      }

   for(i in 1:ns){ mu[i] ~ dnorm(0,0.0001) }

   d[1] <- 0
   beta[1] <- 0
   for (k in 2:nt){
      d[k] ~ dnorm(0,0.00001)
      beta[k] <- B
      }

   betaplac ~ dnorm(0,0.00001)
   tau~dunif(0,2)
   tau.sq<-tau*tau
   prec<-1/(tau.sq)

#baseline mu - based on average of the 31 trials including it.
   for (i in 1:31) { mu1[i]<-mu[i]*equals(b[i*2-1],1) }
   for (i in 1:6) { mu1[31+i]<-mu[31+i]*equals(b[60+i*3],1) }
```

```
   A<-sum(mu1[])/31
   B ~ dnorm(0,0.0001)

# calculate prob of achieving PASI50/75/90 on treat k for adults (Ta) and children (Tc)
   for (k in 1:nt) {
      for (j in 1: Cmax-1) {
         Ta[j,k] <- 1 - phi(A + d[k] + z[j])
         Tc[j,k] <- 1 - phi(A + d[k] + z[j] + B)
         }
      }

# calculate RR PASI50,75,90 on treat k
   for (c in 1:(nt-1)) {
      for (k in (c+1):nt) {
         for (j in 1: Cmax-1) {
            RRa[j,c,k] <- Ta[j,k]/Ta[j,c]
            RRc[j,c,k] <- Tc[j,k]/Tc[j,c]
            }
         }
      }

}
```

12.9 Studies excluded from the NMA analyses

No treatment arm of interest (12 studies)

Lebwohl 2003

Lebwohl M, Tyring SK, Hamilton TK, Toth D, Glazer S, Tawfik NH, et al. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003;349:2004-13

Gordon 2003

Gordon KB, Papp KA, Hamilton TK, Walicke PA, Dummer W, Li N, et al. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. JAMA 2003;290:3073-80

ACD2058g

ACD2058g. Phase III, randomised double blind placebo-controlled study evaluating 12 weeks of therapy with XOMA1 efalizumab administered subcutaneously (SC), followed by either continued treatment for an additional 12

weeks or re-treatment for 12 weeks following relapse. In: Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]. Feltham: Serono Ltd., 2004.

ACD2600g

ACD2600g. Phase IIIb, randomised, double-blind, parallel group, placebocontrolled, multicentre study evaluating 12 weeks therapy with subcutaneously administered Genentech efalizumab in adults with moderate to severe psoriasis who

are candidates for systemic therapy. In: Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]. Feltham: Serono Ltd., 2004.

IMP24011

IMP24011. Phase III, randomised, double blind, placebo-controlled, multicentre study evaluating 12 weeks subcutaneous therapy with Genentech efalizumab in patients with moderate to severe psoriasis who are candidates for systemic therapy. In: Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]. Feltham: Serono Ltd., 2004.

Rich 2013

Rich P, Sigurgeirsson B, Thaci D, et al. Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study. The British Journal of Dermatology. Feb 2013;168(2):402–411.

Papp 2013

Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebocontrolled phase II dose-ranging study. The British Journal of Dermatology. Feb 2013;168(2):412–421.

SCULPTURE 2013

Novartis. Study Comparing secukinumab Use in Long-term Psoriasis maintenance therapy: fixed regimens vs reTreatment Upon start of Relapse SCULPTURE. 2013.

Mroweitz U, et al., editors. Secukinumab retreatment-as-needed maintenance regimen: efficacy and safety outcomes from the SCULPTURE Study2014 2014/03//.

ERASURE 2014

Rich P, et al., editors. Secukinumab efficacy stratified by body weight: A subanalysis from the ERASURE phase 3 study in psoriasis2014 2014/03//.

Papp K, et al., editors. Efficacy in relationship with response to previous biologic psoriasis therapy: A subanalysis from the ERASURE phase 3 study in psoriasis2014 2014/03//.

Lebwohl M, Vender R, Menter A, Karpov A, Papavassilis C. ERASURE: Sekinumab shows sustained efficacy in subjects regardless of previous biologic exposure. European Association of Dermatology and Venereology (EADV) Conference. 2014.

Gottlieb A, et al., editors. Secukinumab time to posriasis response on patient-reported symptoms (ERASURE Study)2014 2014/03//.

Novartis. Efficacy of Response And Safety of 2 Fixed Secukinumab Regimens in Psoriasis (ERASURE). 2013.

FEATURE 2014

Blauvelt A GAPJPRCS. Secukinumab efficacy and safety: Results from the First study of sEcukinumAb in prefilled syringes in subjecTs with chronic plaqUe-type psoriasis REsponse at 12 weeks (FEATURE). Journal of the American Academy of Dermatology. 2014.

Blauvelt A, et al. Secukinumab adminstration by pre-filled syringe: Efficacy, safety and usability results from a randomised controlled trial in psoriasis (FEATURE). BJD. 2014.

Novartis. First study of SEcukinumAb in pre-filled syringes in subjects with chronic plaqUe-type psoriasis: REsponse at 12 weeks (FEATURE). 2014.

JUNCTURE 2015

Paul C LJPYRCS. Secukinumab efficacy and safety in subjects with moderate to severe plaque psoriasis: Results from the Judging the efficacy of secUkinumab in patients with psoriasis using autoiNjector: A Clinical Trial evalUating treatment REsults trial (JUNCTURE). Journal of the American Academy of Dermatology. 2014.

Paul C, Lacour JP, Tedremets L, Jazayeri S, Adams S, Guidon C, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). JEADV. 2014.

Novartis. Judging the Efficacy of SecUkinumab in Patients With Psoriasis using Autoinjector: a Clinical Trial EvalUating Treatment Results (JUNCTURE). 2014.

Rivas E, Griffiths C, Rich P, Gong Y, Papavassilis C. FIXTURE: Secukinumab shows sustained efficacy in subjects regardless of previous biologic exposure. European Association of Dermatology and Venereology (EADV) Conference. 2014.

FIXTURE 2014

Novartis. FIXTURE (Full year Investigative eXamination of secukinumab vs. eTanercept Using 2 dosing Regimens to determine Efficacy in psoriasis). 2013.

Novartis. FIXTURE (Full year Investigative eXamination of secukinumab vs. eTanercept Using 2 dosing Regimens to determine Efficacy in psoriasis). 2013.

Reich K, et al., editors. Sustainability of response with secukinumab to 52 weeks in moderate-to-severe plaque psoriasis: Data from the full year investigative examination of secukinumab vs etanercept using 2 dosing regimens to determine efficacy in psoriasis (FIXTURE) study2014 2014/03//.

PASI outcome reported at irrelevant time points (2 studies)

Van Joost 1988

van Joost T, Bos JD, Heule F, Meinardi MM. Low-dose cyclosporin A in severe psoriasis. A double-blind study. Br J Dermatol 1988;118:183-90.

Ellis 1991

Ellis CN, Fradin MS, Messana JM, Brown MD, Siegel MT, Hartley AH, et al. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. N Engl J Med 1991;324:277-84.

With treatment arm of interest but not recommended dose (4 studies)

Tyring 2006

Tyring S, Gordon KB, Poulin Y et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. Arch Dermatol 2007; 143:719–26.

Bagel 2012

Bagel J, Lynde C, Tyring S, Kricorian G, Shi Y, Klekotka P. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebo-controlled study of etanercept. Journal of the American Academy of Dermatology. Jul 2012;67(1):86–92.

Tyring S, Bagel J, Lynde C, et al. Patient-reported outcomes in moderate-to-severe plaque psoriasis with scalp involvement: results from a randomized, double-blind, placebo-controlled study of etanercept. Journal of the European Academy of Dermatology and Venereology: Jan 2013;27(1):125–128.

Gottlieb 2011

Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. The British Journal of Dermatology. Sep 2011;165(3):652–660.

Strober 2011

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12.10 Evidence synthesis – fixed-effect models' results

NMA results of PASI response for analysis 2 assuming a fixed-effects approach: probability of achieving PASI 50/75/90

Analysis	2 - Fixed-effects approach			
	PASI 50 Mean (95% CrI)	**PASI 75 Mean (95% CrI)**	**PASI 90 Mean (95% CrI)**	**r**
Placebo	0.212 (0.20 to 0.23)	0.087 (0.08 to 0.10)	0.020 (0.02 to 0.02)	5
Etanercept	0.726 (0.68 to 0.77)	0.517 (0.47 to 0.57)	0.259 (0.22 to 0.30)	3
Ustekinumab	0.863 (0.84 to 0.89)	0.704 (0.67 to 0.74)	0.439 (0.40 to 0.48)	2
Adalimumab	0.868 (0.84 to 0.90)	0.711 (0.67 to 0.76)	0.447 (0.40 to 0.50)	1
Methotrexate	0.369 (0.28 to 0.47)	0.187 (0.13 to 0.26)	0.099 (0.03 to 0.09)	4
Residual deviance	938.5*	921.2	959.8	
DIC		1790.3		

r-– ranking of treatments according to point estimates; *Compared with 209 data points.

NMA results of PASI response for analyses 2a (placebo adjusted) assuming a fixed-effects approach: probability of achieving PASI 50/75/90

Analysis	2a - Fixed-effects approach			
	PASI 50 Mean (95% CrI)	**PASI 75 Mean (95% CrI)**	**PASI 90 Mean (95% CrI)**	**r**

Placebo	0.147 (0.13 to 0.17)	0.051 (0.04 to 0.06)	0.010 (0.01 to 0.01)	5
Etanercept	0.595 (0.55 to 0.65)	0.367 (0.32 to 0.42)	0.148 (0.12 to 0.18)	3
Ustekinumab	0.862 (0.83 to 0.89)	0.695 (0.65 to 0.74)	0.422 (0.37 to 0.47)	1
Adalimumab	0.821 (0.79 to 0.85)	0.632 (0.59 to 0.68)	0.356 (0.31 to 0.40)	2
Methotrexate	0.552 (0.49 to 0.62)	0.326 (0.27 to 0.39)	0.124 (0.09 to 0.16)	4
Residual deviance	406.3*	385.7	431.4	
DIC		1259.5		

r-– ranking of treatments according to point estimates; *Compared with 209 data points.

12.12 Consistency assessment

The validity of a NMA depends upon an assumption of homogeneity/exchangeability between all the trials included in the network, i.e. that there are no essential differences between the methods, populations and interventions being studied, and that any differences are due to chance (as in a standard meta-analysis). The lack of homogeneity/exchangeability between studies involving one of the treatments of interest and studies involving the other treatments of interest may generate inconsistency. The main potential threat to consistency of the evidence network is the pooling of evidence across trials in children and young people with those in adult populations.

The main network evidence loops that require close examination are PLB *vs* MTX *vs* ADA, PLB *vs* ETA *vs* APRE and PLB *vs* UST *45vs* UST 90 (Figure 5), as these involve the main agents of interest. As illustrated in Figure 5, these evidence loops contain 1, 1 and 4 three-arm trials, respectively (Figure 5 – discontinued line boxes). Within a three-arm trial no inconsistency exists, and no inconsistency is brought from these multi-arm trials to the evidence network, potentially only between-trial heterogeneity [227]. These 3 evidence loops of interest have a mixture of two- and three-arm trial evidence. In these circumstances defining and assessing inconsistency create inherent technical difficulties. Solutions to this problem are labelled by the NICE DSU TSD4 [227] document on inconsistency of evidence as "not entirely satisfactory" and are "predicated on the assumption that the majority of trials are two-arm trials and there is unlikely to be any material impact on detection of inconsistency".

To overcome these potential inconsistency assessment issues, a scenario analysis was performed which consisted of excluding the evidence from trials in children and young people from the analysis, and only synthesising the evidence from adult populations. Therefore, analysis 2a above (i.e. a baseline risk adjusted random-effects model) was replicated only using the evidence from the 34 adult trials and the results of this scenario analysis was compared to the results from using the full evidence base.

The following table presents PASI response outcomes for the trials in the adult population only. Overall, the results are similar to the ones observed in analyses 2a. Overall, these results bring some reassurance that consistency exists between the two subpopulations.

NMA results of PASI response for analysis 2a restricted to adult evidence: probability of achieving PASI 50/75/90 in adults' subpopulation

Consistency assessment	2a restricted to adult evidence			
Adults subpopulation only	**PASI 50 Mean (95% CrI)**	**PASI 75 Mean (95% CrI)**	**PASI 90 Mean (95% CrI)**	**r**
Placebo	0.144 (0.12 to 0.17)	0.050 (0.04 to 0.06)	0.010 (0.01 to 0.01)	5
Etanercept	0.619 (0.55 to 0.69)	0.389 (0.32 to 0.46)	0.161 (0.12 to 0.21)	3
Ustekinumab 45	0.875 (0.83 to 0.91)	0.714 (0.65 to 0.78)	0.442 (0.37 to 0.52)	1
Adalimumab	0.84 (0.78 to 0.89)	0.654 (0.57 to 0.73)	0.377 (0.30 to 0.46)	2
Methotrexate	0.548 (0.44 to 0.65)	0.322 (0.23 to 0.42)	0.121 (0.07 to 0.18)	4
Residual deviance	360.3	337.2	387.0	
DIC		45.02		

r-– ranking of treatments according to point estimates; *Compared with 191 data points;

12.13 Additional cost-effectiveness results

Scenario results for interventions as an alternative to systemic therapy: EQ-5D utility estimates from adults (TA180)

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children aged 4-17 years						
MTX	34,910	9.156	-	-	-	MTX
ADA	62,019	9.361	27,109	0.204	132,616	

ADA, adalimumab; MTX, methotrexate.

Scenario results for interventions after failed systemic therapy: EQ-5D utility estimates from adults (TA180)

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	7.808	-	-	-	-	
ETA	43,779	8.150	7,373	0.342	21,546	21,546	ETA
ADA	57,230	8.333	13,451	0.183	73,670	39,682	
Children and young people aged 12-17 years							
BSC	21,749	4.306	-	-	-	-	
ETA	33,186	4.585	11,437	0.278	ED ADA	41,085	BSC
ADA	37,848	4.732	16,099	0.426	37,802	37,802	
UST	39,924	4.753	2,075	0.021	100,423	40,700	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.