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Infliximab for the treatment of adults with psoriasis

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Conflicts of Interest:

None

(academic in confidence information included and highlighted)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AE	Adverse event
Anti-TNF	Anti-tumour necrosis factor
BAD	British Association of Dermatologists
BNF	British National Formulary
BSA	Body surface area
CEA	Cost-effectiveness analysis
CI	Confidence interval
CIC	Commercial in confidence
CUA	Cost utility analysis
DLQI	Dermatology Life Quality Index
EQ-5D	Euro quality of life questionnaire
ERG	Evidence review group
HEED	Health Economic Evaluations Database
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
MEIP	Medline in process
MS	Manufacturer's submission
N or n	Number
NAPSI	Nail Psoriasis Severity Index
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NRR	National Research Register
PASI	Psoriasis Area and Severity Index
PGA	Physician's global assessment
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PUVA	Psoralen ultraviolet (light) A
QALY	Quality adjusted life year
QOL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
SF-36	Short Form (version) 36
SF-6D	Short Form 6 Dimensions
SPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology appraisal
TAR	Technology Assessment Report
UK	United Kingdom
US	United States

SUMMARY

Scope of the submission

The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by NICE, and is appropriate to the NHS. The intervention is infliximab for moderate to severe plaque psoriasis. The decision problem deviates slightly from the scope in terms of the patient population. The MS notes that the licence for infliximab is for moderate to severe plaque psoriasis but the populations of the trials were largely those with severe psoriasis. The manufacturer provides a definition of severe, but not of moderate, psoriasis. In addition, it is not clear whether all participants included in the trials reflect those in the scope, i.e. that they have failed to respond, or are intolerant/contraindicated to, other systemic therapies. The intervention, comparators and outcomes are as appropriate and clinically meaningful as possible.

Summary of submitted clinical effectiveness evidence

- The main evidence in the submission comes from four international, randomised controlled trials (RCT) comparing infliximab with placebo. A further eight RCTs were also included: four comparing etanercept with placebo, and four comparing efalizumab with placebo.
- At week 10, patients on infliximab had a significantly higher likelihood of attaining a PASI 75 compared to placebo patients (range 75-88% vs 2-18% respectively) (four trials). It should be noted that there were wide confidence intervals around all four point estimates. There was also a statistically significant difference at 10 weeks in favour of infliximab for the proportion of patients achieving a PASI 50 and 90 (3 trials).
- For both efalizumab and etanercept, a significantly higher proportion of patients achieved a PASI 75 at week 12 compared to patients receiving placebo.
- In terms of secondary outcomes, there were statistically significant differences between infliximab and placebo in PGA score, quality of life, DLQI and NAPSI. The incidence of any adverse event was slightly higher in those receiving infliximab compared to those receiving placebo, though this was not tested statistically.

Summary of submitted cost effectiveness evidence

- The cost effectiveness analysis estimates the mean length of time that an individual would respond to treatment, and the utility gains associated with this response. The model is based closely upon the model reported in Woolacott and colleagues.[1] The

results are presented for infliximab compared to continuous etanercept based upon utility values for 4th quartile DLQI patients and also for all patients (in Appendix C of the MS).

- The model is generally internally consistent and appropriate to psoriasis, in terms of structural assumptions. The cost effectiveness analysis generally conforms to the NICE Reference Case and the scope / decision problem.
- Treatment effectiveness is reported in terms of the numbers of patients achieving PASI 50, 75 and 90 goals at 10 to 12 weeks and is estimated by an indirect comparison using a random-effects model.
- Patients who achieve improvements in PASI were assigned an associated improvement in quality of life with the higher responses associated with larger improvements in quality of life. These utility values have been taken from a previous report and no information was included in the MS on the characteristics of the individuals or the methodology used to obtain these values.
- The base case incremental cost effectiveness ratios (ICER) for infliximab compared to continuous etanercept for patients with severe psoriasis was £26,095 per QALY.

Commentary on the robustness of submitted evidence

Strengths

- The MS conducted a systematic search for clinical- and cost-effectiveness studies of infliximab. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include other databases.
- The four identified infliximab trials were of reasonable methodological quality (with some limitations), and measured a range of outcomes that are as appropriate and clinically relevant as possible.
- Overall, the MS presents an unbiased estimate of treatment efficacy for infliximab based on the results of the placebo-controlled trials.
- The economic model presented with the MS used an appropriate approach for the disease area and given the available data.

Weaknesses

- The processes undertaken by the manufacturer for screening studies, data extraction and applying quality criteria to included studies are not detailed in the MS. In addition, details relating to the searches were not always thorough and were recorded inconsistently. These factors limit the robustness of the systematic review.
- The MS reported very limited data on the comparator trials, and did not undertake a systematic review of these.

- Combining the four infliximab trials in a meta-analysis was not appropriate given the statistically significant heterogeneity between studies. Similarly, pooling data in the indirect comparison was also inappropriate given the known heterogeneity. The resulting pooled mean values should therefore be treated with caution.
- The base case results for the economic model have been presented for 4th quartile DLQI patients. It is unclear precisely what this definition means and how representative this is of severe psoriasis patients.

Areas of uncertainty

- The short intervention period of 10 weeks provides limited information about the longer term efficacy of infliximab.
- The relative risks calculated by the manufacturer have wide confidence intervals around all four point estimates for the primary outcome of PASI 75 achievement (and other outcomes), indicating a lack of certainty regarding the true effect.
- No description of the principles, assumptions or methodology behind the indirect comparison were provided, making it difficult for the ERG to check either the model or the data. Despite asking the manufacturer for clarification, a number of areas remain unclear, such as where the data come from, which trials were included and which placebo groups were included for the pooled estimates.
- A definition of moderate psoriasis was not provided by the MS, and neither were there any inclusion/exclusion criteria for the rating of severity of psoriasis to ensure patients were moderate to severe. The populations of the included infliximab trials were predominantly those with severe psoriasis. In addition, it is unclear what proportion of trial participants had previously been treated with systemic therapy. This causes concern over whether the participants included in the trials reflect those in the scope.
- The PASI is not an ideal measure of the severity of psoriasis in terms of measuring the impact on patients, but is often the best available outcome and is the measure used most in clinical trials. This raises questions regarding the relevance of the PASI outcome to patient experience in practice.
- There is uncertainty over the appropriate group to use in terms of QALY values. The base case presents values for 4th quartile DLQI patients. It is unclear precisely what the characteristics of patients were in this group.
- It was unclear how values for the number of inpatient days per year for a non-responder were derived. There was also uncertainty about the costs associated with inpatient care and the number of outpatient stays required for an individual on supportive care.

- There may be greater variability in the cost effectiveness of treatment than presented in the sensitivity analyses in the manufacturer's submission.
- The drop out rate for patients who no longer respond may be underestimated in the model.

Key issues

- The trials of infliximab efficacy presented by the MS were placebo-controlled trials. No head-to-head studies were identified that directly compared infliximab to etanercept or efalizumab, the comparators stated in the scope. The manufacturer carried out an indirect comparison, but the ERG have reservations about the comparison regarding a lack of information presented and areas of uncertainty in relation to the included data. In addition, the ERG question the appropriateness of pooling data that is statistically heterogenous.
- The ICER is highly sensitive to assumptions about the costs and frequency of inpatient stays for non responders of infliximab,
- It is unclear what severity of psoriasis was represented by the utility values presented in the MS. It is also unclear to what extent moderate psoriasis would be represented in the analysis presented in the MS.

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from Schering-Plough UK Ltd on the clinical effectiveness and cost effectiveness of infliximab for the treatment of moderate to severe plaque psoriasis in adults. It identifies the strengths and weakness of the MS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 17/05/2007. A response from the manufacturer via NICE was received by the ERG on 7/06/2007. These responses have been annotated in the ERG report and can be seen in Appendix 1.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer provides a clear and generally accurate overview of psoriasis. The overview covers aetiology, epidemiology, the burden of disease to patients and conventional management with various types of therapy. Features of the most common type of psoriasis (plaque psoriasis) are described, and the impact the disease has on health-related quality of life, as well as related co-morbidities, is emphasised.

The MS reports that psoriasis affects 1.5% of the population in England and Wales, with about 25% having moderate to severe disease, equating to approximately 305,000 people. However, based on a total population of 53.4 million in England and Wales,[2] the ERG estimate that this would equate to approximately 200,000 people with moderate to severe psoriasis. Clinical opinion is that the prevalence in the UK is around 2%, which would mean approximately 267,000 people in England and Wales have moderate to severe disease, which is more comparable with the manufacturer's estimate.

An explicit definition of what constitutes mild, moderate and severe psoriasis is not provided in the disease overview of the MS, although a definition of severe psoriasis is given in the decision problem (page 6 of the MS). Though not perfect (see section 2.3.4 of the ERG report), the accepted system for classifying the severity of psoriasis is the Psoriasis Area and Severity Index (PASI). The guidance for the use of biological therapies in psoriasis issued by NICE in July 2006 defines severe psoriasis as a PASI of ≥10 combined with a Dermatology Life Quality Index (DLQI) >10.[3] A 2005 review of the PASI as an instrument in

determining severity of chronic plaque-type psoriasis defines severe psoriasis as PASI >12 and moderate psoriasis as PASI ranging from 7-12.[4] Body Surface Area (BSA) and the DLQI are also commonly used as systems for classifying the severity of psoriasis.

2.2 Critique of manufacturer's overview of current service provision

The MS overview of current service provision is adequate. The MS briefly summarises the various therapies available for the management of psoriasis of different severities (page 10-11), with the exception of etanercept and efalizumab which are mentioned only to say that they were approved for treatment in the same patient population in September 2004. A summary of their use, effectiveness and adverse effects is not reported. The MS does not provide a treatment pathway or algorithm for eligibility to receive various therapies, specifically the biological therapies.

A number of guidelines are mentioned by the manufacturer in the submission report which are recognised in clinical practice:

- NICE guidance on etanercept and efalizumab for the treatment of psoriasis[3]
- NICE guidance for the treatment of psoriatic arthritis[5]
- Scottish Medicines Consortium assessment of infliximab[6]
- British Association of Dermatologists (BAD) guidelines for the use of biological interventions in psoriasis[7]
- BAD psoriasis guidelines[8]

In section 4.1, the manufacturer has made reference to the 2005 BAD guidelines for the use of biologics[7] for its summary of standard therapies (page 10), but this should be the 2006 BAD psoriasis guidelines.[8] In section 4.6, the MS refers to recommendations from the NICE guidelines on psoriatic arthritis (page 13), which are irrelevant to the current review.

Regarding current clinical practice, the MS declares that practice in the UK varies substantially. Advice to the ERG from the clinical advisor would suggest that practice varies in terms of how much ultra-violet treatment patients receive before going on systemic medications, and the order in which the various systemic medications are given. The MS states that based on evidence from large centres in the UK, the use of etanercept in the treatment of psoriasis is continuous, and that etanercept treatment is not stopped if a patient is responding, due to concerns regarding potential relapse. In addition, there is evidence that etanercept is used at 50mg twice weekly (twice the dose recommended by NICE[3]) in order to achieve the desired level of response. However, no citation or further information is provided to support these statements on current practice. The ERG's clinical advisor concurs

that etanercept is given continuously in patients in whom it is effective and that some patients in the UK are treated with 50mg twice weekly, although the proportions of etanercept patients receiving either the lower or higher dose is difficult to ascertain and is likely dependent on local authority budgets.

The MS states on page 4 that 4% of psoriasis patients are eligible for treatment with anti-TNFs (the drug class that includes infliximab). According to clinical opinion, it is generally accepted that about 15-20% of all patients with psoriasis attend hospital clinics, and of these, 20% have psoriasis severe enough to warrant systemic therapy. This equates to approximately 4% of the total psoriasis population being eligible for systemic treatment, and is in agreement with the figure stated by the MS. The manufacturer states that 50% of those eligible (4%) are currently being treated with infliximab according to 'market research'. However, no data and no further details are provided regarding this research, and the ERG are therefore unable to provide comments or a critique. The ERG's clinical advisor indicates that the number being treated with infliximab is unlikely to be as much as 50% of eligible patients.

2.3 Critique of manufacturer's definition of decision problem

2.3.1 Population

The final scope issued by NICE states that the population should be people with moderate to severe plaque psoriasis who have not responded to, or who are intolerant to, other systemic therapy including ciclosporin, methotrexate or PUVA, or in whom these treatments are contraindicated. In the decision problem reported in the MS, a specification of the criteria used to measure disease severity is given for severe psoriasis, 'patients who have a PASI score >10, DLQI score >10 and BSA >10 are considered to have severe psoriasis' (page 6), but no definition of moderate psoriasis is provided. As discussed above, if PASI score is taken alone as the measure of severity (i.e. without DLQI or BSA), moderate psoriasis includes PASI 7-12, and therefore PASI 10-12 would be classed as moderate psoriasis. In section 5.2.2 of the MS (page14), one of the inclusion criteria was the necessity of patients in all studies to have active psoriasis at the time of study entry to be relevant to infliximab's licensed indication. However, it is not clear whether all participants included in the trials reflect those in the scope, i.e. that they have failed to respond or are intolerant/contraindicated to other systemic therapies, and the manufacturer makes no reference to this issue in the MS. Consultation with the ERG's clinical advisor suggests that there is no current evidence that effectiveness differs for those who have had previous systemic treatments compared to those who have not had previous treatments.

The population described in the decision problem appears to be appropriate for the NHS, although the majority of the trials' populations were USA patients. The manufacturer notes that USA patients tend to be heavier, thereby affecting the dosing, but otherwise the population is applicable to UK patients in terms of patient characteristics and disease aetiology.

2.3.2 Intervention

The intervention specified in the MS decision problem is infliximab 5mg/kg, administered as an intravenous solution at weeks 0, 2 and 6 and subsequently at 8-weekly intervals, in the population outlined in Section 2.3.1. This is within the licensed indication and is therefore appropriate for use within the NHS. The ERG's clinical advisor concurs that the dose of 5mg/kg is the typical dose used in clinical practice in the UK, and is the dose used in the trials (or in at least one of the arms in those trials which have more than one dose of infliximab[9-11]). The intervention is therefore appropriate to the NICE scope.

2.3.3 Comparators

The MS decision problem specifies the following comparators:

- Etanercept 25-50mg administered twice weekly until remission, then 25mg administered twice weekly for continuous treatment
- Efalizumab, initial single dose of 0.7mg/kg followed by weekly injections of 1.0mg/kg
- Supportive care which includes inpatient stay and clinic visits for symptom management

The comparators outlined in the NICE scope are etanercept, efalizumab and standard treatment without a TNF-inhibitor or efalizumab. Clinical advice to the ERG would suggest that standard care for the population with moderate to severe disease is the use of systemic agents. The comparators therefore appear relevant to the NICE scope. The ERG would point out that the dose of etanercept that is recommended in the current NICE guidance is 25mg.

2.3.4 Outcomes

The NICE scope stated that the outcome measures to be considered include:

- severity of psoriasis
- remission rate
- relapse rate

- adverse effects of treatment
- health-related quality of life

The outcomes specified by the manufacturer in the decision problem reflect those in the NICE scope, and those reported in the trials, with the exception of adverse effects which was not mentioned as an outcome in the MS (although reported in the results section of the MS). The PASI is used in all trials as an outcome measure and this is reflected in the MS. The PASI is not an ideal measure of the severity of psoriasis but is often the best there is. The limits of PASI are well documented[1] but it is the measure used in most clinical trials. That said, the outcomes are as appropriate and clinically meaningful as possible, with no obvious omissions. Outcome measures are discussed in more detail in Section 3.1.4 of the ERG report.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach

3.1.1 Description of manufacturer's search strategy

The manufacturer's search contains some omissions (see below), however it is thought unlikely to affect the identification of key studies. Most of the searches have been taken from a previous Technology Assessment Report (TAR)[1] for the NICE appraisal of etanercept and efalizumab.

3.1.1.1 Clinical effectiveness searches

The manufacturer has adhered to the minimum database search criteria as specified by NICE, (Medline, Embase, Medline in Progress (MEIP) and Cochrane) when undertaking clinical effectiveness searches with the exception of MEIP. No evidence of searches of MEIP is documented within the MS and the ERG requested clarification over this matter from the manufacturer. The response from the manufacturer stated that 'a search of MEIP was conducted but was not considered applicable since none of the papers in this database fit the inclusion criteria'. There is no record of additional searching having been undertaken on other databases, and it is not stated if the searches were restricted to English language.

The date that the clinical searches were undertaken was not recorded in Section 9 Appendix A of the MS.

The search terms selected by the manufacturer included appropriate descriptor and free text terms (the latter were adequately truncated). The documented strategies were appropriately

run on the specified databases. An acceptable RCT filter was applied to the search strategy. The numbers from each search line have not been recorded on pages 86-87 of the MS.
On page 14 section 5.2.2 (inclusion and exclusion criteria) of the MS the manufacturer notes that "systematic review papers were scanned manually to identify any new RCTs referred therein." It was unclear to the ERG if this meant items identified from the searches listed in the appendix, or from some other form of hand searching or database searching, and clarification from the manufacturer was requested. The manufacturer responded that the searches for the clinical review included systematic reviews, but that in practice the procedure of scanning reference lists was only carried out for the Woolacott and colleagues 2006[1] review as it was the only relevant systematic review identified.

The ERG re-ran searches in Medline and Ovid with an arbitrary date selection of 1996-2007 and the numbers retrieved were similar to those of the manufacturer.

Ongoing Trials
It is noted on page 17 section 5.2.5 of the MS that there are no relevant ongoing RCT's. However the search for ongoing trials was not recorded in the MS (Section 5.2.5 page 17 "Ongoing studies"). For example, there is no mention of using datasets such as National Research Register or Clinical Trials.gov. There is no record of searching for papers presented at key conferences or symposia. The MS does report that the BAD is planning a registry study to track psoriasis patients receiving anti-TNF treatments. This registry is expected to start recruiting in the near future but no further details were reported in the MS.

3.1.1.2 Cost effectiveness searches

The cost-effectiveness searches that appear in Appendix B page 93 of the MS exceed the minimum database criteria set by NICE (Medline, Embase, MEIP, NHS EED and HEED). The manufacturer has additionally searched Biosis, Derwent Drug file, Current Content/clinical medicine, and Pubmed. MEIP per se is not documented as being searched although Pubmed would have been a good substitute. It is unusual to select Biosis and Derwent Drug File for cost effectiveness searches. However, this is unlikely to have impacted in a negative way on the searches. Biosis holds general life science and meetings information which may have been more applicable for the clinical effectiveness searches, and Derwent Drug File is used more at the drug development stage.

The date for the economic searches is recorded on page 93 in Appendix B of the MS as taking place on April 26th 2007 spanning 2004-2007 which is a limited period. It was not stated that this was an update search.

In Appendix B of the MS the cost effectiveness search strategy is presented primarily as a list of terms. There is no syntax to indicate which items are descriptors and which items were applied to the strategy in free text. The MS also only provides one listing for all the databases searched. However, the descriptor terms would differ in the various databases. Consequently each database strategy should have been displayed separately as per the clinical effectiveness search strategy. There is no evidence of using exploded terms for descriptors nor for using truncation for free text.

The cost effectiveness search strategy is further confused by mixing up the "condition" part of the search with the "treatments" section. For example, line 12 of the search (or/2-11) on page 93 is wrong in terms of mixing plaque psoriasis in with the drugs. This also impacts throughout the rest of the search on other lines such as 13, 23, 24 and 30.

There is also a distinct error (or typographical error) on line 23 of the search strategy listing or/1-23. This should read or/1-22.

The ERG requested further clarification over the cost effectiveness search strategy and this can be found in Appendix 1. This "revised" strategy is appropriately documented and contains a cost filter. For the sake of consistency, the term psoriasis/ could have been exploded (exp psoriasis/) to match with the search strategy in the clinical effectiveness searches.

It is noted in Section 9.3.5 of Appendix B (page 93) "Details of any additional searches" that in-house searches of their databases is not applicable. The ERG would question whether this is not applicable as it would be expected that the manufacturer would have cost effectiveness or health economic data in house, and as such requested clarification over this matter from the manufacturer. The manufacturer responded that the U.S license holder for infliximab, Centocor, was contacted by Schering-Plough to supply all relevant reports and were advised that there were no relevant on-going trials.

There is an error in the bibliographic listing on page 81 of the MS, last reference on the page, Feldman SR. In the bibliography the lead author is stated as Feldman. However, the

ERG checks suggest the lead author for this reference is Nelson. Feldman is the final co-author.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The MS specified the following inclusion criteria for the systematic review of the literature (page14):

- RCTs of infliximab efficacy were selected as relevant if they were placebo-controlled, with randomised and double-blinded allocation to study arms. Baseline matching of key patient characteristics was also required: namely age, sex, as well as treatment and disease history. It was necessary that patients in all studies had active psoriasis at time of study entry, to be relevant to infliximab's licensed indication.

- It was also required that the studies had as their primary, or co-primary, endpoint a relevant psoriasis severity score such as the PASI.

The specified inclusion/exclusion criteria were appropriate and largely reflect the information given in the decision problem. However:

- The MS does not report any inclusion criteria relating to the comparator treatments etanercept and efalizumab.

- The MS does not specify dose as an inclusion criteria and may therefore include patients not reflective of UK clinical practice.

- The MS provides no criteria for the rating of severity of psoriasis to ensure patients were moderate-to-severe.

- There was no description of what would constitute a failure to respond, or intolerance/contra-indication, to prior systemic treatments, as per the NICE scope. The ERG clinical advisor suggests that most patients entering trials for biologics will have failed other treatments in a clinical setting or been contra-indicated according to what co-morbidities they had.

- Baseline matching on certain patient demographics was an additional requirement for inclusion.

- The MS does not state clearly whether conference abstracts would be included or excluded. The ERG requested clarification from the manufacturer about the inclusion/exclusion of these types of publications. The manufacturer noted in their response that these were not eligible for inclusion. However, one conference proceeding was included for the comparator interventions (see Table 2 below)

- The MS state that they applied the same criteria to the selection of RCTs of competitor products etanercept and efalizumab. A flow chart of included and excluded studies of these comparator interventions was not provided.

- A list of excluded studies for the cost effectiveness searches were presented in the MS but not for the searches of clinical effectiveness. The MS gave numbers and brief reasons for exclusion of clinical studies in the flow chart on page 17. The ERG requested further information on the excluded studies in order to check the appropriateness of their exclusion from the MS. A full list was provided in the manufacturers response breaking down the list into reasons for exclusion. This appears to the ERG to be satisfactory.

- The MS does not describe the processes undertaken for screening references for inclusion in the systematic review. The ERG requested further information as to the processes undertaken. However, the manufacturer's response did not clarify further to the ERG the processes undertaken for the application of the inclusion or exclusion criteria (see Appendix 1).

3.1.2.1 Identified studies

Four RCTs comparing infliximab with placebo were included in the systematic review. No RCTs comparing infliximab with comparator drugs were identified. The MS included four RCTs comparing etanercept with placebo, and four RCTs comparing efalizumab with placebo for indirect comparisons, but no systematic review of these trials were undertaken. The patients in these trials do appear to be comparable with the patients in the infliximab trials in terms of age ranges, gender mix and severity of psoriasis.

The MS provides summary details of the trial design, intervention, population, patient numbers, outcomes, and analysis of the four infflliximab trials. Data presented in the MS is representative of the data within the trials with a few exceptions (see below). Limited detail on the comparator trials is reported. Four trials of efalizumab and four trials of etanercept were included in the MS and summary information was provided in the form of tables seen in Appendix A (page 88, 89) of the MS. The summary data presented in these tables reflects the data found in the publications of the comparator trials with the exception of two minor omissions. In the efalizumab studies there is a reporting error in the 'intervention' column for the Leonardi and colleagues trial[12] where there should be a second treatment group (2mg) presented. In the table of etanercept RCTs there is a reporting error in the 'length' column for the Tyring and colleagues trial[13] where the duration is reported at 96 weeks, however this should read 12 weeks for the randomised comparison as the remaining 84 weeks was an open-label extension where all participants received etanercept.

The processes undertaken by the manufacturer for the extraction of data from the infliximab or comparator trials are not detailed in the MS. The ERG requested clarity on this from the manufacturer, however the response did not adequately answer the question. The manufacturer noted that data extraction was sourced from results tables and copied into the submission, but does not describe if this was undertaken by one or two researchers, and how independent this was or if this was checked (see Appendix 1).

Table 1 Characteristics of the included infliximab RCTs

Reference	Methods	Participants	Outcomes
Infliximab trials			
Chaudhari et al (2001)[9]	*Design:* Placebo controlled RCT. *Interventions*: infliximab 5 mg/kg; infliximab 10 mg/kg; placebo *Duration*: 10 weeks	Adults with clinically stable plaque psoriasis; >5% BSA affected. *Numbers:* infliximab 5 mg/kg (n=11); infliximab 10 mg/kg (n=11); placebo (n=11)	*Primary:* % patients achieving at week 10: PGA (good/minimal/ clear) *Secondary:* % patients achieving PASI 75 at week 10
Gottlieb et al (2004)[10] SPIRIT study	*Design:* Placebo controlled RCT *Interventions:* infliximab 3 mg/kg; infliximab 5 mg/kg; placebo *Duration:* 30 weeks[a] (primary endpoint analysis at 10 weeks. Outcomes also assessed at	Adults with clinically stable plaque psoriasis; >10% BSA; baseline PASI ≥12[b] *Numbers:* infliximab 3 mg/kg (n=99); infliximab 5 mg/kg (n=99); placebo (n=51)	*Primary:* % patients achieving PASI 75 at week 10. *Secondary:* % patients achieving at week 10: PASI 90 PASI 50 PGA (minimal/cleared)

	26 weeks. Any outcomes reported thereafter not included by ERG as some patients had additional assigned treatments).		DLQI change from baseline
Reich et al (2005)[14] EXPRESS study	*Design:* Placebo controlled RCT *Interventions:* infliximab 5 mg/kg; placebo *Duration:* 50 weeks (primary endpoint analysis at 10 weeks. Outcomes also assessed at 24 weeks. After 24 weeks results do not reflect the randomised comparison as there was patient cross-over).	Adults with clinically stable plaque psoriasis; ≥ 10% BSA; baseline PASI ≥ 12 *Numbers:* infliximab 5mg/kg (n=301); placebo (n=77)	*Primary:* % patients achieving PASI 75 at week 10 *Secondary* % patients achieving at week 10 PASI 90 PASI 50 PGA (minimal/cleared) DLQI change from baseline Change in SF-36 scores[c] NAPSI Nail Psoriasis Score
Menter et al (2006)[11] EXPRESS II study	*Design:* Placebo controlled RCT Interventions: infliximab mg/kg; infliximab 5 mg/kg; placebo *Duration:* 50 weeks (primary endpoint analysis at 10 weeks of 14 week induction period). Remaining 36 weeks a maintenance period where there was patient cross-over)	Adults with moderate-to-severe plaque psoriasis; ≥ 10% BSA, baseline PASI ≥ 12 *Numbers*: infliximab 3 mg/kg (n=313); infliximab 5 mg/kg (n=314); placebo (n=208)	*Primary* % patients achieving PASI 75 at week 10 *Secondary* % patients achieving at week 10: PASI 90 PGA (minimal/cleared) DLQI change from baseline PASI change from baseline

[a]MS reports follow-up 50 weeks whereas trial reports 30 weeks
[b]MS reports baseline PASI >10 whereas trial reports PASI ≥12.
[c] MS reports change in SF-36 as outcome. This is not reported in the trial publication only the full trial report.

Table 2 Characteristics of the comparator RCTs (efalizumab and etanercept)

Reference	Methods	Participants	Outcomes
Efalizumab trials (for indirect comparison)			
Lebwohl et al (2003)[15]	*Design*: Placebo controlled RCT *Interventions:* efalizumab 1mg; efalizumab 2mg; placebo *Duration:* 36 weeks (endpoint analysis at 12 weeks)	Adults with clinically stable moderate-to-severe plaque psoriasis; >10% BSA; baseline PASI >12 *Numbers*: efalizumab 1 mg (n=232); efalizumab 2 mg (n=243); placebo	*Primary* % patients achieving PASI 75 at week 12 *Secondary* % patients achieving at week 12: PASI 50 PASI 90

		(n=122)	Mean % change in PSA frequency PSA severity Itching score
Gordon et al (2003)[16]	*Design*: Placebo controlled RCT *Interventions:* efalizumab 1mg; placebo *Duration:* 12 weeks	Adults with clinically stable moderate-to-severe plaque psoriasis; >10% BSA; baseline PASI >12 *Numbers:* efalizumab 1mg (n=369); placebo (n=187)	*Primary* % patients achieving PASI 75 at week 12 *Secondary* % patients achieving PASI 50; PGA (excellent/clear) Mean % change in PSA frequency PSA severity Itching score DLQI score
Leonardi et al (2005)[12]	*Design*: Placebo controlled RCT *Interventions:* efalizumab 1mg; efalizumab 2mg; placebo *Duration:* 24 weeks (endpoint analysis at 12 weeks after which patient cross-over)	Adults with clinically stable moderate to severe plaque psoriasis; >10% BSA; baseline PASI >12 *Numbers:* efalizumab 1mg (n=162); efalizumab 2mg (n=162); placebo (n=170)	*Primary* % patients achieving PASI 75 at week 12 *Seconday* % patients achieving at 12 weeks PASI 50 PASI 90 PGA (excellent/clear) PASI 50 response
Papp et al. (2005)[17] Conference proceeding (poster)	*Design*: Placebo controlled RCT *Interventions:* efalizumab 1mg; placebo *Duration:* endpoint analysis at 12 weeks (after which patients either continued with open-label treatment straight away or after up to 24 weeks delay)	Adults with clinically stable moderate to severe plaque psoriasis; >10% BSA; baseline PASI >12. Many patients were 'high need', at least 2 systemic therapies unsuitable. *Numbers:* efalizumab 1mg (n=529); placebo (n=264)	*Primary* % patients achieving PASI 75 at week 12 *Secondary* PGA (excellent/clear) PASI 50 response. % improvement PASI % improvement BSA
Etanercept trials (for indirect comparison)			
Leonardi et al (2003)[18]	*Design*: placebo controlled RCT *Interventions*: etanercept 25 mg once a week; etanercept 25 mg twice a week; etanercept 50 mg twice a week; placebo	Adults with clinically stable plaque psoriasis; >10% BSA; baseline PASI >10 *Numbers:* etanercept 25 1/52 (n=160); etanercept 25 2/52 (n=162); etanercept 50 mg 2/52	*Primary* % patients achieving PASI 75 at week 12 *Secondary* % patients achieving at 12 weeks PASI 50 PASI 90

	Duration: 24 weeks (endpoint analysis at 12 weeks after which patients crossed over)	(n=164); placebo (n=166)	PGA (clear/excellent)
Papp et al (2005)[19]	*Design*: placebo controlled RCT *Interventions*: etanercept 25 mg twice a week; etanercept 50 mg twice a week; placebo *Duration*: 24 weeks (endpoint analysis at 12 weeks after which patients crossed over)	Adults with clinically stable plaque psoriasis; >10% BSA; baseline PASI >10 *Numbers:* etanercept 25 (n=196); etanercept 50 (n=194); placebo (n=193)	*Primary* % patients achieving PASI 75 at week 12 *Secondary* % patients achieving at 12 weeks PASI 50 PASI 90 PGA (clear/almost clear) Mean PASI score, % change in PASI score
Tyring et al (2006)[13]	*Design*: placebo controlled RCT *Interventions*: etanercept 50 mg twice a week; placebo *Duration*: 96 weeks (endpoint analysis at 12 weeks after which patients crossed over)	Adults with clinically stable plaque psoriasis; >10% BSA; baseline PASI >10 *Numbers*: etanercept 50 (n=311); placebo (n=307)	*Primary* % patients achieving PASI 75 at week 12 *Secondary* % patients achieving at week 12: PASI 50 PASI 90 change in DLQI score change in BDI change in FACIT-F change in Ham-D
Gottlieb et al (2003)[20]	*Design*: placebo controlled RCT *Interventions*: etanercept 25 mg twice a week; placebo *Duration*: 24 weeks (primary endpoint analysis at 12 weeks)	Adults with clinically stable plaque psoriasis; >10% BSA. *Numbers*: etanercept 25 (n=57); placebo (n=55)	*Primary* % patients achieving PASI 75 at week 12 *Secondary* % patients achieving at week 12: PASI 50 PASI 90 PGA (clear/excellent) Mean PASI score % change in PASI score % change in DLQI score

3.1.2.2 Details of any irrelevant studies that were included in the submission

The manufacturer did not include any inappropriate studies.

3.1.2.3 Ongoing studies

In section 5.2.5 page 17 of the MS it is noted that there are no relevant ongoing RCTs. The search for ongoing trials was not recorded in the MS. For example, there is no mention of using datasets such as the National Research Register (NRR) or Clinical Trials.gov.

Searches undertaken by the ERG identified the following ongoing studies which may be of relevance.

- The effects of infliximab versus methotrexate in the treatment of moderate to severe psoriasis (study P04271). This is a phase 3b randomised, parallel-group, multicentre, active-controlled, open label study of the efficacy and safety of infliximab compared with methotrexate in the treatment of moderate to severe psoriasis in adults who were diagnosed with moderate to severe plaque-type psoriasis for at least six months. The study, which is sponsored by Schering-Plough, aims to recruit 800 participants and commenced in 2005.

- Long-term effects of infliximab in the treatment of moderate to severe psoriasis [extension of study p04271 above]. This is a long-term, randomised, multi centre, open-label study of infliximab treatment in adults with moderate to severe plaque-type psoriasis. The objectives are to assess the efficacy and safety of long-term maintenance therapy versus intermittent therapy with 5mg/kg infliximab. The study is sponsored by Schering-Plough, and aims to recruit 500 participants and commenced in 2006.

3.1.2.4 Additional studies

From searches undertaken, the ERG did not identify any relevant studies that were not included in the submission.

3.1.3 Description and critique of manufacturer's approach to validity assessment

The MS does not provide a formal appraisal of the validity of the included infliximab trials using the quality assessment criteria developed by NICE. The MS presents information on key criteria relating to randomisation, statistics, follow-up, cross-over and centres and geography (page 32). No details are provided of how the quality criteria are applied in the MS. Also, no formal quality assessment is undertaken on the comparator trials. The ERG assessment of the four infliximab trials can be seen below and differs from the MS for some of the trials (although this is difficult as there is no formal assessment in which to compare it

with). For example, differences are evident in the assessment of allocation concealment and randomisation for the Chaudhari and colleagues[9] and SPIRIT[10] trials.

- How was allocation concealed?

The MS reports that randomisation was carried out for all four trials via a telephone-based recruitment and allocation software solution. No further discussion of the allocation concealment is made. The ERG assessment of the methods of allocation concealment in each of the four included trials would suggest that it is unclear from the information provided in the Chaudhari and colleagues trial[9] and the SPIRIT study[10] if allocation concealment was adequate. In the SPIRIT study the trial reports the use of an adaptive treatment allocation. However, this is related to stratification of participants rather than the allocation procedure itself. For the EXPRESS[14] and EXPRESS II[11] trials, the ERG assessment of the methods of allocation concealment is adequate.

- What randomisation technique was used?

As above, the MS reports that randomisation was carried out via a telephone-based recruitment software. No further discussion of the adequacy of the randomisation of participants is provided but it is assumed that the MS is suggesting this is appropriate for all trials. The ERG assessment is that from the details found in the trials, randomisation is adequate only for the EXPRESS[14] and EXPRESS II[11] trials and is unknown for the Chaudhari and colleagues[9] trial and the SPIRIT study.[10]

- Was a justification of the sample size provided?

The MS supplies details of the power calculations for the four included infliximab trials (Table 9, page 32) and states for each study seen in the table under section 5.3.5 (statistical analysis and definition of study groups, page 30-31) that the power for all four studies was adequate. The ERG assessment of the adequacy of the power in each of the studies was as follows. For the Chaudhari and colleagues[9] trial a justification of the power of the study was provided. However, the sample size was very small and the study only had an 85% power to detect a difference. For the SPIRIT study[10] the MS states that the study was powered but the ERG have not identified a power calculation that was adequate in the publication. Sample sizes in the EXPRESS[14] and EXPRESS II[11] trials were justified, although the ERG would note that this appeared in the manufacturer's full trial report rather than the publication for the EXPRESS study.

- Was follow-up adequate?

The MS reports that all trials assessed primary endpoints across short follow-up intervals of ten weeks and that this offers limited information about the longer-term efficacy of infliximab in promoting remission in psoriasis.

- Were the individuals undertaking the outcomes assessment aware of allocation?

The MS states that [for all trials] 'clinicians carrying out the regular assessment of psoriasis outcomes were also blinded as to patient allocation' (page 32, second sentence). However, the ERG assessment from the trial information is that blinding of outcome assessors is unclear in all four trials. The manufacturer focuses on double blinding (patients and drug administrators) and this is adequate across the four trials.

- Was the design parallel-group or crossover?

A parallel-group design was undertaken for the ten-week endpoint analyses in each trial. Longer term analyses were reported for EXPRESS,[14] EXPRESS II,[11] and for SPIRIT,[10] and for the EXPRESS II study much of this was not of a treatment/placebo comparison as there was cross-over in some participants.

- Was the RCT conducted in the UK?

Only the EXPRESS study[14] included centres from the UK; the remainder were either just USA based or USA, Canada and European based trials. The MS states that clinical practice is unlikely to be different in these countries.

- How do the included RCT participants compare with patients who are likely to receive the intervention in the UK?

The MS notes that patients from the USA tend to be heavier therefore affecting the dosing of the intervention, but otherwise the dominance of US citizens is unlikely to make the results less applicable in terms of disease aetiology. It is not clear to the ERG whether all participants included in the trials reflect those in the license, i.e., that they have failed to respond or are intolerant/contraindicated to other systemic therapies. In the SPIRIT trial[10] 87% had previous systemic agents and 32% had previous biologic agents; in EXPRESS[14] 29% had acitretin, 30% ciclosporin, 43% methotrexate; in EXPRESS II[11] 43% had methotrexate, 15% acitretin, 12% had ciclosporin. In addition, in EXPRESS II 14% of participants had had previous biological agents.

- Were the study groups comparable?

The MS does not comment on the overall comparability of the groups between trials in their critical appraisal section. In the 'short-overview' section (page 18) the MS notes under 'inclusion/exclusion' that all studies involved adults with a diagnosis of moderate-to-severe plaque-type psoriasis and notes some small differences in the inclusion criteria between the trials in terms of body surface area affected and prior treatments. The baseline characteristics from each of the trials were reported. All four trials report that participants were comparable on key factors between groups. The ERG assessment of comparability between the four trials is that participants were largely similar (based on observation of the data). The proportion of male/female participants was similar across trials and the age ranges were similar. In three trials the disease duration was similar; in the Chaudhari and colleagues trial[9] this is not reported although the participants were required to have had psoriasis for at least 6-months. In the Chaudhari and colleagues trial participants had 5% or more BSA affected, while the other trials had 10% or more. Participants in the EXPRESS trial[14] had higher BSA affected than the other three trials but PASI scores were largely similar.

- Were the statistical analyses used appropriate?

The MS does not make any comment on the statistical analyses undertaken in the trials. However, the ERG suggests that analyses appear to be appropriate.

- Was an intention-to-treat analysis undertaken?

The MS notes in the summary table of statistical analyses that intention-to-treat analyses were undertaken for all four infliximab trials and the information provided in the trials would suggest that ITT analysis was undertaken for the end-point analyses. The analysis of safety in the SPIRIT study[10] was not ITT.

- Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?

No details were provided in the trials clarifying that additional drugs were not given to any participants. However, as all stated that additional drugs were not allowed the ERG have assumed that no participants received additional drugs.

- For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?

There was a 5mg/kg infliximab arm in each trial which is within the license.

3.1.4 Description and critique of manufacturer's outcome selection

The MS presents all relevant outcome measures reported in the four trials and these are appropriately reproduced in the MS. Three trials (SPIRIT,[10] EXPRESS[14] & EXPRESS II[11]) reported proportions achieving a 75% reduction in PASI as their primary outcome; Chaudhari and colleagues reported this as a secondary outcome, with Physician Global Assessment (PGA) status as their primary outcome. Other outcome measures included in the trials and reported in the MS are PASI 50; PASI 90; Quality of life measures (DLQI; NAPSI; SF-36) and adverse events.

The MS provides limited detail about the PASI system but does not discuss any of the issues that surround the use of the PASI (as mentioned in section 2.3.4). PASI 75 is the most commonly used outcome measure with PASI 50 and PASI 90 often also reported. The ERGs clinical advisor suggests that for most patients achieving 90 – 100% clearance would be ideal but many accept 75% clearance if their disease affected a lot of their skin. Similarly, while most patients would like more than 50% improvement those with severe disease are willing to accept this so they can live outside of hospital. There is also no discussion in the MS about what proportion of patients with a PASI 50, 75 or 90 would be deemed to be clinically significant.

3.1.5 Description and critique the statistical approach used

In the MS the achievement of PASI 50, 75 and 90 are reported as proportions of patients (numbers and %); p values are reported for comparisons between groups in the trial publications, but these are not presented in the MS. Relative risks and confidence intervals are calculated by the manufacturer and reported in the MS. Some have wide confidence intervals but this is not discussed by the manufacturer.

The MS presents data on improvement from baseline in PASI score from two included studies (Chaudhari and colleagues[9] and EXPRESS[14]). The mean change/improvement is presented, with standard deviation (SD) where available (EXPRESS). The MS calculated the mean difference and 95% CI. Taking data from the trial for Chaudhari and colleagues[9] the MS suggests a mean difference of –15.5 score units (the ERG estimate the mean percentage improvement to be approximately a 70% difference between groups).

PGA status is reported as proportions of patients (numbers and %); p values are reported for comparisons in the trial papers, but not in the MS. Relative Risks and 95% CI are calculated

by the manufacturer and reported in the MS. No baseline PGA or change scores are presented in any of the trials. The methods of scoring the PGA is provided in the MS on page 19. However no detail is provided on how the PGA is undertaken, how standardised it is and whether there is inter-rater differences in scoring the PGA.

The MS reports that SF-36 Quality of Life score was reported comprehensively in the EXPRESS trial, but this data is not presented in the published paper (it is reported in the manufacturer trial report but it is unclear if this remains CIC; the ERG have treated it as such). SF-36 QoL scores are presented as mean improvement from baseline (the ERG have presumed the figures in brackets are SD). The MS has calculated mean differences and 95% CI.

The MS reports that sub-group analysis was carried out (by 2 trials: EXPRESS14 and EXPRESS II11) on PASI 75 by prior treatment history and patients' disease history characteristics. Only the former are reported in the MS submission; the latter are reported in the full trial report only. For the EXPRESS II study, the full trial report only presents results for the combined infliximab groups (3mg/kg and 5mg/kg) versus placebo, and results for the 5mg/kg infliximab group versus placebo are not presented. The ERG have therefore been unable to check the data in Figure 13 (page 41 of the MS) which presents data for the infliximab 5mg/kg group. In addition data reported are for infliximab versus placebo only, not a comparison between the relevant subgroups (i.e use of previous treatment, no use of previous treatment). These subgroups appear to have been defined apriori in the full trial reports however the ERG would note that there is uncertainty over whether there would have been enough statistical power for these analyses due to the sample sizes.

Very little narrative is provided to complement the tables of data provided.

Meta-analysis

The MS pooled data on PASI outcomes from the included infliximab trials. The meta-analysis presents relative differences, although the data in Table 11 (page 43 of the MS) reports relative risks for the individual trials but the table suggests the pooled estimate is odds ratios. The ERG have checked these figures and this is an error in the MS as the pooled estimate is RR's.

The manufacturer undertook a fixed effects model for the meta-analysis but found statistically significant heterogeneity. The MS states on page 43 that the indirect comparison with comparator trials (discussed below) therefore used a random effects model as a fixed

effects model would have been inappropriate. The MS does not make any comment about the appropriateness or not of using a fixed-effects model, or the appropriateness of pooling the data generally, for the primary meta-analysis of the infliximab data and continues to present data based on a fixed-effects model.

The MS uses a statistical test to measure heterogeneity but does not provide an explanation of what threshold was used to constitute statistical significance. On observation of the data in the MS the ERG note that two analyses have p-values less than 0.05 (PASI 50, 75) and the PASI 90 analysis has a p-value of 0.839. The ERG would therefore suggest that this latter analysis does not show statistically significant heterogeneity. The ERG have re-run the data through the Revman software and this shows that (taking a p-value of 0.10 as the cut-off for heterogeneity) there is statistically significant heterogeneity in PASI 50 and PASI 75 (p values same as presented by MS) analyses but no statistically significant heterogeneity in PASI 90 (p-value slightly different, p=0.70). The I^2 statistic (also a test of heterogeneity) for these from the ERG analysis are 79% for PASI 50, 65.7% for PASI 75 and less than 1% for PASI 90, again suggesting that the PASI 90 does not show statistically significant heterogeneity (when I^2 >50%). Running the data with a random effects model continues to show statistically significant heterogeneity for the PASI 50 and PASI 75 outcomes and it is the view of the ERG that it is therefore not appropriate to pool this data.

The MS pools data from all four studies on the PASI 75 (primary outcome in all but one trial); three studies on the PASI 90 and two studies on the PASI 50.

The data on EXPRESS II for PASI 75 was noted in the MS as CIC in the table on page 34 but is presented in Table 11 (meta-analysis) on page 43 of the MS. [redacted]

The results of the meta-analysis are presented in Table 11 of the MS but no further description is provided in section 5.5 or in the conclusions of the submission.

Indirect comparison

The MS report a mixed treatment comparison of the four infliximab trials with four efalizumab and four etanercept trials using placebo as the common comparator.

On page 44 of the MS, section 5.6 “Indirect/mixed treatment comparisons”, the MS reports that data extracted from all RCTs were pooled using a fixed-effects model but that the

analysis suggested that the degree of variability was such that a random effects model was more appropriate. The ERG would question the appropriateness of pooling data in the indirect comparison that is known to be heterogenous.

The manufacturer reports on page 44, second paragraph, that the endpoints of the trials were jointly modelled using an ordered probit model. Full details of the working of the model are also provided in Appendix A (page 91-2) of the MS. The details of the equations within the ordered probit model are provided. However, no description of the principles or assumptions behind the indirect comparison are provided in the MS. Similarly, no discussion of the limitations of such an approach were reported. It is unclear which trials are included in the treatment and placebo groups. The ERG requested further detail on the methods of the indirect comparison to aid their review and for a clearer explanation of where the data seen in Tables 12 to 14 (page 45, 46) of the MS comes from (see further comment below which elaborates on this point). The manufacturer responded that the methods were the same as undertaken in the previous HTA report[1] and that explanations regarding the choice of method were given in section 5.6 and a detailed explanation of the methods can be seen in the appendix. However the ERG consider that the level of detail for full exploration remains insufficient and therefore the ERG are unable to check the model, and the data from the model, for accuracy.

Comparison of PASI outcomes

Table 12 on page 45 of the MS shows 'failure to attain PASI goals relative to infliximab'. It is not entirely clear to the ERG why the data is presented in this way rather than those achieving PASI goals as all other outcomes are reported. It is also unclear which trials are included for each of the drugs and each of the outcomes. The ERG would also question why the placebo/standard care proportions failing to attain PASI 90 appears to be considerably lower than the proportions failing to attain PASI 50 or 75 when the PASI 90 is a tighter criteria. Also an error is noted in the text describing the table (paragraph 3 under 'comparison of PASI outcomes, page 44 of the MS) where infliximab is reported to increase the likelihood of achieving PASI 75 by 63.3% compared with efalizumab but in the table this is reported to be 51.6%.

Table 13, page 45 of the MS demonstrates the probability of achieving PASI scores. The ERG also comment that it is unclear where the data comes from, which trials are included and whether the pooled endpoints for the placebo groups include placebo arms from all trials. The ERG also note that the placebo mean probability of a response is particularly small in each of the three PASI states shown but are unable to check the data.

Table 14, page 46 of the MS reports the likelihood of achieving reductions in PASI score at 24 weeks. It is unclear what data was used for these pooled estimates (this is particularly important as EXPRESS and SPIRIT were the only trials of infliximab that had a randomised comparison at 24-weeks). However the manufacturer correctly points out that the data were insufficient to truly ascertain the effects at 24-weeks.

In general there was little narrative to accompany the tables of results from the indirect comparison and little description of the methods undertaken by which the ERG could check. No data is provided on any other outcomes provided in the trials or on adverse events. However the data does appear to be of the same direction and magnitude as the pooled data seen in the Woolacott and colleagues TAR.[1]

3.2 Summary statement of manufacturer's approach

The manufacturer's approach identified all relevant trials which met their inclusion criteria and although there were some discrepancies between the scope and the decision problem the ERG would suggest that there were no missed studies using this inclusion criteria. The clinical effectiveness searches are viewed by the ERG as sound. The search strategies were taken from a previous publication for the NICE appraisal of etanercept and efalizumab. It is unclear what dates were searched for the MS and whether there were any restrictions, for example on the use of English language publications. Details of any searches for ongoing studies appears to be omitted.

The four infliximab versus placebo controlled trials meet the inclusion criteria, although the inclusion criteria did not mention how the severity of the participants should have been defined. In the Chaudhari and colleagues trial[9] participants were required to have greater than 5% BSA affected, whereas in the other studies participants were required to have greater than 10% BSA affected. On baseline characteristics the EXPRESS trial[14] participants had higher BSA affected but the PASI scores appear to be largely similar. The proportion of male to female participants and the age ranges of participants were similar. In three of the included trials the duration of disease was similar, in Chaudhari and colleagues[9] this is not reported, although the participants were required to have had psoriasis for at least 6-months.

There was no inclusion criteria set for the comparator trials, however, all eight comparator trials were randomised comparisons of (comparator) treatment versus placebo and had comparable populations and used similar outcomes to the infliximab trials.

Quality assessment

The ERG have assessed the MS for its quality as a systematic review using the questions in CRD report 4.[21] For the placebo controlled infliximab trials, the quality of the MS was reasonable (see Table 3).

Table 3 Quality assessment (CRD criteria) of MS review of infliximab studies

CRD Quality Item; score Yes/No/Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Partially – there was no criteria on severity
2. Is there evidence of a substantial effort to search for all relevant research?	Partially
3. Is the validity of included studies adequately assessed?	Partially
4. Is sufficient detail of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

For the placebo controlled comparator trials (etanercept and efalizumab) the quality of the MS systematic review was weak (see Table 4). There was no inclusion/exclusion criteria stated, no critical appraisal/quality assessment of the studies and very little detail was presented. On page 44 of the MS, (second paragraph) the MS notes that an evidence synthesis of these interventions was undertaken. However, it is the view of the ERG that there was no evidence synthesis. A previous TAR undertaken for the NICE appraisal[1] of the comparator interventions included many of these studies and the ERG feel that it would have been acceptable to have reviewed/summarised this. The previous TAR identified one other trial of efalizumab but at that time this was CIC. It is unclear to the ERG whether this has been published and therefore should have been picked up in the MS searches. The MS does identify one other etanercept trial since the completion of the TAR.

Table 4 Quality assessment (CRD criteria) of MS review of comparator studies

CRD Quality Item; score Yes/No/Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	No – there was no criteria presented only implicit criteria used
2. Is there evidence of a substantial effort to search for all relevant research?	Partially
3. Is the validity of included studies adequately assessed?	No - there was no quality assessment undertaken
4. Is sufficient detail of the individual studies presented?	No – there was limited detail presented
5. Are the primary studies summarised appropriately?	No – limited data.

The submitted evidence generally reflects the decision problem defined in the MS. The lack of head-to-head comparisons have led to an indirect comparison. However, the ERG have reservations about the appropriateness of this analysis.

3.3 Summary of submitted evidence

3.3.1 Summary of results from RCTs

In this section of the report, the ERG concentrates primarily on the main outcomes of the included RCTs of infliximab after 10 weeks of treatment. The MS also presented data at additional time points (24/26 weeks and 50 weeks) from the EXPRESS and EXPRESS II trials. However, except for data at 24 weeks in the EXPRESS trial, these results are not of a treatment/placebo comparison (patients are crossed over). Therefore, the ERG's summary is restricted to 10 week data. The MS summarises results on PASI 75 response from the comparator RCTs (efalizumab and etanercept) in Appendix 1, page 90 and these results are also presented here.

3.3.1.1 PASI

PASI 75 – infliximab trials

Achieving a 75% reduction in PASI at week 10 was the primary endpoint of SPIRIT,[10] EXPRESS[14] and EXPRESS II[11] trials, and was also measured in Chaudhari and colleagues[9] as a secondary endpoint. Table 5 shows that patients on infliximab 5mg/kg have a significantly higher likelihood of attaining an improvement in PASI of at least 75% at week 10 compared to placebo patients (all four trials). It should be noted that there are wide confidence intervals around all four point estimates indicating a lack of certainty regarding the true effect, but this is not discussed by the manufacturer. However, in three of the four trials the lower 95%CI is well above one, indicating a strong beneficial effect, albeit with large variation. The MS suggests that data from the EXPRESS II trial is CIC, but this data is available in the published trial paper.

Table 5 PASI 75 response (infliximab trials)

Study	Placebo	Infliximab	RR (95% CI)
Proportion of Patients Achieving PASI 75			Week 10
Chaudhari *et al*.[9]	2/11 (18.0%)	9/11 (82.0%)	4.5 (1.9, 10.4)
Spirit[10]	3/51 (5.9%)	87/99 (87.9%)	14.9 (8.1, 27.7)
Express[14]	2/77 (3%)	242/301 (80%)	31 (11.9, 80.5)
Express II[11]	4/208 (1.9%)	237/314 (75.5%)	39.2 (24.2, 63.6)

In the meta-analysis conducted by the MS (page 43), PASI 75 scores were pooled for the four trials using a fixed effects model. The MS reported a pooled RR (not OR) of 25.48 (95% CI 14.04, 46.23) indicating a significant difference in favour of infliximab. However, studies were statistically heterogeneous (p=0.033, I^2=65.7% (as calculated by ERG)), thus the ERGs view would be that pooling was not appropriate – see section 3.1.5.

No discussion is made in the MS about what proportion achieving a PASI 75 is clinically significant. However, proportions achieving PASI 75 are in the region of 80% which the clinical advisor to the ERG suggests is appropriate and relevant to clinical practice.

PASI 75 – comparator trials

The PASI 75 results reported in the MS for the comparator trials reflect that presented in the original trial papers. For both efalizumab and etanercept, a significantly higher proportion of patients achieved a PASI 75 at week 12 compared to patients receiving placebo (Table 6).

Table 6 PASI 75 response (comparator trials)

Efalizumab			
Study	Efalizumab	Placebo	RR (95% CI)
Proportion of Patients Achieving PASI 75			
Lebwohl *et al*.[15]	52/232 (22.4%)	6/122 (4.9%)	4.56 (2.02, 10.31)
Gordon *et al*.[16]	98/369 (26.6%)	8/187 (4.3%)	6.21 (3.09, 12.49)
Leonardi *et al*.[12]	63/162 (38.9%)	4/170 (2.4%)	16.53 (6.16, 44.37)
Papp *et al*.[17]	166/529 (31.4%)	11/264 (4.2%)	7.53 (4.17, 13.61)
Pooled RR Test for heterogeneity			7.47 (5.20, 10.73) Q=4.16 (df=3), *P*=0.244
Etanercept 25mg			
Study	Etanercept 25 mg	Placebo	RR (95% CI)
Proportion of Patients Achieving PASI 75			
Leonardi *et al*.[18]	55/162 (34.0%)	6/166 (3.6%)	9.39 (4.16, 21.21)
Papp *et al*.[19]	67/196 (34.2%)	6/193 (3.1%)	11.00 (4.89, 24.75)
Gottlieb *et al*.[20]	17/57 (29.8%)	1/55 (1.8%)	16.40 (2.26, 119.10)
Pooled RR Test for heterogeneity			10.68 (6.15, 18.57) Q=0.28 (df=2), *P*=0.869

The trials for each of the comparator drugs were pooled in a meta-analysis. The MS states that a random effects model was used, but data is presented using a fixed-effects model. For efalizumab, the pooled RR (not OR as reported in the MS) for the four trials[12;15-17] was 7.47 (95% CI 5.20, 10.73) indicating a significant difference in favour of efalizumab. The studies were not statistically heterogeneous (Q=4.16, p=0.244). A similar trend was found for 25mg etanercept, with pooled data for three of the trials[18-20] giving an RR (not OR as reported in the MS) of 10.68 (95% CI 6.15, 18.57), and thus significantly favouring etanercept. There was no statistical heterogeneity between studies (Q=0.28, p=0.869). The ERG have not restated the results for 50mg etanercept as this is outside the licensed indication.

PASI 50 – infliximab trials

Attainment of a 50% reduction in PASI response was measured as a secondary endpoint in three trials[10;11;14] at week 10. For all three trials, a significantly higher proportion of patients on infliximab achieved a PASI 50 response compared to placebo patients (Table 7).

Table 7 PASI 50 response (infliximab trials)

Study	Placebo	Infliximab	RR (95% CI)
Proportion of Patients Achieving PASI 50			Week 10
Spirit[10]	11/51 (21.6%)	96/99 (97.0%)	4.5 (3.9, 5.2)
Express[14]	6/77 (8%)	274/301 (91%)	11.7 (8.6, 15.8)
Express II[11]	[redacted]	[redacted]	11.3 (10.2, 12.6)

In the meta-analysis conducted by the MS (page 43), PASI 50 scores were pooled for two trials.[9;14] The MS presents CIC data on PASI 50 for the EXPRESS II trial, but this is not included in the meta-analysis. (There is a typographical error in the MS submission in the PASI 50 table (Table 11, page43) where Chaudhari is noted as one of the studies in the meta-analysis, but this outcome is not presented in the Chaudhari and colleagues published paper. On observation of the patient numbers, this should read SPIRIT). Using a fixed effects model, the pooled RR (not OR) was 7.35 (95% CI 4.65, 11.61) indicating a significant difference in favour of infliximab. However, studies were statistically heterogeneous (p=0.029, I^2=79% (as calculated by ERG)), thus the ERGs view would be that pooling was not appropriate – see section 3.1.5. [redacted]

PASI 90 – infliximab trials

Achievement of a 90% reduction in PASI at week 10 was measured in three trials.[10;11;14] Across all the trials, the improvement in PASI 90 score was significantly better with infliximab compared to placebo. It should be noted that there are very wide confidence intervals around all four point estimates indicating a lack of certainty regarding the true effect, but this is not discussed by the manufacturer. The MS suggests that data from the EXPRESS II trial is CIC, but this data is available in the published trial paper.

Table 8 PASI 90 response (infliximab trials)

Study	Placebo	Infliximab	RR (95% CI)
Proportion of Patients Achieving PASI 90			Week 10
Spirit[10]	1/51 (2.0%)	57/99 (57.6%)	29.4 (4.2, 203.6)
Express[14]	1/77 (1%)	172/301 (57%)	44 (6.3, 306)
Express II[11]	1/208 (0.5%)	142.314 (45.2%)	94.1 (13.3, 666.5)

In the meta-analysis conducted by the MS (page43), PASI 90 scores were pooled for the three trials using a fixed effects model. The MS reported a pooled RR (not OR) of 53.94 (95% CI 17.65, 164.89) indicating a significant difference in favour of infliximab. Confidence intervals were wide, but there was no statistical heterogeneity between studies (p=0.839, I^2<1% (as calculated by ERG)).

3.3.1.2 PGA

Physician's global assessment (PGA) status was the primary outcome in Chaudhari and colleagues[9] and a secondary outcome in the other three trials.[10;11;14] Significantly more infliximab patients achieved a 'good, excellent or clear' PGA rating compared to placebo at week 10 (three trials[9-11]). The range across the three studies was quite large for placebo patients ([redacted] to 45.1%), but less so for infliximab patients (range 82% to [redacted]). [redacted]

Results are similar for achievement of an 'excellent or clear' PGA rating, with infliximab patients (range 76% to 82%) doing significantly better than placebo (range 1% to 9.8%). Results for the EXPRESS II study[11] are highlighted as CIC data, but proportions of patients (but not numbers) in each group are reported in the trial paper, and are therefore not CIC. There is also a mistake in the results reported for the EXPRESS study[14] – the denominator should be 292 infliximab patients, not 301 as reported. This mistake carried through to the RR being calculated as 20.6, but it should be 21.3. It does not affect the overall results.

3.3.1.3 Quality of life

Quality of life was measured using the SF-36 general quality of life score and was reported only in the EXPRESS study.[14] Since this data is only available in the manufacturer's full trial report and not in the published trial paper, the data is treated as CIC (although this was not highlighted as CIC by the manufacturer). At week 10, infliximab patients experienced a significantly greater mean improvement from baseline in SF-36 scores than placebo patients. For the physical component scores, the mean difference between groups was 5.4 (95% CI 3.3, 7.5); for the mental component scores, the mean difference between groups was 7.1 (95% CI 4.4, 9.8).

3.3.1.4 DLQI

The Dermatology Life Quality Index (DLQI) was reported in three trials,[10;11;14] but only CIC data for two trials[11;14] were presented in the MS. In the DLQI a lower score relates to improvement. Two studies[11;14] reported mean change in DLQI score, whilst the third[10] presented median change from baseline. However, the trend of results was the same across all three studies in favouring infliximab. In the SPIRIT trial,[10] the median change from baseline to week 10 was –10 in the infliximab group compared with 0 in the placebo group (p<0.001). [redacted]

3.3.1.5 NAPSI

The Nail Psoriasis Severity Index (NAPSI) score was reported in one trial.[14] At week 10, infliximab patients experienced a significantly greater improvement from baseline in NAPSI score compared to placebo patients (mean difference 31.9 (95% CI 19.4, 44.3)).

3.3.1.6 Adverse events

The MS provides an overview of the safety of infliximab from the included RCTs which gives a reasonable representation of the data presented in the trials. The MS presents data for three of the trials (SPIRIT, EXPRESS, EXPRESS II) on incidence of adverse events, changes in laboratory parameters and the presence of antibodies. The MS reports that the incidence of any adverse event was slightly higher in those receiving infliximab compared to those receiving placebo although this has not been tested statistically. The majority of adverse events were reported to be upper respiratory tract infection and headache. Table 15 on page 47 of the MS presents incidence rates of participants with any adverse event for the SPIRIT study, the EXPRESS study and the EXPRESS II study. Data show rates between 56-71% in placebo groups compared to 69-82% in infliximab groups. Data was censored at different time points in each of these three studies; for the SPIRT study[10] data is from the 30 week follow-up where there were high levels of losses to follow-up; for the EXPRESS study[14] data was from 24-week follow-up and for the EXPRESS II study[11] data is from a 14-week follow-up. In Table 15 (page 47) of the MS, data from Chaudhari are not reported as they are presented with a different denominator in the trial publication, and for each adverse event rather than any adverse event. However, the ERG would comment that

data could have been presented narratively. In the Chaudhari and colleague trial[9] no differences were shown in rates of adverse events in the infliximab 5mg/kg group compared with the placebo group.

The MS also reports data on infusion reactions from the SPIRIT[10] and EXPRESS[14] studies. In section 5.7, 4th paragraph 'Infusions reactions….' There is an error in the data presented from the SPIRIT study[10] where patients receiving the licensed dose of infliximab should be 22.2% rather than 18.4% as presented in the MS. The MS has also omitted data on severe infusion reactions from the SPIRIT study[10] where two of the infusion reactions were classed as severe. Data is not presented in this paragraph from EXPRESS II[14] where patients with ≥ 1 infusions reaction was 9.6% in the treatment group and 5.8% in the placebo group. The higher rate of infusion reactions in the treatment arms of the studies is not discussed further in the MS.

A minor query the ERG have relates to Table 16 on page 48 of the MS. In Table 16 the title is incorrect as the table presents data for both EXPRESS and EXPRESS II and also presents adverse events occurring in less than 5% of patients rather than in at least 5% as the table suggests.

Serious adverse events are discussed on page 48, (1st paragraph) of the MS. The 12 serious adverse events reported for the SPIRIT[10] study were from the 3mg and 5mg infliximab groups combined and hence should be interpreted with caution. Data from EXPRESS II[11] is also not presented in this section, where patients with one or more serious adverse event were 9 (2.9%) in the treatment group and 5 (2.4%) in the placebo group. In Chaudhari and colleagues[9] there were no serious adverse events but this is not reported in the MS.

The MS also presents safety data from infliximab's other indications (rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, psoriatic arthritis) which has not been checked by the ERG.

The MS does not provide an overall summary of the adverse event profile of infliximab treatment.

Evidence of safety for comparative trials came from the Summary of Product Characteristics (SPC's) of the drugs rather than from the trial evidence and therefore this has not been

checked by the ERG. Data from comparator trials (not presented in the MS) is summarised by the ERG as follows:

- Four efalizumab trials reported rates of adverse events at week 12. Rates of adverse events in the treatment arms (patients with at least one) were between 72-86% and rates in the placebo arms between 60-75%. Serious adverse events were 2-3% in the treatment arm compared with 1% in the placebo arms.

- Two etanercept trials reported rates of adverse events at week 12. Rates were similar between arms (49% intervention, 45% placebo had at least 1 adverse event), and serious adverse events were 2% in the intervention arm and 1% in placebo arm.

The manufacturer has made no attempt to compare the data on safety between the comparator drugs, either narratively or quantitatively. The ERG note on observation of the data the rates of adverse events were similar across the three treatments versus their respective placebo groups.

3.4 Summary

Overall the MS contains an unbiased estimate of treatment efficacy for infliximab, etanercept and efalizumab based on the results of their respective placebo-controlled comparisons. The ERG have reservations over the appropriateness of the meta-analysis (as there was demonstrated statistical heterogeneity), and in particular the indirect/mixed treatment comparisons. The MS does not provide an overall statement as to the effectiveness of the intervention in section 5.9 (page 51).

The MS discusses the relevance of the evidence base to the decision problem. They state that there are two principal issues over whether the trial populations correspond to the treatment population as stated in the license. These are prior treatment history and the severity of psoriasis. The MS notes that the evidence suggests no difference in efficacy between those who were systemic-therapy naïve and those who previously failed systemic therapy. This is related to a sub-group analysis of CIC data that the manufacturer undertook to which the ERG have noted comments (above). The ERG would reiterate the concerns over whether all participants included in the trials reflect those in the license, i.e. that they have failed to respond or are intolerant/contraindicated to other systemic therapies. The MS also notes that the license for infliximab is for moderate to severe (plaque) psoriasis but the

populations of the trials were predominantly those with severe psoriasis. The ERG would concur with this finding.

The MS also reports in section 5.9 a statement concerning the relevance of the outcomes in the trials to patient experience in practice. The MS does not discuss the limitations of the outcomes except in one statement that the PASI scale does not fully capture the impact of psoriasis on a patients health and quality of life. The MS provide CIC data on the relationship between higher PASI response and improvement on the DLQI for the treatment arm of one included trial to demonstrate that higher PASI leads to more improvement on DLQI. The ERG would note that this is based on observation of the data alone, no statistical analysis was undertaken, and that the numbers were generally small.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturers submission includes:

(i) A systematic review of published economic evaluations of infliximab, etanercept, and efalizumab for the treatment of moderate/severe psoriasis or severe plaque psoriasis. The search strategy is given in section 6.1.1 of the MS and in appendix B. Studies were only included if they were carried out in the UK. The time horizon was January 2004 to April 2007. Appendix B listed 25 studies as being identified and excluded. There was one study included, this was Woolacott and colleagues[1].

(ii) A report of the economic evaluation undertaken by the manufacturer, for the NICE STA process. This compares infliximab versus supportive care, etanercept (with various dose and continuation regimes), and efalizumab. These are detailed in section 6.2.3 of the MS (page 57). The treatment group is patients with severe psoriasis, again detailed in section 6.2.3 of the MS. The model is divided into two periods, an initial trial phase lasting either 10 or 12 weeks, and a treatment phase that would last for up to 10 years. In the base case results are given for incremental cost per quality adjusted life years (QALY) for infliximab compared to continuous etanercept for severe patients only, Table 6.3.1 (page 71) of the MS.

4.2 Cost-Effectiveness Analysis Methods

The CEA estimates the mean length of time that an individual would be expected to be on infliximab, etanercept, or efalizumab through a Markov type process. These values are

combined with estimates of progression to PASI response states, QALY data, and costs of being a responder or non responder to estimate the cost-effectiveness of the alternatives. The model is based closely upon the model reported in Woolacott and colleagues.[1] This model will be extensively referred to in the following sections of the ERG report (4.2 to 4. 4.3) as the York model.

4.2.1 Natural history

The model of disease progression is based upon that reported in Woolacott and colleagues[1]. There are two states in the model, responders and non-responders. These are based upon reductions in PASI scores. The change in PASI score and associated response categories are given in Table 9. Those on supportive care can have any of these PASI responses. There is assumed to be zero mortality in the model. In addition, there are no adverse events associated with any treatment in the model.

Table 9 Definition of responders and non-responders used in the economic model

Change in PASI score	Response Category
<50%	Non-responder
≥50% AND <75%	Non-responder
≥75% AND <90%	Responder
≥90%	Responder

As patients in the model are assumed to be either non-responders to other treatments, or unsuitable for these, only supportive care and the three biological drugs (infliximab, etanercept, and efaluzimab) are evaluated in the model.

4.2.2 Treatment effectiveness

The effectiveness of treatment, in terms of the number achieving different levels of PASI reductions, is taken from the MS in Table 13 (page 45). This is estimated by an indirect comparison and is given by the numbers achieving PASI 50, 75, and 90 goals at 10 to 12 weeks. This is not an absolute measure of effectiveness, rather it is a change in severity compared to an individual's baseline value. For example an individual with a starting PASI of 20 who achieved a PASI score of 10 would be equivalent in the model to an individual who had a starting PASI of 10 and achieved a PASI of 5.

4.2.3 Health related quality-of-life

The determinant of patient's quality of life in the model was assumed to be change in PASI score from baseline. Changes in quality of life were assigned to each of the PASI responses, with the higher responses associated with larger improvements in quality of life. These changes in quality of life were not derived from infliximab trials. Instead values were taken from those quoted in the York Model. These were derived using a two-stage process from two different data sources, and are discussed in more detail in section 4.4.1.2 of this report. QALYs were estimated by applying these quality of life differences associated with changes in PASI scores to the proportions who achieve each PASI score derived from Table 13 in the MS (page 45).

4.2.4 Resources and costs

Quantification of resource use is divided into two time periods, the initial trial period (10 weeks for infliximab and 12 weeks for etanercept and efaluzimab), and subsequent treatment period (average of 186 weeks). Resource categories cover the costs of drug acquisition and administration. Also covered are NHS costs associated with monitoring individuals on biological drug therapy and also routine NHS psoriasis care. The model distinguishes between the cost of supportive care for those who are considered responders (PASI response >75%) and those on supportive care who are non-responders, with non-responders receiving inpatient care. Those who receive biological drugs in the trial period may be responders or non responders in the treatment period, non-responders having the same costs as supportive care non-responders.

Evidence on required resource use (apart from drug acquisition) were referenced to the York Model.[1] In this study, resource use for infliximab, etanercept, and efaluzimab were taken from the manufacturers' SPCs (York Model[1] references 63,64,129) and the British Society of Rheumatology's guidelines (York Model[1] reference 136). Other resource use data were taken from expert opinion.

Unit cost of drugs were taken from the British National Formulary (where available).[22] Costs of outpatient and inpatient care were taken from NHS reference costs[23] as were the costs of laboratory tests. The cost year used was 2005/6. Costs measured were direct costs to the NHS.

4.2.5 Discounting

A discount rate of 3.5% was used for both costs and benefits.

4.2.6 Sensitivity analyses

The results of one-way sensitivity analyses for selected variables are given in Table 6.3.2 of the MS (page 73) for the base case model. All base case results given in this table are for infliximab compared to continuous etanercept and only apply to 4th quartile DLQI individuals. The results of the base-case probabilistic sensitivity analysis (PSA) are given in section 6.3.2.6 of the MS (page 74). Appendix C of the MS gives the results of deterministic and probabilistic analysis for all patients.

4.2.7 Model validation

The MS states that the primary method of model validation was by comparing the results with the results obtained from the York model, see section 6.2.13 (page 70).

4.2.8 Results

The results of the model are reported as incremental costs, QALYs, and cost per QALY. The base case reports these values for infliximab compared to continuous etanercept. However, sensitivity analyses are included where the comparator used was supportive care, these are presented in the MS in Appendix C. The PSA gives 95% CIs for both costs and QALYs. The MS summarises the results for the base case analysis stating on page 8 that: "Overall, Infliximab is a cost-effective treatment option for patients with severe psoriasis who have failed treatment with systemic therapy". Compared to continuous etanercept, infliximab generated 0.205 extra QALYs at an additional cost of £4,562. This results in an ICER of £26,095.

Table 10: Summary of base case and scenario analyses results (ICERS)

Analysis	Comparator	ICER (deterministic)	ICER (PSA)
Base case	Continuous Etanercept	£26,095	£26,589
Base case	Supportive Care	£22,240	£22,418
All patients	Supportive Care	£41,351	£41,726

4.3 Critical appraisal of the manufacturer's submitted economic evaluation

4.3.1 Critical appraisal of economic evaluation methods

The ERG have considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 11 below, drawn from common checklists for economic evaluation methods (e.g. Drummond *et al*. 1997).

Table 11 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	On page 8 the MS states the aim as "to estimate the incremental cost-effectiveness of infliximab compared to current clinical practice in severe plaque psoriasis". Severe psoriasis was here defined as PASI ≥ 10, DLQI >10 and poor baseline QoL. (fourth quartile DLQI)
Is there a clear description of alternatives?	Yes	Section 6.2 states that the comparator has been specified in the decision problem. Section 6.2.3 specifies these comparators, and what doses and durations are involved. These are: • Infliximab 5mg/kg at 0, 2, and 6 weeks, then every 8 weeks thereafter. • Etanecept 25mg twice weekly as continuous treatment • Etanercept 25-50mg twice weekly until remission • Efalizumab initial dose of 0.7mg/Kg then weekly injections of 1.0 mg/Kg Supportive care including inpatients stay and clinic visits.
Has the correct patient group / population of interest been clearly stated?	Yes?	Base-case analysis focuses only on those patients with the most severe symptoms. These are patients with a 4th quartile DLQI only. In Appendix C, an all patient group is presented. However, it is unclear precisely what patients are represented by both these analyses and whether the all patient group is moderate/severe psoriasis or also severe psoriasis.
Is the correct comparator used?	Yes	Comparator used is etanercept 25mg continuous treatment. This is used instead of supportive care. The comparison with supportive care is not reported in the base case analysis. In the analysis presented in the MS, and in the York Model, etanercept 25mg continuous is dominated by etanercept 25mg intermittent. Therefore in a conventional ICER framework this should be the comparator. However, the clinical expert consulted stated that continuous etanercept is more representative of routine clinical practice
Is the study type reasonable?	Yes	Cost-utility analysis is reasonable, as the major effects of successful psoriasis treatment would be expected to be on Quality of life.
Is the perspective of the analysis clearly stated?	Yes	Section 6.2.4. Perspective is that of the NHS in England and Wales. Direct costs and benefits to the NHS only.
Is the perspective employed appropriate?	Yes	Appropriate given NICE framework. However, patients have to make frequent visits to hospital to receive the drugs and so may incur travel costs. These are not allowed for but may be minor in effect. In addition there may be substantial productivity costs associated with the condition if individuals are unable to work.
Is effectiveness of the intervention established?	Yes?	The clinical effectiveness was derived from a random effects multiple treatment comparison, Table 13. See section 3.1.5 of the ERG for a full discussion of the methods used. The effect in terms of quality of life improvements caused by response to treatment was taken from Woolacott and colleagues.[1] Full details were not given because of CIC issues.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes?	Time horizon was 10 years. This was justified on the basis that it would allow sufficient time for all future costs and outcomes to be included, section 6.2.5. The results of the trials were short term and these results were extrapolated out to a 10 year time horizon.

Are the costs and consequences consistent with the perspective employed?	Yes	Only looks at NHS costs
Is differential timing considered?	Yes	Costs and health benefits discounted at 3.5% per year
Is incremental analysis performed?	Yes	Given in Tables 6.3.1, 6.3.2 and 6.3.3 for base case. Also, in sensitivity analysis in Appendix C.
Is sensitivity analysis undertaken and presented clearly?	Yes	One way sensitivity analysis is presented in Table 6.3.2 of the MS. PSA is given for the base-case in section 6.3.2.6 of the MS. Sensitivity analysis is also presented in Appendix C of the MS.

NICE reference case

Table 12 NICE reference case requirements

NICE reference case requirements (see detail in NICE report)**:**	Included in Submission
Decision problem: As per the scope developed by NICE Comparator:	?[a]
Alternative therapies routinely used in the UK NHS	Yes
Perspective on costs: NHS and PSS	Yes[b]
Perspective on outcomes: All health effects on individuals	?[c]
Type of economic evaluation: Cost effectiveness analysis	Yes (CUA)
Synthesis of evidence on outcomes: Based on a systematic review	?Yes[d]
Measure of health benefits: QALYs	Yes
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Yes?[e]
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	No[e]
Source of preference data: Representative sample of the public	No
Discount rate: 3.5% pa for costs and health effects	Yes

N/A=not applicable

a. Base-case includes 4th quartile DLQI utility values from the York Report. Scope calls for moderate/severe.
b. Costs are NHS only
c. Only health effects were those associated with reductions in PASI scores
d. Yes, with reference to caveats raised in sections 3.2
e. Full details of QALY elicitation unclear due to CIC, however, is based on EuroQol instrument.

4.4 Modelling methods

An outline critical review of modelling methods has been undertaken by the ERG. The review has used the framework for good practice in modelling presented by Philips and colleagues[24] as a guide, addressing issues of model structure, structural assumptions, data inputs, consistency, and assessment of uncertainty.

4.4.1 Modelling approach / Model Structure

The MS presents a schematic for the model in Figure 6.2.6.1, page 60. This consists of two health states, responders and non-responders. This schematic is taken from the York report. The schematic did not have an accompanying explanation in the MS but the

manufacturer provided this upon request (see Appendix Q10). Patients on supportive care receive a package of care that is dependent on whether they are a responder or not. Responders receive two outpatient visits a year. Non-responders receive an average of 18 outpatient visits and 21 days of inpatient care per year, Table 6.2.6.10 in the MS (page 62). Patients in each of the drug treatment groups incur costs associated with acquiring and administering the drug, and patient monitoring.

The model comprises two periods, a trial and a treatment period. The trial period lasts for 12 weeks (10 weeks for infliximab) and all patients in each group receive the intervention being evaluated. Patients in the trial period are assigned a probability of achieving PASI goals as determined by the random effects, indirect comparisons model as detailed in Table 13 of the MS (page 45). Costs of each therapy for this period are detailed in the MS, section 6.2.6 on pages 61 to 62. The QALY gains achieved in the trial period are calculated by multiplying the probability of being in any particular PASI response state by the quality of life benefit provided by that PASI response, detailed in the MS, section 6.2.8 (page 65). After the trial period comes the treatment period. An annual drop out rate of 20% is used to calculate both the non-discounted and the discounted average duration of treatment for those who respond to treatment in the trial period (defined as PASI >75 or PASI >90). The discounted average duration of treatment was calculated as 169 weeks (186 weeks undiscounted). Those who respond to treatment incur both the drug treatment cost and the QALY benefit for this 169 week period. Those who do not respond to treatment receive non-responder supportive care, again for this same time period. These results are compared with supportive care where individuals who do not get the drugs are assumed to receive supportive care, based on their expected probability of being a responder, for a length of time equivalent to the trial and the treatment period.

4.4.1.1 Structural Assumptions

The model structure is poorly reported and no justification of the choice of model structure is given beyond that it has previously been used in the York report[1] for etanercept and efalizumab. The structure of the model seems reasonable. Patients achieve a level of PASI response at the beginning of the trial period and are assumed to stay at this level of improvement for a period of time and then become a non responder. The ERG clinical expert reviewer felt this assumption was reasonable. Furthermore non responders with PASI 50 are not considered in the model although there may still be a utility gain for this group. The model assumes all those with a PASI response ≥ 75% have a 100% continue treatment. None of those with a PASI response ≥ 50% but <75% have continue treatment. However,

NICE guidance indicate that these patients may continue to receive these agents if they also have a more than 5-point improvement in DLQI score.[3] Therefore, a proportion of these individuals may in practice receive further treatment. Quality of life benefits in the trial period are assumed to be achieved instantaneously, i.e. the QOL benefit obtained from a PASI response is assumed to last for the entire trial period. However, ERG sensitivity analysis suggested this last point was unimportant. The ERG is unclear how these structural changes would affect the model results.

The model uses a cycle length of 12 months. As there is a high drop out rate used in the analysis a shorter cycle length would have been more appropriate. However with only two states in the model this was thought unlikely to make a significant difference. The model takes a 10-year time horizon. At this point only about 10% of patients would be assumed to be still having treatment. For the duration of treatment individuals were assumed to remain in the PASI response state obtained in the trial period. In addition, the MS also assumes that response to treatment is constant over time, i.e. drop out rates calculated over the short term can be applied to the full ten year span of the model. Also, the model assumes that for an individual on treatment the transition from treatment to supportive care is costless, i.e. it is not associated with any inpatient or outpatient care. This was also felt to be reasonable by the ERG clinical expert reviewer.

The comparator used in the base case model is 25mg continuous etanercept. Both the York model[1] and the MS report that this is dominated by intermittent 25mg etanercept. In a conventional incremental cost-effectiveness analysis intermittent etanercept would be used as the comparator for infliximab rather than continuous etanercept. However, the MS states that continuous etanercept is assumed to be standard clinical practice across the UK, section 6.2.9.9, page 67. In addition, the ERG clinical expert reviewer felt that continuous etanercept would be more representative of clinical practice.

4.4.1.2 Data Inputs

Clinical Effectiveness

The clinical effectiveness in terms of the reduction in PASI score is taken from the random effects indirect comparisons model presented in Table 13 (page 43 of the MS). The ERG critique of these methods is given in section 3.1.5, page 26. The indirect comparison only covered the PASI response at the end of the trial period. This was either 10 or 12 weeks for infliximab and comparator interventions respectively. The model assumed that individuals would maintain these responses for the entire duration of the treatment period. Additionally no allowance for adverse events was made in the model and the model assumed all patients

would be alive for the entire model period, i.e. there was no mortality included. The effect of this assumption would depend on the assumed starting age of cohort being evaluated (the effect may be equivalent to an increase in the drop out rate), but the ERG have not investigated this effect. In addition, the model does not evaluate the effect of any mortality caused by psoriasis and any effect that successful treatment might have on this mortality. This is presumably due to a lack of data to quantify this effect.

The MS assumes a drop out rate of 20% based on the number of responders to PASI 75 and PASI 90. However the EXPRESS[14] and EXPRESS II[11] trials show there is a reduction in responders of this magnitude in six months (between weeks 24 and 50, see Table 13 below). For example in the EXPRESS II trial, 30% of PASI 75 responders had dropped out in six months (between weeks 26 and 50) and if responders continued to drop out at this rate the annual drop out rate would be 60%. Consequently the ERG suggests that the drop out rate is much higher than 20% per year and could be as much as 50% per year, see 4.4.1.4 ERG sensitivity analysis. Clearly, it would be easier to estimate the drop out rate if longer-term trial follow up data were available.

Table 13 Psoriasis area and severity index (PASI) results at weeks 24 and 50 in patients with moderate to severe plaque psoriasis.

	EXPRESS (Reich and colleagues)[14])			EXPRESS II (Menter and colleagues[11])		
	Week 24	Week 50	'Drop out' rate*	Week 26	Week 50	'Drop out'* rate
PASI75	82%	61%	26%	78%	54.5%	30%
PASI90	58%	45%	22%	56%	34.3%	39%

*Drop out rate is the proportion of responders who drop out between week 24 and week 50.

Patient outcomes

Patient outcomes used in the model were utility changes associated with changes in PASI scores. The MS references these values from the York model. However, it was not obvious from reading the York report exactly how these values had been calculated. The ERG understands that utilities were calculated in a two-stage process. Firstly, a relationship between PASI response and change in DLQI was estimated from etanercept trials for patients with different levels of PASI responses and DLQI baseline scores. The second stage involved data from a different source, the Health Outcomes Data Repository, (HODaR) database (http://www.hodar.co.uk/). This provided data on EQ-5D and DLQI scores. A linear regression analysis, using ordinary least squares (OLS) regression, was used to relate EQ-5D scores to DLQI and this was used to quantify the utility change associated with changes in PASI scores.

The sample size for this regression was 86. However, details of the regression equation and the PASI response by DLQI have been removed from the York report[1] as they are CIC. It is therefore difficult to form an opinion of the validity of these values. The process assumes a linear relationship between DLQI score and EQ5D. This implies that a change in DLQI from 2 to 1 would have the same utility gain as a change from 20 to 19, i.e. the utility gain is independent of initial severity. If this was not a valid assumption then differences in severity between the patients in the trials and the patients in the HODaR database may be important. However, no details were available on the characteristics of individuals taken from the HODaR database, in particular their severity of disease. As QOL scores were obtained from the HODaR database they would be on individuals who would not be taking drug treatments so these would exclude any effects on utility values caused by drug related adverse events. This may produce different results than a situation where values for quality of life were taken from the trials themselves since any effect of adverse events would have been expected to be included in utility scores.

Mean values for utility gains reported in the MS are the same as in the York report. Values given are divided into all subjects and those who had baseline 4th quartile DLQI scores from the etanercept trials. The ERG team were unclear as to what severity of psoriasis was implied by these two classifications. It states in the York report,[1] (Table 4 on page 17), that the included trials of etanercept had an inclusion criteria of PASI ≥ 10 and BSA >10 (two trials, total N= 1235) or BSA>10 (1 trial, N=112). Therefore, many of the individuals in these trials may have been severe (NICE definition[3] of PASI ≥ 10 and DLQI > 10). If the all patient group are severe, then it would be unclear what severity of psoriasis the 4th quartile DLQI group would represent. In addition, the ERG felt that the method for defining the 4th quartile group was not adequately explained in either the MS or the York report. It could be that 25% of individuals with the worst DLQI or any individuals who had a DLQI score in the upper quartile of the permissible DLQI range.

The above discussion is based on the ERG's interpretation of the analyses presented in the York report[1]. However the methods used could differ from our understanding of them. The discussion presented by the ERG may not be entirely applicable. However there remains uncertainty over the definitions of patient populations and what these mean in terms of severity of psoriasis.

The MS carried out analyses for the 4th quartile group and the 'all subjects' group - the ERG would question why the second group were 'all subjects'. The ERG would have expected the two groups to be 4th quartile DLQI and non-4th quartile DLQI. The base case analysis in the

MS evaluates giving infliximab to patients with 4th quartile DLQI scores. If this question is answered then the next question would be to evaluate infliximab for the remaining psoriasis patients. This question would be addressed by using utility values for non 4th quartile patients only, and not all patients. As the utility differences were larger for 4th quartile DLQI compared to all patients the expected utility differences for a non-4th quartile group would be lower than for 'all patients'. The ERG were unclear as to the exact magnitude of the effect this would have on the cost per QALY ratio but the likely effect would be to increase the ratio.

The York report[1] (p62 and p63) states that the probabilistic sensitivity analysis used the standard error from the OLS regression and also the standard error from the change in DLQI conditional on PASI response. It was not clear how these were combined or whether these adequately captured all the uncertainty inherent in this process.

The MS reports the use of the SF-36 in the EXPRESS and EXPRESS II trials, (Table 7, page 25 and 26). However, it states that this was only captured comprehensively in the EXPRESS trial, page 38 of the MS. Given that SF-36 values were available the ERG is unsure why these were not used to estimate utilities directly from this trial via the use of the SF-6D (this provides utility values and can be estimated from SF-36 questions). These seem more directly applicable to the infliximab for psoriasis models than values obtained by the two-stage process used. Even if these were not used in the model it would have been useful to see SF-6D scores related to changes in PASI scores in order to compare these with the values used.

For both groups (4th quartile DLQI and all patients), the utility differences are combined with the same data on progression to PASI response states. The ERG question how appropriate this was or which set of utility differences would best match the data on progression.

Resource use

These were detailed in the MS on pages 61 to 62, and in Tables 6.2.6.6 to 6.2.6.10. These resource categories were:

1. Drug acquisition
2. Administration of infliximab
3. Monitoring costs associated with required blood tests
4. Outpatient visits for monitoring individuals on drugs who are responding to treatment or on standard care who are responders

5. Outpatient visits to provide care for individuals who are non-responders
6. Annual inpatient care to provide care for those who are responders.

This list of resource usage appears to be comprehensive and follows the categories reported in the York Model.

Infliximab administration is based upon three standard outpatient visits in the trial period. It also requires a visit every eight weeks during the treatment period, or 6.5 visits per year. The MS states that 2-hours would be required for infusion of infliximab, (MS, section 7.6, page 79). Furthermore, out-patient care is also assumed to occur in this visit so that those in the infliximab arm require fewer outpatient visits. For example, Table 6.2.6.4 (page 61 of the MS) states that those on infliximab require 4-5 visits in the trial period and 5-6 visits per year in the treatment period. As 3 visits are needed to receive infliximab in the trial period and 6.5 per year in the treatment period individuals on infliximab receive 1.5 outpatient visits in the trial period and zero in the treatment period.

The use of outpatient services was included in both the trial and treatment periods. There were three outpatient visits for etanercept and efalizumab and 1.5 for infliximab. This is because, as previously stated, some of the necessary outpatient care for those with infliximab would be assumed to occur in the administration visits. For supportive care, individuals who were responders would receive two outpatient visits per year. However, those who were deemed to be non-responders were assumed to receive 18 outpatient visits per year. This was taken from expert opinion and differs with the approach taken in the York Model. For infliximab in the treatment period there were assumed to be no outpatient visits per year. Again, this is presumably as care is assumed to be given in administration visits. For the other biological therapies four visits per year were assumed.

The main resource associated with supportive care was inpatient stays. All individuals on supportive care who have a PASI response below 75% are assumed to be non-responders. This would comprise approximately 95% of individuals (MS, Table 13, page 45). These individuals are assumed to have one inpatient stay per year which has a duration of 21 days. The value of one stay per year is derived from expert opinion. The duration of 21 days is supported with reference to Hospital Episode Statistics data where an average stay of 18.1 days is quoted (MS, page 61). In addition, the MS states that “Dermatologists questioned across the UK supported that at least 21 days annually would be necessary to treat patients with severe psoriasis only being treated with supportive care.” The MS goes into no detail as to how this expert opinion was gathered, for example no information was presented in the

MS on the number of experts, their credentials, the process of gaining opinion, or how the questions were phrased. The manufacturer responded to questions from the ERG by stating that twelve consultant dermatologists with a specific clinical interest in plaque psoriasis were consulted (see Appendix 1, Q14, page 66 of this report). What is not clear is the details of the questions asked and the scenarios used to elicit values. This meant the ERG were unsure of the suitability of the estimates presented, particularly that of 21 days inpatient care per year.

Unit Costs

Drug acquisition costs are taken from the BNF[22] and appear to be reasonable. For Infliximab and efaluzimab the required dose is body weight dependent. The base case assumes a mean body weight of 70 Kilograms (kgs). For infliximab, one vial of the drug is sufficient for 20 kgs of body weight. The costs appear to be calculated on the basis that costs would be rounded up to the next vial, i.e. a 70 kg individual would require four vials. Efaluzimab is calculated in the same way.

The MS also includes a calculation of the costs required to administer the drugs. For etanercept and efaluzimab these costs are assumed to be zero, presumably as individuals are assumed to self-inject. However, the York model includes a cost for administration of £102 for etanercept and efalizumab based upon three 1-hour nurse sessions being needed for learning to self inject. Hospital pharmacy costs were not included in the MS, these could include the costs of dispensing injectables and preparing infusions.

The MS assumes the cost of visits to receive infliximab equate to those for a standard dermatology outpatient visit, (Tables 6.2.6.8 to 6.2.6.10, page 62). This may be an underestimate of necessary costs. The MS states that a cost of £124 (section 7.6, page 79) would be associated with the administration of infliximab, however, this was not used in the model (£65 being used).

Monitoring costs are those required for drug tests, a cost of £2.80 and £1.83 are used for haematology and biochemistry tests respectively. These costs would be acceptable if they are assumed to occur within contacts that are already taking place, i.e. no extra contacts would be necessary to carry out these tests and discuss the results with patients. This assumption appears reasonable. The MS specifically excludes any tests required to initiate individuals on biological therapies (MS page 61). This was done on the basis that these would already be carried out in routine care. In the opinion of the ERG clinical expert these

tests would be simple and low cost and in general the same for all biologics so again this assumption seems reasonable.

The MS uses a value of £295 per bed day derived from two elective inpatient HRG codes to cost this stay. This would give a value of £6195 per year for inpatient stays. The MS (Table 6.2.6.10) gives a value of £7365 for inpatient care. The MS also adds an estimate of 18 outpatient visits per year to this (18*£65=£1170) for a total cost of £8535. The MS appears to have added the cost for the outpatient visits to the inpatient stays twice in Table 6.2.6.10, the correct total costs appears to be £7365. However, the correct value appears to have been used in the model.

There are a number of questions regarding the cost used for an inpatient admission. Firstly, it is unclear why only elective codes are used given that there are nearly three times as many non-elective admissions as elective admissions under these codes. Secondly, the finished consultant episode (FCE) average length of stay reported for these codes varies between 10 and 12 for elective admissions (and 4-7 days for non-elective). It is therefore not clear whether an average cost per day derived from these shorter stays would be appropriate. NHS reference costs provide excess bed days costs which are generally lower. Using a cost per day of £295 for 21 days gives a value of £6189. However, if we calculate the cost of a stay using the HRG cost for an episode plus excess bed days for the difference between 21 days and the average length of that episode we get figures of either £5,091 or £5488 depending upon whether only elective or both elective and emergency admissions are included.

4.4.1.3 Consistency

Internal consistency

Random checking of the model has been done for some of the key equations in the model. The ERG have not undertaken a comprehensive check of all cells in the model. The model is fully executable and inputs changed on the 'Inputs' worksheet produce changes in the deterministic results by clicking on a button on the 'Results' sheet. These can be used to replicate the results presented in the MS and the univariate sensitivity analyses for the base case model, as reported in Table 6.3.2 of the MS. However no input values were provided for the univariate sensitivity analyses and the ERG were unable to replicate sensitivity analyses A-B. The ERG asked for clarification of these input values but the manufacturer did not provide them.

The model is generally poorly presented and documented and is not particularly user friendly. The model includes a worksheet that summarises the model inputs (clinical effect parameters, cost and utilities) on the 'Inputs' worksheet. However the ERG view the model as a reasonable approach to modelling the cost effectiveness of infliximab and from random checking the 'wiring' of the model appears to be accurate.

Checking of the model was carried out to see if results were in the expected directions and had expected magnitudes. Changing the drop out rate for infliximab and keeping the drop out rate for the other biological therapies constant produced non-intuitive results. For example, if only the infliximab drop out rate increases, infliximab becomes more cost effective rather than less cost effective.

External consistency

The MS states that the "primary validation of the model was by comparison with the results from the model used by the York assessment group in the multiple technology appraisal for etanercept and efalizumab for the treatment of psoriasis." This is given in section 6.2.13 of the MS. No other detail on external validity of the model is given. The MS states in section 6.2.13 that the costs and outcomes in the MS are calculated differently than for the York model as a result of different mathematical formulae being used and cites Appendix B as an explanation of this. However, the ERG could not find this explanation as Appendix B appears to cover the economic evaluation systematic review with included and excluded studies and search strategy only.

The MS states that the ICERs reported for etanercept and efalizumab in the MS model are lower than those obtained in the York model, (see section 6.3.4.1, page 76). The MS give as the reason for this the additional costs assigned to individuals who are non-responders to supportive care, section 6.3.4.1, page 76. The MS states that there was no published model evaluating the cost-effectiveness of infliximab, section 6.3.4.1 page 76. However, the York report does cover infliximab as a secondary analysis. This is part of an analysis that includes a wide range of treatments for psoriasis. In the York model the incremental cost-effectiveness of infliximab compared to supportive care is £51,748 per QALY.

4.4.1.4 Assessment of Uncertainty

One-way sensitivity analyses

A series of one-way sensitivity analyses were carried out on the base case model. The MS provided no rationale for the choice of variables included (or excluded) in the sensitivity analysis. The following variables were subjected to sensitivity analysis: patient weight,

response rates, utilities, annual withdrawal (or drop out rate), length of trial period, length of hospital admission for non responders, number of additional clinic visits for responders. Some key input parameters (such as cost of infliximab and cost of an inpatient stay) which might be expected to be highly influential on the cost-effectiveness estimates have been omitted from the sensitivity analysis. The MS did not provide details of the input values used in the sensitivity analyses and the ERG asked for clarification of these. Consequently the ERG was unable to replicate the 'best response for etanercept continuous, worst for infliximab. In general the ranges used to vary the parameters were reasonable. For utility values the ranges were varied by +/- 1 standard error instead of using the upper and lower CI which is more usual.

According to the MS, the model is most sensitive to the length of inpatient stay for non responders and patient weight. From the values presented in Table 6.3.2 of the MS (page 73), the model is also sensitive to the response rates to treatment for infliximab and etanercept and the utility range. In addition to the above, a number of two-way and multi-way sensitivity analyses were conducted as combinations of the one-way sensitivity analysis. The model seems very sensitive to simultaneous changes in two or more variables. There was also a best and worst case analysis of £11,657 and £251,565 respectively for infliximab. All sensitivity analyses presented in Table 6.3.2 of the MS are for infliximab compared to etanercept 25mg continuous use.

ERG sensitivity analysis

The ERG presents an updated table of sensitivity analyses in Table 14. Where indicated, the ERG used the confidence intervals for the parameters as ranges in the sensitivity analyses. These were taken from the manufacturer's calculations on Excel sheet *'Inputs'*. The ranges for other parameters were chosen arbitrarily. Based on these analyses, the results were most sensitive to patient weight, the cost of infliximab, and the utility gain for responders.

Table 14 Amended one-way sensitivity analyses

Variable	Base case	Inputs		CE ratios		Range
		Left	Right	Left	Right	
Patient weight, kg	70	50	90	£4,984	£47,205	£42,221
Utility gain for responders, eg PASI>=90%†	0.41	0.59	0.23	£18,524	£44,133	£25,609
Best case response for etanercept vs. worst for infliximab†, eg PASI 90	0.129 E 0.543 I	0.092 E 0.616 I	0.173 E 0.472 I	£22,601	£32,633	£10,032
Annual drop out rates	20%	10%	50%	£24,191	£36,886	£12,695
Trial period for infliximab, weeks	12	18	6	£22,199	£28,195	£5,996
Inpatient stay for non responders, days/yr	21	25	10	£21,513	£38,694	£17,181
Outpatient visits for non responders / year	18	25	10	£24,327	£28,115	£3,788
Cost of inpatient stay (+/- 20%)	£294.96	£353.95	£235.97	£21,284	£30,906	£9,622

Cost of infliximab per vial (+/- 20%)	£419.62	£335.70	£503.54	£9,206	£42,983	£33,777
Notes † Ranges for sensitivity taken from lower and upper 95% confidence limits. E etanercept;I infliximab						

The ERG investigated the effect of using an inpatient cost derived using excess bed days cost. Using a value of £5091 instead of £6194 increased the ICER to £30,379. Furthermore the ERG considered that the cost of a two hour visit to receive infliximab (and receive other outpatient care) seems low. The ERG carried out sensitivity analysis for a value of £124 (quoted as being the associated cost of administration of infliximab in the MS, section 7.6, page 79). This increased the ICER to £29,062.

Scenario Analysis

In Appendix C both deterministic and probabilistic analyses are presented for some additional scenarios. Results are estimated for all patients rather than 4th quartile DLQI patients. Compared to supportive care the ICER for infliximab was £41,351 for all patients. As the ICER compared to supportive care was £22,240 for 4th quartile DLQI patients it suggests that the ICER for non-4th quartile patients would be substantially higher than £40K per QALY. However, insufficient data was presented to be able to estimate these values. Scenarios were also presented where efalizumab was assumed to be a second line therapy. The result of these was a very slight lowering of the ICER for infliximab compared to standard care.

In an additional sensitivity analysis provided by the manufacturer, in response to a question from NICE and subsequently sent to the ERG, the results are sensitive to the assumed weight of the patient. The base case results are £26,095 for a 70kg patient and increase to £47,205 for a 90kg patient. The same sensitivity analysis shows the effects of vial optimisation. With perfect vial optimisation the cost per QALY decreases from £26,095 to £15,540 for a 70kg patients. With 50% wastage the cost per QALY would be £20,817 per QALY.

ERG scenario analysis

The ERG investigated the effects of relaxing the assumption that benefits in the trial period would be realised instantaneously. It was assumed that benefits were realised linearly over the whole trial period. This made only a very small difference as it caused the ICER to increase to £26,639.

The results reported in the MS assume that patients who achieve either PASI 75 or PASI 90 continue with treatment with infliximab whereas those with lesser responses discontinue

treatments. The MS model provides an alternative scenario where only those with PASI 90 continued treatment. In addition the ERG analysed the scenario where all those with PASI 50 or better responses continued treatment with infliximab. The cost effectiveness varies between £23,224 and £31,019 for treatment of reponders above PASI 90 and PASI 50 respectively for infliximab versus continuous etanercept.

The cumulative effect of alternative assumptions for key model parameters was examined in scenario analyses. The parameters included, and assumptions used, are as follows:

- Drop out rate of 50% per year;
- Cost of annual inpatient stay of £5091 instead of £6194,
- Utility estimates gained from the all patient group rather than the 4th quartile DLQI group.

The outcome of these cumulative analyses are reported in Table 15. For example the cumulative effect of an analysis of utility values from the all patient group with a drop out rate of 50% per year and an annual inpatient cost of £5091 instead of £6194 would increase the ICER to £76,961 per QALY.

Table 15 Scenario analysis for base case with cumulative effect of assumption for key parameters

	Incremental cost	Incremental QALY	ICER
Base case	£3031	0.116	£26,095
Drop out rate of 50% per year;	£4224	0.115	£36,886
Inpatient cost of £5091	£4722	0.115	£41,229
All patients	£4722	0.062	£76,961

Probabilistic Sensitivity Analysis

No explanation or rationale was given in the MS for the variables included in the PSA. Input variables in the PSA were not shown. Generally gamma / beta distributions are used for costs, normal distributions used for utilities and normal distribution used for treatment response. The distributions chosen seemed reasonable. In addition to a PSA on base case values the MS also supplies PSA results for a number of different situations, as presented in Appendix C of the MS and shown here in Table 16. These included using utility values from all patients rather than just 4th quartile DLQI and using efaluzimab as the second line therapy. The results for all patients were less cost effective than the baseline results with infliximab being very unlikely to be cost-effective at £30,000 per QALY (results around 0%). For all patients there were less utility gain for each group of responders and the results were very sensitive to the utility differences used.

Table 16 Probabilistic Sensitivity analysis results

	Incremental QALYs			Incremental Costs			
	mean	2.5% CI	97.5% CI	mean	2.5% CI	97.5% CI	ICER
Base case: Severe patients							
Continuous etanercept 25mg twice weekly	0.089	0.064	0.117	£ 1525	£ 750	£ 2190	
infliximab 5mg/kg	0.205	0.164	0.251	£ 4609	£ 2696	£ 6190	£ 26,589
All patients							
Continuous Etanercept 25mg twice weekly (PASI 75)	0.048	0.038	0.06	£ 1532	£ 708	£ 2236	
Infliximab 5mg/kg (PASI 75)	0.11	0.094	0.127	£ 4609	£ 2685	£ 6155	£ 49,629
Severe patients with efaluzimab as second line therapy							
Continuous Etanercept 25mg twice weekly (PASI 75)	0.135	0.101	0.171	£ 2339	£ 1233	£ 3315	
Infliximab 5mg/kg (PASI 75)	0.218	0.172	0.263	£ 4857	£ 2951	£ 6513	£30,337
Etanercept 50mg twice weekly (PASI 75)	0.16	0.123	0.2	£ 5065	£ 3744	£ 6346	Dominated

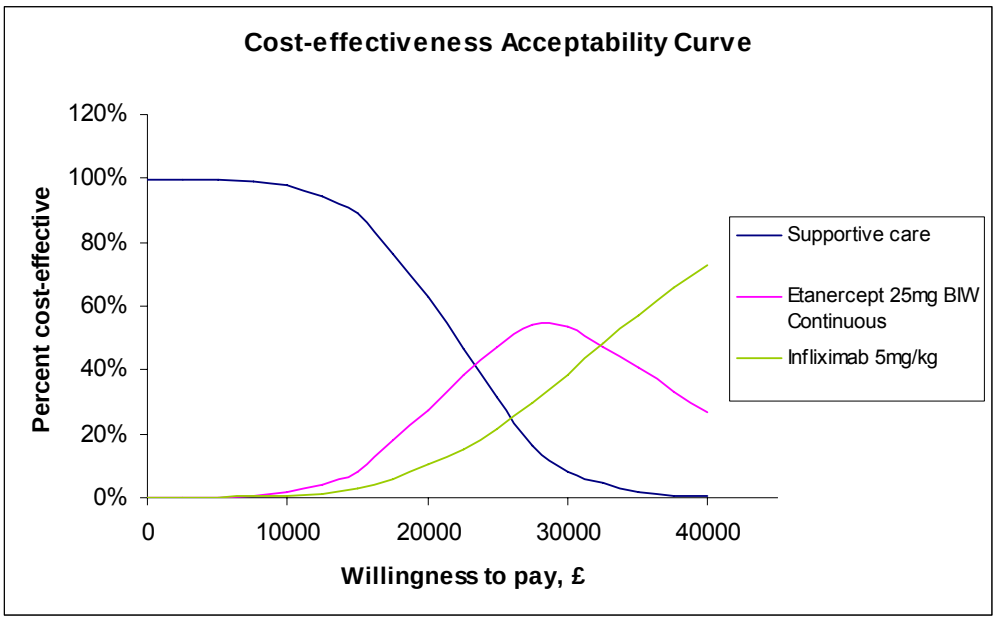
4.4.1.5 ERG probabilistic sensitivity analysis

The MS did not include uncertainty in the cost of infliximab, hospital costs, or the drop out rate in their analysis. The ERG varied these parameters – for a drop out rate between 0.2 and 0.5 and for the other variables with CI of +/-20% as used for the sensitivity analyses in Table 17.

Table 17 ERG probabilistic sensitivity analysis

Parameter	Mean	St dev	Distribution	ICER	Pr(ICER < 30k)
Annual drop out rate	35%	a = 0.2, b = 0.5	Uniform	£36.9k	10%
Cost of infliximab per vial	£419.62	40	Gamma	£26.9k	64%
Length of inpatient stay (days)	21	2.3	Gamma	£26.6k	68%
Number of outpatient visits	18	2	Gamma	£26.5k	73%
All above				£33.2k	38%

Figure 1 Cost-effectiveness acceptability curve with the inclusion of uncertainty on variables previously assumed certain.



As can be seen from Table 17 and Figure 1, changes in these parameter values have the effect of increasing the value of a QALY at which infliximab is the intervention most likely to be cost-effective.

4.4.2 Comment on validity of results presented with reference to methodology used

In general the approach taken to model disease progression and cost-effectiveness seems reasonable. As there are only two groups considered (responders and non-responders) an explicit Markov model framework may not have produced different results.

4.4.3 Summary of uncertainties and issues

Key areas of uncertainty were felt to be the following:

1. The values of response rates taken from the mixed treatment comparisons model. There are quality of life benefits associated with being a responder and the proportion of patients who receive these benefits (and avoid supportive care costs) are determined by these response rates.
2. The values assigned to utility differences associated with PASI responses. Because of the methods used there is considerable uncertainty surrounding these values. As can be seen from the one-way sensitivity analysis (using upper and lower 95% CIs) changes in these utility differences can have large impact on the model results.

3. There is uncertainty over the appropriate group to use in terms of utility values. The base case presents values for 4th quartile DLQI patients. It is unclear precisely what this means and how many patients would fall into this category. If this represents standard severe patients then the results would meet the MS stated research question of addressing severe plaque psoriasis.
4. The number of inpatient days per year for a non-responder. It was unclear as to how these values were derived from expert opinion (i.e. what questions were used).
5. The costs associated with inpatient care.
6. The number of outpatient stays required for an individual on supportive care.
7. The cost of a visit required to receive infliximab. A standard outpatient cost was used, these may be higher than this value.
8. The uncertainty assigned to variables in the PSA. The PSA in the MS did not include uncertainty on all variables. The PSA presented by the ERG shows that adding in uncertainty on some of these can cause shifts in the CEAC and the probability that infliximab is cost-effective at £30,000 per QALY.
9. The drop out rate of responders to treatment.

In addition to the above there is uncertainty around some of the structural assumption in the model, such as: the stability of PASI responses obtained in the trial period, the assumption that no individuals with change in PASI score ≥ 50% and <75% will be treated, and that there are no exit costs for quitting drug treatment. The ERG is unclear of the precise effect of these assumptions.

5 Discussion

5.1 Summary of clinical effectiveness issues

The clinical evidence for infliximab comes from four placebo-controlled trials. The main results focus on the efficacy of infliximab after 10 weeks of treatment. Other longer-term data (24/26 weeks and 50 weeks) is presented, but the majority is not of a treatment/placebo comparison. This short follow-up provides limited information about the longer term efficacy of infliximab. This is acknowledged by the manufacturer and supported by the ERG.

The relative risks calculated by the manufacturer have wide confidence intervals around all four point estimates for the primary outcome of PASI 75 achievement (and other outcomes), indicating a lack of certainty regarding the true effect. The four infliximab trials were combined in a meta-analysis using a fixed-effects model, but found statistically significant

heterogeneity. The heterogeneity persists with a random effects model, and it is the view of the ERG that it was not appropriate to pool the data.

Since no RCTs comparing infliximab with comparator drugs were identified, an indirect comparison was carried out with four efalizumab and four etanercept placebo-controlled trials. The MS did not undertake a systematic review for the comparator trials, limited data on the trials was presented, and no description of the principles, assumptions or methodology behind the indirect comparison were provided.

5.2 Summary of cost effectiveness issues

The manufacturer's submission to NICE includes a report on the cost effectiveness literature, and an economic evaluation using a decision-analytic model. The cost effectiveness analysis estimates the mean length of time that an individual would respond to treatment, and the utility gains associated with this response. The model is based closely on the model reported in Woolacott and colleagues.[1] The results are presented for infliximab compared to continuous etanercept for those with severe psoriasis only.

The model is generally internally consistent and appropriate to psoriasis, in terms of structural assumptions, and the cost effectiveness analysis generally conforms to the NICE Reference Case and the scope / decision problem. However, the results are sensitive to the values taken by a number of parameters: including, inpatient stays for those on supportive care and the quality of life gain achieved by responders. The values assigned to these parameters are important in determining the cost-effectiveness of infliximab for the treatment of psoriasis.

6 References

(1) Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health Tech Assess 2006; 10(46).

(2) UK Population Estimate (mid-2005). National Statistics . 2007. 4-6-2007.

(3) National Institute for Health and Clinical Excellence. Etanercept and efalizumab for the treatment of adults with psoriasis. 2006. NICE Technology Appraisal Guidance 103.

(4) Schmitt J, Wozel G. The Psoriasis Area and Severity Index Is the Adequate Criterion to Define Severity in Chronic Plaque-Type Psoriasis. Dermatology 2005; 210(3):194-199.

(5) National Institute for Health and Clinical Excellence. Etanercept and infliximab for the treatment of adults with psoriatic arthritis. 2006. NICE Technology Appraisal Guidance 104.

(6) Scottish Medicines Consortium. Infliximab 100mg powder for intravenous infusion (Remicade) No. 318/06. 2007.

(7) British Association of Dermatologists. Guidelines for the use of biological interventions in psoriasis. 2005.

(8) British Association of Dermatologists. Psoriasis Guideline 2006. 2006.

(9) Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-tryp psoriasis: a randomised trial. The Lancet 2001; 357:1842-47.

(10) Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D et al. Inflximab induction therapy for patients with severe plaque-type psoriasis: A randomised, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004; 51:534-42.

(11) Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C et al. A randomised comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2006; 56:e1-15.

(12) Leonardi CL, Papp KA, Gordon KB, Menter A, Feldman SR, Caro I et al. Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomized phase III trial. J Am Acad Dermatol 2005; 52:425-33.

(13) Tyring SK, Gottlieb AB, Papp K, Gordon KB, Leonardi CL, Wang A et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. The Lancet 2006; 367:29-35.

(14) Reich K, Nestle FO, Papp K, Ortonne J-P, Evans R, Guzzo CA et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phas III, multicentre, double-blind trial. The Lancet 2005; 366:1367-74.

(15) Lebwohl M, Tyring SK, Hamilton TK, Toth D, Glazer S, Tawfik NH et al. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. NEJM 2003; 349:2004-13.

(16) 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.

(17) Efficacy and Safety of Efalizumab Therapy in High-Need Psoriasis Patients (poster). AAD 2005; 2005.

(18) Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A et al. Etanercept as monotherapy in patients with psoriasis. NEJM 2003; 349:2014-22.

(19) Papp K, Tyring SK, Lahfa M, Prinz J, Griffiths CEM, Nakanishi AM et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 2005; 152:1304-12.

(20) Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003; 139:1627-32.

(21) CRD. Undertaking Systematic Reviews of Research on Effectiveness. 4. 2001. York, Centre for Reviews and Dissemination.

(22) British National Formulary. [53]. 1-3-2007. London, British Medical Association and Royal Pharmaceutical Society of Great Britain.

(23) NHS reference costs. webpage [2007 [cited 2007 June 6]; Available from: URL:http://www.dh.gov.uk/en/Policyandguidance/Organisationpolicy/Financeandplanning/NHSreferencecostsdatacollection/index.htm

(24) Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Tech Assess 2004; 8(36).

7. Appendices

Appendix 1: Manufacturers response to clarification queries

Q1) Searches – the manufacturer states that an in-house search of their databases was 'not applicable' on page 93 of their submission (economic searches section) and there is no mention of using in-house databases in the clinical effectiveness appendix or in the identification of studies described in section 5. Could the manufacturer provide further explanation of why a search was not undertaken to identify company research reports and ongoing trials relevant to the submission?

A1) The U.S. license holder for infliximab, Centocor®, holds all copies of company research reports and information about ongoing trials.. The license holder was contacted by Schering-Plough with a request to supply all relevant clinical study reports as well as information about ongoing trials. The two clinical study reports were supplied by Centocor, and advice was given that there were no relevant on-going trials.

Q2) Searches - could the manufacturer supply the full cost search strategies that were run for all the databases? In Appendix B page 93 there is only one list of terms and it is unclear which rows have been applied as descriptors and which as free text. The descriptor terms would vary among the databases, hence the need to record each search strategy separately. Some of the cost filter descriptor terms are also missing and there is no evidence of truncation for free text.

A2) Please find the full cost search strategies below (HEED and NHS HEED were previously stated in error).
Note, full tables of searches provided but not included in this appendix.

Q3) Searches – the MS states that Medline was used in clinical and cost searches, does this include Medline in Progress? Also were abstracts and conference proceedings eligible for inclusion or not?

A3) *A search of Medline in Process was conducted but was not considered applicable since none of the papers in this database fit the inclusion criteria.*

Abstracts, conference proceedings, and short surveys were not eligible for inclusion.

Q4) Clinical effectiveness – on page 14, section 5.2.2, second paragraph, the MS reports that 'systematic review papers were scanned manually to identify any new RCTs referred therein'. Could the manufacturer provide details of these systematic reviews and also note the search terms that they used to identify systematic reviews?

A4) The main clinical literature review included a search of the Cochrane database of systematic reviews, and published systematic reviews were also identified through the Medline and Embase searches. Section 5.2.2 sets out that the systematic reviews which were identified in the main literature search had their reference lists scanned to ensure no RCTs had been 'missed'. In practice this procedure was carried out only on the Wollacott 2006 systematic review of etanercept and efalizumab, as it was the only relevant systematic review identified in literature search.

Q5) Clinical effectiveness – the MS doesn't provide a description of the processes undertaken in applying the inclusion and exclusion criteria, the data extraction and the quality assessment of the trials. Could this be provided please?

A5) Data extracted from the clinical references were sourced from results tables and copied into the submission document. Relative risks were calculated from numbers of subjects without adjustment; estimates from the original papers (e.g. odds ratios) were not used. An overview of the quality of included trial data is given in the clinical effectiveness section. As the overview indicates, all papers were of sufficient quality to include in the indirect comparison with respect to their study design, population and treatment methods. However, as their results were heterogeneous and as their sample size differed, a random-effects analysis was undertaken.

Q6) Clinical effectiveness - the flow chart on p.17 provides the reasons for excluding RCTs, could we be provided with the numbers relating to each of the reasons and a list of the references for the excluded studies with their respective reasons for exclusion? Also could we be provided with this data for the comparator interventions?

A6) Please see the attached appendix for a detailed breakdown of the literature search strategy and exclusions.
Note, full tables of excluded studies provided but not included in this appendix.

Q7) Indirect treatment comparisons – the method of the indirect comparisons has not been made sufficiently clear for the ERG group to review the approach taken and therefore the outcomes of the analysis. Could the manufacturer provide a clearer description of the methods undertaken and provide a clearer explanation of where the data in Tables 12 to 14 comes from?

A7) The methods used by Schering-Plough for the indirect comparison are identical to those reported in the York assessment report (section 4.5, Woolacott et al 2005). As well as an explanation regarding the choice of method employed in the Schering-Plough analysis (section 5.6 of submission), a detailed explanation of the methods is included in an appendix to the Schering-Plough submission. This appendix provides a comprehensive description of the methodology employed. However, if there are further specific questions relating to particular aspects of the methodologySchering-Plough would be happy to address these.

Q8) Health Economics - Table 6.2.6.1 and Table 6.2.11.2. Could the manufacturer explain what the point estimates are (and uncertainty where relevant) for all the variables listed in these tables?

Point estimates and uncertainty were provided to the ERG in the form of a table of parameters which is not reproduced here.

Q9) Health Economics - Equations on page 58. Not all the variables included in the equations were defined in Table 6.2.6.1. Those not defined were .sc (presumably variables related to standard care arm, .t (treatment arm?), .p (unclear). Also not defined was c^{clinic}. Could these be defined please?

A9) - sc: supportive care;
- t: t^{th} treatment;
- p: placebo
- cclinic: cost of an outpatient appointment;

Q10) Health Economics - Figure 6.2.6.1. Could we have a written explanation of the model schema given in this diagram as we did not feel the diagram was clear?

A10) Patients commence active treatment and remain on it for a "trial" period during which treatment response is assessed. Patients who do not respond are then assumed to receive

supportive care and responders continue treatment - the treatment period. The mean length of the treatment period is calculated using a 10 year Markov model with an annual cycle (Figure 6.2.6.1). Patients can "fail" for any reason during the "treatment" period and are assumed to switch to supportive care. This probability of failure is the annual drop out rate. The calculated value for the treatment period is then input into the cost-effectiveness analysis.

Q11) Health Economics - P. 61 states that "the analysis adjusted the number of outpatient visits for infliximab by the number of infusion visits". An explanation of what this means would be useful.

A11) The number of outpatient visits for infliximab does not include the number of visits for infusions. To illustrate: for a patient receiving 7 infusions of infliximab in a given year, the number of outpatient appointments for this patient in the same year will be estimated as total expected outpatient appointments (ie 18 per year) less the number appointments for infusions of infliximab (ie 7). In this case, the number of outpatient appointments in the model would therefore be 11.

Q12) Health Economics - Table 6.2.7.6. Variable d^{trial} included, this was defined as the duration in years of the trial period of infliximab. Could the manufacturer provide an explanation of the meaning of this 'trial' period?

A12) Variable dtrial: the number of weeks of the trial period for infliximab (10 weeks) divided by the number of weeks in a year (52 weeks), in order to express the trial period in years instead of weeks.

Q13) Health Economics - Utility values were given for two types of individual. Severe (those with a 4th quartile DLQI) and all subjects. For all subjects, could the manufacturer provide the proportion who had 4th quartile DLQI?

A13) Please refer to table 6.2.8.2 in the submission for the proportion of patients who had 4th Quartile DLQI.

The table below has utility values for ALL patients.

	Gains in utility (mean (se))
PASI Response Category	***ALL patients***
<50	*0.05 (0.01)*
>=50 and <75	*0.17 (0.04)*
>=75 and <90	*0.19 (0.04)*
>=90	*0.21 (0.05)*

Q14) Health Economics - Section 6.2.9.9. This states that the assumption around hospitalisations and outpatient visits were verified by clinical experts. Could we have more details about this exercise, i.e. the definition of a clinical expert here, how many were included, and the details of the consultation exercise please?

A14) A consultation exercise with clinical experts was conducted to review and validate key assumptions relating to the economic evaluation of infliximab for the treatment of plaque psoriasis.
The consultation exercise with clinical experts commenced with a detailed explanation and discussion of the decision problem for the STA of infliximab in psoriasis.
Following this introductory discussion, the key input parameters and assumptions in the Schering-Plough economic model were explained and presented for validation.

A detailed description of each assumption was presented, including the base case. This was followed by a roundtable discussion, which concluded with a summary and overall consensus on the parameter values to be assigned for each assumption.
All twelve clinical experts involved with the consultation exercise were registered consultant dermatologists, with a specific clinical interest (e.g. publications) in plaque psoriasis.

Q15) Health Economics - For the base case and other models what is the assumed starting ages in the cohorts. Also for the all subject sensitivity analysis, what is the assumed proportion of this group with severe psoriasis (4th quartile DLQI).

A15) There was no consideration of starting ages in the cohort for the base case and other models. The model adjusted for age and therefore any assumption regarding age is not applicable.
The sensitivity analysis for disease severity was run for two different, but not mutually exclusive, groups of patients. The two analyses are run separately - either for patients with severe psoriasis (4th quartile DLQI) or for all patients.
When the 'all patient' analysis is conducted, the model does not account separately for patients with 4th quartile DLQI, rather the set of utility values for all patients, as per the York assessment report, are applied. It is therefore not necessary to apply an assumption regarding the percentage of patients with severe psoriasis for this analysis.