Golimumab for Psoriatic Arthritis

Submission to National Institute of Health and Clinical Excellence

Single technology appraisal (STA)

June 2010

Manufacturer

Schering-Plough Ltd (part of MSD)

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Executive summary

Background

Current evidence suggests that in Psoriatic Arthritis (PsA) patients, TNF-α inhibitors represent an efficacious and safe treatment. In a previous single technology appraisal of adalimumab in PsA (TA 125) and the ongoing appraisal of TNF-α inhibitors in PsA (appraisal of infliximab, adalimumab and etanercept), the Appraisal Committee considered all the TNF-α inhibitors to have comparable efficacy and safety and viewed them as a class whilst issuing the guidance.

Schering-Plough in this appraisal has submitted evidence to show golimumab as having comparable efficacy and safety to the existing TNF-α inhibitors. The presented clinical and cost effectiveness evidence suggests golimumab to be a cost effective treatment alternative, well within the NICE threshold of acceptability. The incremental cost effectiveness ratio (ICER) of golimumab compared to palliative care is similar to ICERs of other TNF-α inhibitors who are currently recommended for treatment in NHS. Therefore, with no head-to-head trials of any TNF-α inhibitors for the treatment of PsA and therefore no clear evidence of comparative efficacy, it is important to consider the advantages that golimumab provides over existing treatment options.

Clinical and patient unmet needs in Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy associated with psoriasis. The prevalence is between 0.1% and 1% of the population. It is a life long progressive disease that can lead to chronic joint damage, disability and increased mortality. Patients with PsA have significantly impaired quality of life with patients experiencing more pain and role limitations due to emotional problems compared to Rhuematoid Arthritis (RA) patients.

With their favourable impact on both the skin and joint component of the condition, the introduction of TNF-α inhibitors has revolutionised the treatment of PsA. There is a growing body of evidence from both randomised controlled trials (RCTs), and observational studies supporting the effectiveness of TNF-α inhibitors for the treatment of PsA. However there are further patient unmet needs and areas where patient experience can be improved including

injection site reactions and ease of administration (McInnes, 2009). A recent mutlinational survey also suggested that 72% of current subcutaneous users would like to inject less often and 81% would be willing to try an injectable biologic if it involved less frequent treatment.

Golimumab in treatment of psoriatic arthritis

Golimumab (Simponi®) is a novel once monthly subcutaneous TNF-α inhibitor for treatment of patients with PsA. Golimumab also has indications in rheumatoid arthritis and ankylosing spondylitis. Golimumab 50mg is available as a solution for injection in pre-filled auto-injector (SmartJect™) or pre-filled syringe. Golimumab is delivered in a novel L-histidine buffer (compared to citrate-buffered solution of other TNF-α inhibitors) and has low injection volume of 0.5ml thus leading to low incidence of injection site reactions of 5.8% compared to 36% with etanercept and 15% with adalimumab. Golimumab received marking authorisation in the UK on 1st October 2009.

In line with the BSR recommendations, golimumab is licensed for use in PsA patients with active PsA (≥3 tender joints and ≥3 swollen joints) who have failed to respond to adequate treatment (>6 months) of at least two nonbiologic disease-modifying anti-rheumatic drugs (DMARDs). A randomised controlled trial (GO-REVEAL) has demonstrated significant benefit of golimumab 50mg in achieving Psoriatic Arthritis Response Criteria (PsARC; 73% vs 28%), Disease Activity Score in Rheumatology (DAS28; 66% vs 24%), American College of Rheumatology Criteria (ACR20; 51% vs 9%) and Psoriasis Area Severity Index (PASI75; 40% vs 3%) responses at week 14 compared to placebo. Similar benefits in signs and symptoms were observed at 24 weeks with ACR response (52% vs 12%) and PASI75 (56% vs 1%) and maintained through 104 weeks. Significant improvement in other major endpoints such as Health Assessment Questionnaire (HAQ), Short Form 36 (SF-36), Nail Psoriasis Severity Index (NAPSI), physician's global assessment of psoriatic nail disease and the PsA modified MASES index was also observed at week 14 and was maintained through week 24. Golimumab is the only TNF-α inhibitor to have demonstrated improvement in nail psoriasis (NAPSI), an important outcome for PsA patients. In addition, golimumab is also the only TNF-α inhibitor to have demonstrated significant inhibition of the structural damage in patients with active PsA through Week 24 (p=0.011) and maintained that benefit through

Week 52 (-0.22 vs 0.22). Golimumab was well tolerated with serious adverse events (2% vs 6%) and serious infections (<1% vs 4%) comparable to placebo through week 24.

The economic analysis

The annual acquisition cost of Golimumab to the NHS is anticipated to be comparable to adalimumab. Assuming this price parity with adalimumab, the annual treatment cost of scheduled maintenance treatment with golimumab per patient is estimated to be £9,608. This includes 12 monthly injections to be administered once every calendar month on the same date.

The economic analysis focussed on cost effectiveness of golimumab compared to palliative care and other TNF-α inhibitors. A decision analytic model based on previous studies in literature was used to estimate the costs and benefits of available treatments over 40 years. The comparative efficacy of TNF-α inhibitors was estimated based on the data obtained from RCTs using indirect comparison techniques. The results demonstrated golimumab to be superior to palliative care and comparable to other TNF-α inhibitors on the intermediate outcomes of PsARC, HAQ and PASI. The treatment benefits of HAQ and PASI were then used to estimate the final model outcome of Quality Adjusted Life Years (QALYs).

The results of the base case analysis are displayed in Table 1 below.

Table 1: Base-case cost effectiveness results

	Golimumab	Palliation	Adalimumab	Etanercept	Infliximab
Technology acquisition cost	£37,873	£0	£28,949	£38,546	£45,768
Other costs	£56,278	£62,224	£57,461	£56,032	£54,923
Total costs	£94,151	£62,224	£86,410	£94,578	£100,691
Difference in total costs	-	£31,927	£7,741	- £428	- £6,540
QALYs	7.34	5.44	6.97	7.69	7.69
QALY difference	-	1.90	0.37	- 0.35	- 0.35
ICER	-	£16,811	£20,922	N/A (£1,223)	N/A (£18,868)

QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

The results indicate golimumab to be a cost effective treatment alternative compared to palliation. The ICERs for golimumab compared to palliation were comparable to ICERs of other subcutaneuous TNF-α inhibitors already recommended by NICE in PsA. The incremental analysis has been displayed in the Table 2 below.

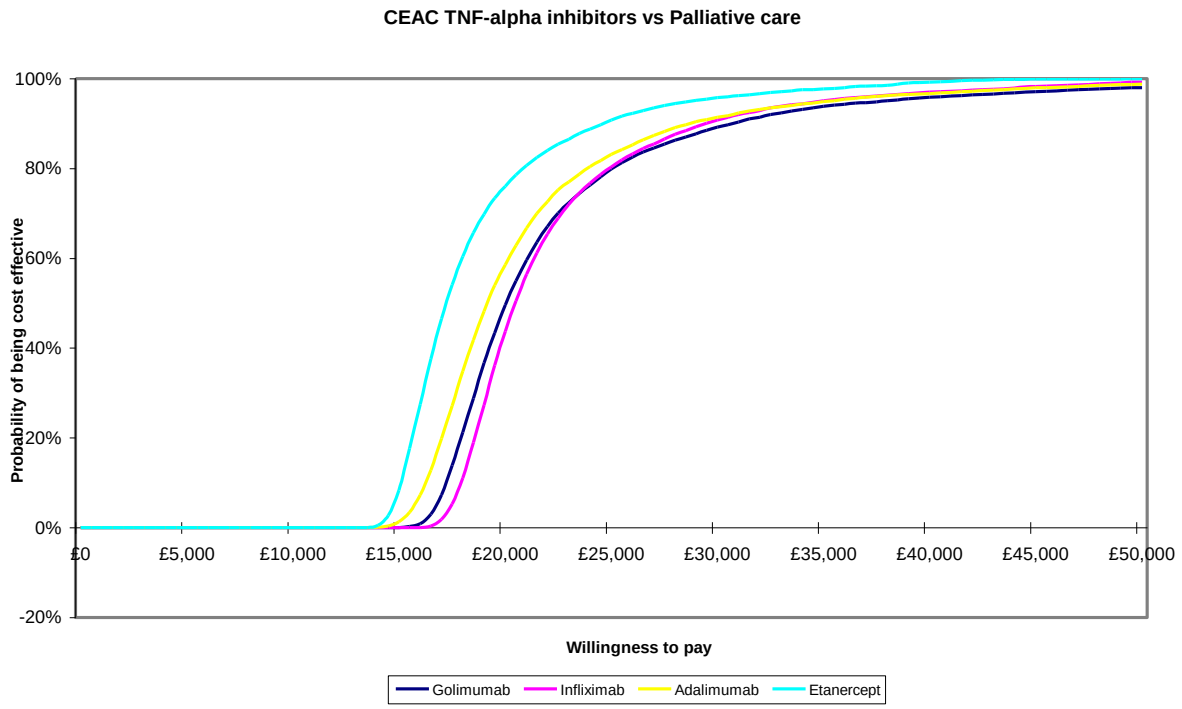
Table 2: Incremental cost effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (Palliation)	Incremental analysis
Palliation	£62,224	5.44				
Adalimumab	£86,410	6.97	£24,186	1.53	£15,820	£15,820
Golimumab	£94,151	7.34	£7,740	0.37	£16,811	£20,901
Etanercept	£94,578	7.69	£428	0.35	£14,402	£1,232
Infliximab	£100,691	7.69	£6,112	0.00	£17,149	Dominated

It is important to note that due to the limited evidence available, there is significant uncertainty around the indirect comparison estimates leading to uncertainty around the incremental analysis. The TNF-α inhibitors are comparable to each other on the entire rheumatic as well as the psoriatic treatment outcomes. It is therefore appropriate to view them as a class with golimumab as a novel addition, in line with the previous appraisals of TNF-α inhibitors in PsA (TAG 104, TAG 125, FAD for the ongoing appraisal of TNF-α inhibitors in PsA)

The uncertainty around model parameters was assessed using probabilistic sensitivity analysis (PSA). The results indicate golimumab to be cost effective compared with palliative care with a probability of 50% and 89% at a willingness to pay threshold of £20,000/QALY and £30,000/QALY, respectively. The results also were comparable to other TNF-α inhibitors as displayed in Figure 1 below.

Figure 1: The cost effectiveness acceptability curve of TNF-α inhibitors compared to palliative care



Two separate subgroups of patients were analysed. These included patients with predominantly rheumatic condition and patients with significant psoriasis in addition to arthritis. The results are displayed in Table 3 and Table 4 below.

Table 3: Results of the subgroup analysis (rheumatic patients only)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (Palliation)	Incremental analysis
Palliation	£40,275	5.85				
Adalimumab	£66,377	7.35	£26,102	1.50	£17,405	£17,405
Golimumab	£74,542	7.71	£8,165	0.36	£18,378	£22,378
Etanercept	£74,767	8.06	£225	0.35	£15,557	£638
Infliximab	£81,990	8.04	£7,223	-0.03	£19,069	Dominated

Table 4: Results of the subgroup analysis (rheumatic patients with significant psoriasis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (Palliation)	Incremental analysis

Palliation	£70,342	5.30				
Adalimumab	£93,820	6.83	£23,478	1.54	£15,249	£15,249
Golimumab	£101,403	7.21	£7,583	0.37	£16,245	£20,366
Etanercept	£101,906	7.55	£503	0.35	£13,982	£1,456
Infliximab	£107,608	7.56	£5,702	0.01	£16,462	£912,114

The results for both the above subgroups indicate golimumab to be comparable to other subcutaneous TNF-α inhibitors and a cost effective treatment alternative compared to palliation.

Conclusion

In conclusion, golimumab is a highly effective and well-tolerated therapy for the management of moderate-to-severe PsA patients and provides significant clinical benefit over palliative care. Economic analyses demonstrate that the incremental costs associated with achieving these clinical benefits are reasonable, and that golimumab represents a cost-effective treatment option well within the NICE threshold compared to palliative care without biologic DMARDs. The network meta-analysis indicated that golimumab is comparable to other TNF-α inhibitors in terms of its efficacy and safety. With comparable costs and benefits to the other TNF-α inhibitors, golimumab offers additional choice to patients and physicians at no additional costs.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Golimumab (Simponi®) 50 mg solution for injection in pre-filled pen (auto-injector) or pre-filled syringe. One 0.5 ml pre-filled pen/syringe contains 50 mg of golimumab.

1.2 What is the principal mechanism of action of the technology?

Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of TNF-α to its receptors.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Golimumab has received marking authorisation in the UK on 1st October 2009.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

None.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Rheumatoid arthritis (RA)

Simponi, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate. Simponi has also been shown to improve physical function in this patient population.

Psoriatic arthritis (PsA)

Simponi, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Simponi has also been shown to improve physical function in this patient population.

Ankylosing spondylitis (AS)

Simponi is indicated for the treatment of severe, active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

There are no ongoing studies. The evidence from completed studies has already been included in the clinical sections.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

September 2010

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Approved in the US and EMEA

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Scottish Medicines Consortium Assessment planned later in 2010.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A1: Unit costs of technology being appraised

Pharmaceutical formulation	One 0.5 ml pre-filled pen/syringe contains 50 mg of golimumab
Acquisition cost (excluding VAT)	£9,294.96
Method of administration	Subcutaneous injections
Doses	50 mg
Dosing frequency	Once a month
Average length of a course of treatment	Continuous treatment until response
Average cost of a course of treatment	£774.58
Anticipated average interval between courses of treatments	Continuous treatment once a calendar month
Anticipated number of repeat courses of treatments	Continuous treatment until response
Dose adjustments	In patients weighing more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

None

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Methotrexate, Disease Modifying Antirheumatic Drugs/Systemic Immunosuppressive therapy, corticosteroid therapy, NSAIDs and other analgesics.

2 Context

2.1 *Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.*

Psoriatic arthritis (PsA) is a chronic, debilitating spondylarthropathy characterized by inflammatory arthritis that affects the joints and connective tissue and is associated with psoriasis of the skin or nails (Gladman 2006; Gottlieb 2008). Patients with PsA are rheumatoid factor-negative (seronegative). The classification criteria developed by Moll and Wright in 1973 (Table A2) identify five clinical patterns of joint involvement that have been used to classify patients with PsA, in combination with the presence of psoriasis and arthritis (Moll 1973).

Table A2: Moll and Wright classification of joint involvement in PsA

Moll and Wright Classification	
Patients must have psoriasis and inflammatory arthritis (peripheral arthritis and/or spondylitis), be seronegative for rheumatoid factor, and present with ≥1 of the below clinical subtypes:	
Predominantly DIP arthritis	Classic form of PsA although accounts for only 5% of cases Symmetric or asymmetric Involves many joints or just a few Adjacent nails may have psoriatic changes Progressive bony erosions are common
Arthritis mutilans	Occurs in 1% to 5% of PsA cases Characterized by severe disease with osteolysis of the phalanges, metatarsals, and metacarpals.
Oligoarthritis (<5 joints)	Inflammation of the metacarpals and the proximal interphalangeal joints is prominent Milder case compared to RA
Spondylitis and/or sacroiliitis	Resembles ankylosing spondylitis HLA (IILA)-B27 is less likely to be present Axial skeleton tends to be involved in an atypical fashion Lumbar spine is the most common site Sacroiliitis is present in one third of cases Spondylitis may occur alone or with peripheral arthritis

Moll and Wright Classification
Key: DIP=distal interphalangeal; HLA=human leukocyte antigen; PsA=psoriatic arthritis; RA=rheumatoid arthritis

2.2 *How many patients are assumed to be eligible? How is this figure derived?*

Psoriatic arthritis occurs more commonly in patients with psoriasis. Although the prevalence of PsA is between 0.04% and 0.1% in the general population (Gladman 2006), up to 30% of patients with psoriasis develop PsA. Severe PsA with progressive joint damage occurs in at least 20% of patients with psoriasis (Feuchtenberger 2008).

A recent survey of the United States (US) population conducted in collaboration with the National Psoriasis Foundation found that the prevalence of PsA was greatest in middle age (45-54 years) and increased as the level of psoriasis body surface area involvement increased (Gelfand 2005). PsA is equally likely to occur in males and females unlike other inflammatory spondylarthropathies (Taylor 2002), the prevalence and incidence of PsA varies geographically, as shown in Table A3 (Alamanos 2008).

Table A3: Prevalence and incidence studies in PsA

Country and Study Year	**PsA Definition**	**Prevalence Estimate / 100,000 Population (95% CI)**
US, 2000 US, 2005	Arthritis + psoriasis	101 (81-121) 250 (180-310)
Greece, 2003 Greece, 2005	ESSG criteria	57 (50-63) 170 (100-240)
France, 2005	ESSG criteria	190 (80-350)
Italy, 2005	Arthritis + psoriasis	420 (310-610)
Sweden, 1969	Arthritis + psoriasis	20 (9-40)
Norway, 2005	Arthritis + psoriasis	195 (180-210)
Netherlands, 1984	Arthritis + psoriasis	40 (6-80)
Japan, 2001	Arthritis + psoriasis	1 (NR)
Country and Study Year	**PsA Definition**	**Annual Incidence / 100,000 (95% CI)**
US, 2000	Arthritis + psoriasis	6.6 (5.0-8.2)

Greece, 2003	ESSG criteria	3.0 (1.6-4.5)
Sweden, 2002	Arthritis + psoriasis	8 (4-15)
Finland, 1996 Finland, 2003	Arthritis + psoriasis	6.1 (4.6-7.6) 23.1 (13.2-37.5)
Japan, 2001	Arthritis + psoriasis	0.1 (NR)
Key: CI=confidence interval; ESSG=European Spondylarthropathy Study Group; NR=not reported; PsA=psoriatic arthritis; US=United States		

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

TAG 104

Etanercept, within its licensed indications, is recommended for the treatment of adults with severe active psoriatic arthritis only when the following criteria are met.

- The person has peripheral arthritis with three or more tender joints and three or more swollen joints.

- The psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying anti-rheumatic drugs (DMARDs), administered either individually or in combination.

Infliximab, within its licensed indications, is recommended for the treatment of adults with severe active psoriatic arthritis if, under the above said circumstances, treatment with an anti-TNF (tumour necrosis factor) agent is considered appropriate and the person has been shown to be intolerant of, or have contraindications to, treatment with etanercept or has major difficulties with self administered injections.

Treatment with Etanercept as well as Infliximab should be discontinued in patients whose psoriatic arthritis has not shown an adequate response when assessed (using the Psoriatic Arthritis Response Criteria (PsARC) in case of etanercept) at 12 weeks. An adequate response is defined as: an improvement in at least two of the four PsARC criteria, one of

which has to be joint tenderness or swelling score, with no worsening in any of the four criteria.

It is recommended that the use of etanercept or infliximab for psoriatic arthritis should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of psoriatic arthritis. If a person has both psoriatic arthritis and psoriasis their treatment should be managed by collaboration between a rheumatologist and a dermatologist.

TAG 125

Adalimumab should be offered as an option for treating adults with active and progressive psoriatic arthritis when:

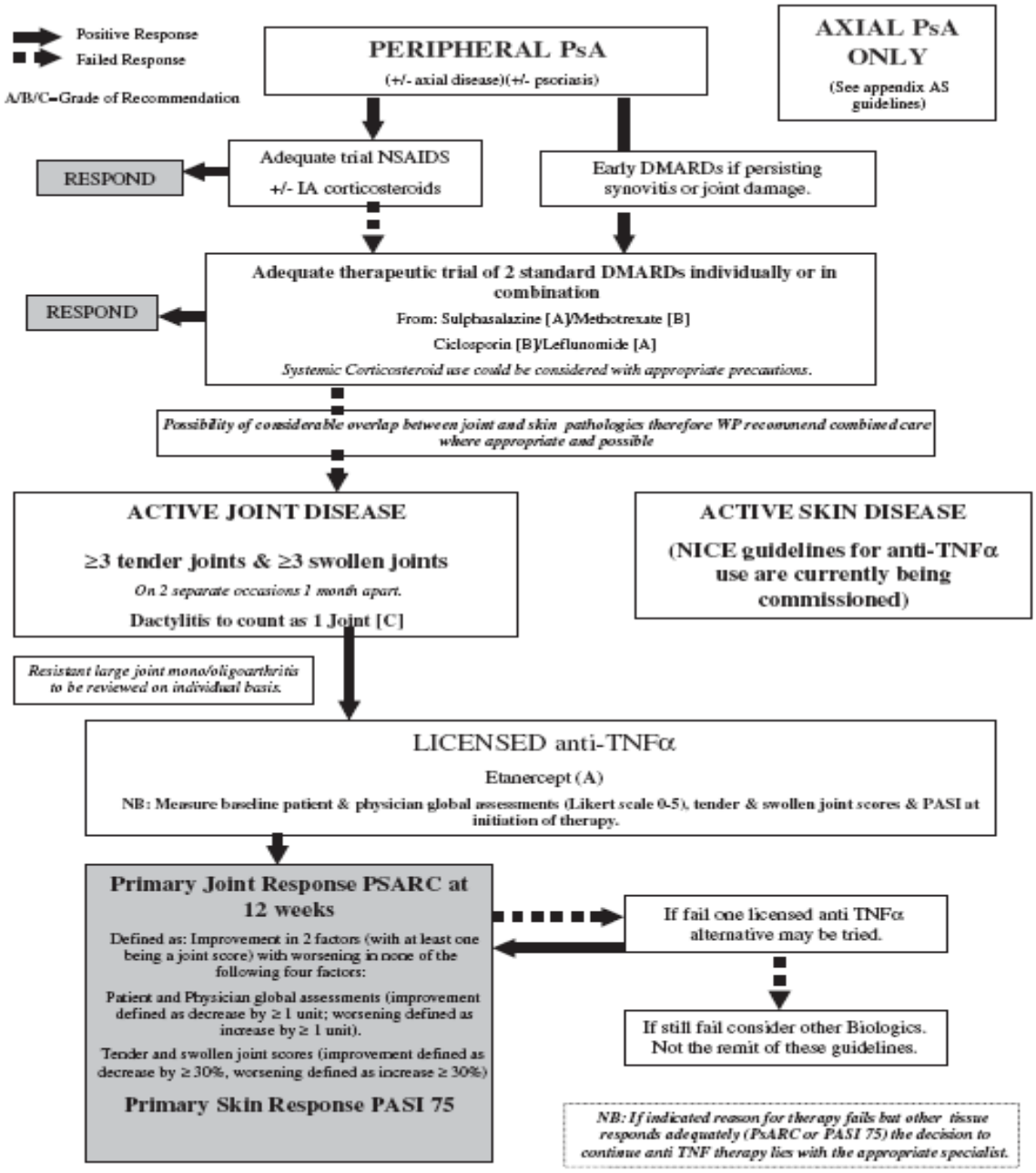
- the person has arthritis with three or more tender joints and three or more swollen joints, and
- at least two other disease-modifying anti-rheumatic drugs (DMARDs), given on their own or together, haven't worked.

Treatment with adalimumab should be started and supervised by a specialist physician who is experienced in diagnosing and treating psoriatic arthritis. If the person's psoriatic arthritis has not shown a measured response at 12 weeks, their treatment with adalimumab should be stopped.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

No NICE treatment guidelines have been published in PsA. The current treatment algorithm as recommended by British Society of Rheumatology (BSR) for treatment of psoriatic arthritis is displayed below in Figure A1 (Kyle et al. 2005).

Figure A1: The treatment algorithm for patients with active, progressive PsA



The proposed technology which is a TNF-α inhibitor fits into the current treatment pathway after failure of two DMARDs. This will be along side etanercept in the figure A1 above.

2.5 ***Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.***

None

2.6 Please identify the main comparator(s) and justify their selection.

Standard therapy: Management of PsA is aimed at suppressing joint, tendon and entheseal inflammation. NSAIDs and corticosteroid injections remain an important initial intervention but current practice is aimed at early diagnosis and early use of potential DMARDs to suppress persistent inflammation. Sulphasalazine or methotrexate is widely used in clinical practice as DMARD therapy. Patients with a poor clinical response are changed to an alternative DMARD or are commenced on combination therapy.

TNF-α inhibitor therapy – Patients failing standard care are likely to be offered TNF-α inhibitor therapy. Etanercept, Infliximab and Adalimumab are currently in use for management of active PsA in the UK. All three agents are likely to be used in the current practice depending on the patient and physician choice and are therefore deemed to be appropriate comparators.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

No significant adverse reactions of these treatments are known.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Since this technology attempts to replace an existing TNF alpha inhibitor, no additional costs are involved. Please check economic section for details.

2.9 Does the technology require additional infrastructure to be put in place?

No

3 Equity and equality

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

None

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

None

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

N/A

4 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with active and progressive psoriatic arthritis who have responded inadequately to previous DMARDs	People with active and progressive psoriatic arthritis who have responded inadequately to previous DMARDs	N/A
Intervention	Golimumab	Golimumab	N/A
Comparator(s)	• Alternative TNF-α inhibitors • Conventional management strategies for active and progressive psoriatic arthritis that has responded inadequately to previous DMARD therapy excluding TNF-α inhibitors	• Alternative TNF-α inhibitors • Conventional management strategies for active and progressive psoriatic arthritis that has responded inadequately to previous DMARD therapy excluding TNF-α inhibitors	N/A
Outcomes	The outcome measures to be considered include: • pain and other symptoms • functional capacity • effect on concomitant skin condition • joint damage • disease progression (e.g. imaging) • adverse effects of treatment • health-related quality of life.	The outcome measures addressed include • pain and other symptoms • functional capacity • effect on concomitant skin condition • joint damage • disease progression (e.g. imaging) • adverse effects of treatment • health-related quality of life.	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost	Cost effectiveness of treatments expressed in terms of incremental cost per quality-adjusted life year.	N/A

	per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Time horizon considered is lifetime of the patient. Costs are considered from an NHS and Personal Social Services perspective.	
Subgroups to be considered	Where the evidence allows, subgroup analysis may be carried out according to the combined severity of psoriatic arthritis and the concomitant skin condition Where the evidence allows, sequencing of different drugs may be considered. Guidance will only be issued in accordance with the marketing authorisation.	Subgroups include • patients with predominantly rheumatic condition • patients with significant psoriatic condition Sequencing not considered due to lack of robust evidence Submission in line with the current marketing authorisation.	N/A
Special considerations, including issues related to equity or equality	NIL	NIL	N/A

Section B – Clinical and cost effectiveness

5 Clinical evidence

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

The following databases were searched to draw relevant information pertaining to clinical effectiveness:

- MEDLINE
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)
- ClinicalTrials.gov

Searches of major bibliographic databases were undertaken in two branches – for RCTs and for studies of serious adverse effects. Search strategies used were identical to the Rodgers et al and we updated the searches to reflect additional interventions (golimumab) and recent publications (2009 onwards) (Rodgers et al, 2009). Internet resources were also searched for information on adverse effects. No language or other restrictions were applied. In addition, reference lists of all included studies and industry submissions made to NICE were hand-searched to identify further relevant studies (Bravo Vergel, 2007).

5.2 *Study selection*

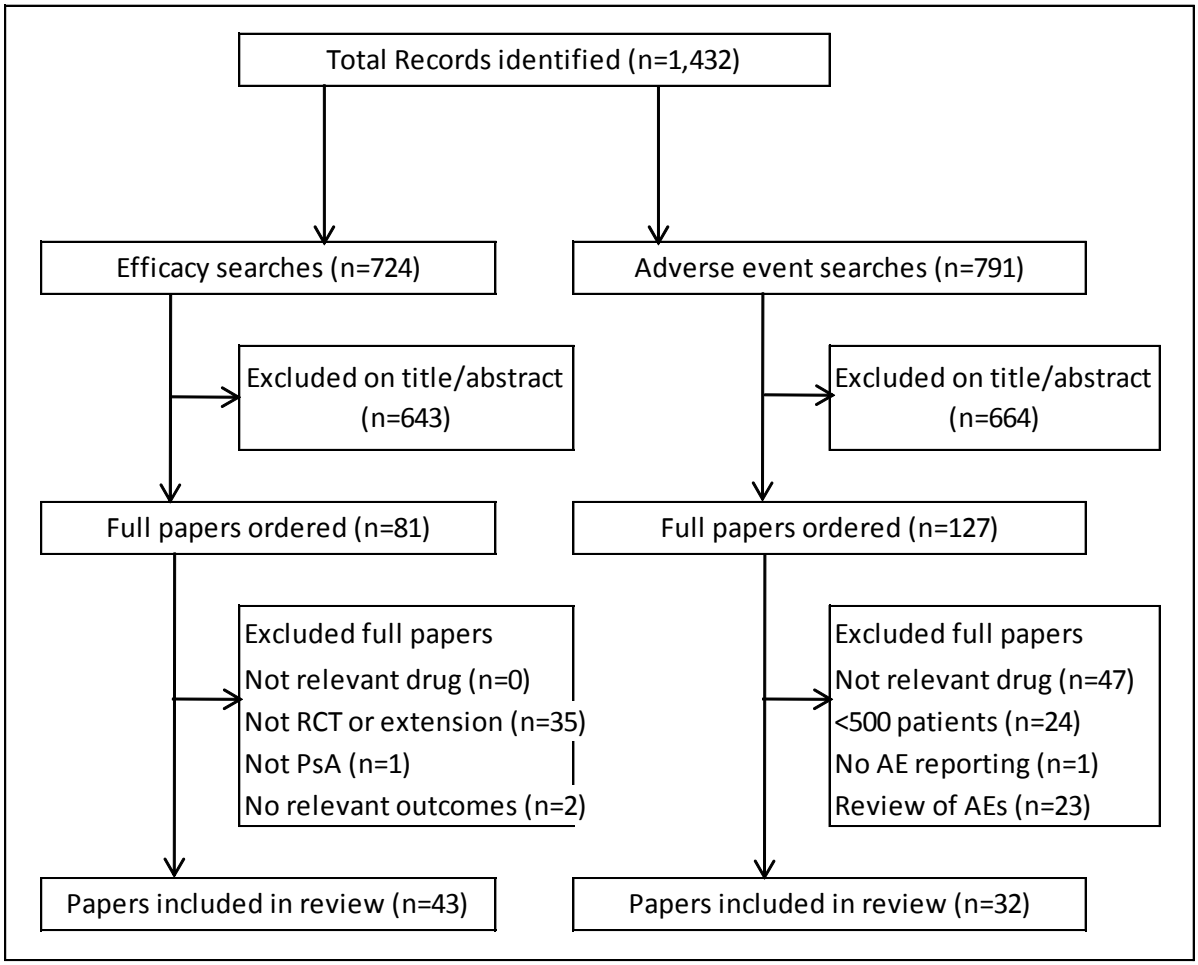
5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table B1: Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	**Study design** • Randomised controlled trials (RCTs) (including any open-label extensions of these RCTs) • Non randomised trials only when the information was not available in RCTs **Interventions** • Etanercept • Infliximab • Adalimumab • Golimumab • Palliative care which included NSAIDs and DMARDs **Participants** • Active and progressive PsA with an inadequate response to previous standard therapy (including at least one DMARD). **Outcomes** • PsARC • PASI • HAQ • Quality of life assessments including DLQI, EQ-5D, SF-36 etc. **Language restrictions** - No Language restrictions were applied.
Exclusion criteria	**Study design** • Observational studies • Retrospective database studies • Prospective non-RCTs **Population** • Patients suffering from other rheumatic or dermatological conditions **Interventions** • Other biologics excluding TNF-α inhibitors

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

Figure B1: Study selection flow diagram



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Data presented in this report is based on Clinical Study Reports (CSRs) and published papers.

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table B2: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
GO REVEAL	Golimumab	Placebo	Patients with a diagnosis of PsA for at least 6 months prior to first study agent administration who had active PsA despite current or previous disease-modifying antirheumatic drug (DMARD) or nonsteroidal anti-inflammatory drug (NSAID) therapy, and who had not previously been treated with anti-tumor necrosis factor (TNF) α therapy.	Kavanaugh et al, 2009
ADEPT	Adalimumab	Placebo	Patients over 18 years of age with moderately to severely active PsA and a history of inadequate response or intolerance to nonsteroidal antiinflammatory drugs	Mease et al, 2005
Genovese 2007	Adalimumab	Placebo	Patients at least 18 who had ≥ 3 swollen joints and ≥ 3 tender or painful joints, and either an active cutaneous lesion of chronic plaque psoriasis or a documented history of chronic plaque psoriasis. All patients enrolled in the study were receiving concomitant DMARD therapy or had a history of DMARD therapy with an inadequate response.	Genovese et al, 2007
Mease 2000	Etanercept	Placebo	Adults between 18 and 70 years who had active psoriatic arthritis (defined as ≥3 swollen joints and ≥3 tender or painful joints) at the time of study enrolment who have had an inadequate response to non-steroidal anti-inflammatory drugs and are suitable for immunomodulatory therapy.	Mease et al, 2000

Mease 2004	Etanercept	Placebo	The study population were in the age group of 18–70 years and had active PsA, with at least 3 swollen and 3 tender joints at screening and a previous inadequate response to nonsteroidal anti-inflammatory drug therapy. Patients had at least 1 of the following clinical subtypes of PsA including distal interphalangeal (DIP) joint involvement, polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis), arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis–like arthritis. Patients needed to have stable plaque psoriasis with a qualifying target lesion (at least 2 cm in diameter).	Mease et al, 2004
IMPACT	Infliximab	Placebo	Patients 18 years and older with an established diagnosis of PsA of 6 months duration or longer. Eligibility criteria included previous failure of treatment with ≥ 1 DMARDs. At enrollment, patients were required to have active peripheral polyarticular arthritis, defined as the presence of ≥5 swollen and tender joints in conjunction with at least 1 of the following criteria: erythrocyte sedimentation rate (ESR) ≥28 mm/hour, C-reactive protein (CRP) level ≥15 mg/liter, and/or morning stiffness lasting 45 minutes or longer. Patients also were required to have negative results of serum tests for rheumatoid factor and negative results for active or latent tuberculosis by purified protein derivative skin test and chest radiography.	Antoni et al, 2005
IMPACT 2	Infliximab	Placebo	Adult patients with active PsA diagnosed at least 6 months before the first infusion of Infliximab. Active articular disease was defined as five or more swollen joints and five or more tender joints and either C reactive protein (CRP) levels of at least 15 mg/l and/ or morning stiffness lasting 45 minutes or longer. Patients were required to have had an inadequate response to current or previous DMARDs or non-steroidal anti-inflammatory drugs (NSAIDs). In addition, patients had to have active plaque psoriasis with at least one qualifying target lesion at least 2 cm in diameter. Patients also were required to have a negative test for rheumatoid factor in their serum.	Antoni et al, 2005

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

All studies compare golimumab with placebo. No head to head studies were available.

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

No studies have been excluded.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

No non-RCT evidence was included in the clinical section.

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Table B3: Comparative summary of methodology of the RCTs

Trial no. (acronym)	GO REVEAL	ADEPT	Genovese 2007	Mease 2000	Mease 2004	IMPACT	IMPACT 2
Location	58 centres: 36 in North America (18 in the US and 18 in Canada), 22 in Europe (5 in Belgium, 10 in Poland, 3 in Spain, and 4 in the UK)	50 sites, located in Austria, Belgium, Canada, France, Germany, Italy, the United Kingdom, and the US	16 sites in Canada and US.	1 site in the US	17 sites in the US	9 centres in Europe, US and Canada,	36 centres; 19 in the US, 9 in Europe and 8 in Canada.
Design	Multicenter, randomized, double-blind, placebo-controlled study was designed to assess the efficacy, safety, and clinical	Randomized, double-blind, parallel-group, placebo-controlled trial of adalimumab therapy every other week.	Placebo controlled, double-blind, randomized, multicenter study, in which patients were treated with	Randomised, double-blind, placebo controlled, study to assess the efficacy and safety of etanercept (25 mg twice-	Placebo-controlled double-blind trial that evaluated etanercept therapy in patients with psoriatic	The study was conducted in 2 phases. Phase 1 - patients were randomly assigned to receive placebo or	Phase III, double blind, placebo controlled, randomised, parallel group study to evaluate the efficacy of

	pharmacology of golimumab 50 mg or 100 mg administered subcutaneously q4 weeks in adult subjects with active PsA.		subcutaneous injections of adalimumab 40 mg every other week or placebo, followed by a period of open-label treatment with adalimumab 40 mg every other week	weekly subcutaneous injections) or placebo in patients with psoriatic arthritis and psoriasis.	arthritis	infliximab 5 mg/kg at weeks 0, 2, 6, and 14. Phase 2 - patients in infliximab group received placebo infusions at weeks 16 and 18, followed by infliximab 5 mg/kg at weeks 22, 30, 38, and 46; patients in placebo group received infliximab 5 mg/kg at weeks 16, 18, 22, 30, 38, and 46.	infliximab in patients with active psoriatic arthritis.
Duration of study	52 weeks	24 weeks	24 weeks	12 weeks	48 weeks	50 weeks	24 weeks
Method of randomisation	Subjects were to be randomized in	Patients were stratified	Following a screening	Patients with psoriatic	Eligible patients were	In stage 1, the double phase -	Eligible patients were

	a 1:1.3:1.3 ratio to 1 of 3 treatment groups: placebo, golimumab 50 mg & golimumab 100 mg. In order to ensure relatively even treatment balance within sites, within baseline MTX usage (yes/no), and within the study overall, subject allocation to a treatment group was performed using an adaptive stratified randomization design.	according to methotrexate use (yes or no) and degree of psoriasis involvement (≥3% or < 3% of body surface area) at baseline, and then randomized in a 1:1 ratio by site to receive either adalimumab or placebo.	period of up to 14 days, patients were stratified by DMARD use at baseline (yes/no), then randomized in a 1:1 ratio to receive a subcutaneous injection of adalimumab 40 mg every other week or placebo for 12 weeks. Patients were randomized in blocks of 4 using an interactive voice-response system. Patients who completed the blinded phase could elect to receive open-	arthritis were randomised to receive either placebo or etanercept twice weekly; patients who continued on methotrexate were randomised separately. A block randomisation was used: within each group of four patients enrolled, two were assigned at random to the placebo group and two to the etanercept group.	randomly assigned to receive placebo or etanercept at a dosage of 25 mg subcutaneously twice weekly in an initial 24-week blinded phase. Patients who continued receiving methotrexate were randomized separately from those not receiving methotrexate. Patients continued to receive blind-labelled therapy in a maintenance phase until all patients had	Eligible patients were randomly assigned to receive placebo or infliximab 5 mg/kg at weeks 0, 2, 6 and 14. In stage 2, the crossover phase, patients in infliximab group received placebo infusions at weeks 16 and 18, followed by infliximab 5 mg/kg at weeks 22, 30, 38, and 46; patients in placebo group received infliximab 5 mg/kg at	randomly assigned in a 1:1 ratio to receive infusions of either placebo or infliximab 5 mg/kg at weeks 0, 2, and 6 followed by maintenance dosing at weeks 14 and 22. Randomisation was stratified by investigational site and baseline MTX use and was performed using a dynamic patient allocation algorithm.

			label therapy with adalimumab 40 mg every other week, the first 12 weeks.		completed the 24-week blinded phase. After the study was unblinded, all patients were eligible to receive open-label etanercept in a 48-week extension.	weeks 16, 18, 22, 30, 38, and 46.	
Intervention(s) (n =) and comparator(s) (n =)	Golimumab 50 mg (n=146) Golimumab 100 mg (n=146) Placebo (n=113)	Adalimumab 40 mg (n = 151) Placebo (n = 162)	Adalimumab 40 mg (n= 51), Placebo (n = 49)	Etanercept 25 mg (n = 30) Placebo (n = 30)	Etanercept 25 mg (n = 101) Placebo (n = 104)	infliximab 5 mg/kg (n = 52), placebo (n = 52)	Infliximab 5 mg/kg (n = 100); placebo (n = 100)
Primary outcomes (including scoring methods and timings of assessments)	• Proportion of subjects achieving an American College of Rheumatology (ACR) 20 response at Week 14 • Change from	• American College of Rheumatology 20% improvement (ACR20) response at week 12 • Change in the modified	• Percentage of patients who met the American College of Rheumatology (ACR20) core criteria at Week 12.	• The proportion of patients who met the Psoriatic Arthritis Response Criteria (PsARC) at	• Comparison of the proportion of patients in the study groups who met the American College of Rheumatolo	• Achievement of American College of Rheumatology 20% criteria for improvement in rheumatoid	• The primary efficacy assessment included components of the American College of Rheumatol

	baseline in the PsA modified van der Heijde-Sharp (vdH-S) score at Week 24 (a radiographic indicator of disease progression).	total Sharp score of structural damage at week 24.		12 weeks	gy 20% improvement criteria (ACR20)	arthritis (ACR20) at week 16.	ogy (ACR) core set, assessed at weeks 2, 6, 14, and 24.
Secondary outcomes (including scoring methods and timings of assessments)	• ACR 20 response at Week 24 • Psoriasis Area and Severity Index (PASI) 75 improvement at Week 14 in a subset of subjects with ≥ 3% body surface area (BSA) psoriasis skin involvement at baseline; • HAQ score at	• ACR20 response rate at week 24, as well as ACR50 and ACR70 response rates at weeks 12 and 24. • Response rates on the modified Psoriatic Arthritis Response Criteria (PsARC) • The	• Modified Psoriatic Arthritis Response Criteria (PsARC) • Assessments of disability, psoriatic lesions, and quality of life.	• The proportion of patients meeting the American College of Rheumatology preliminary criteria for improvement (ACR20) at 12 weeks • Improvement in ACR50 and ACR70	• ACR50 and ACR70 responses • Psoriatic Arthritis Response Criteria (PsARC), • Dermatologist's static global assessment of psoriasis • Psoriasis Area and Severity Index (PASI 50 and PASI	• Psoriasis Area and Severity Index (PASI) score • ACR50 and ACR70 criteria • Disease Activity Score in 28 joints • Health Assessment Questionnaire • Ratings of	• Psoriatic Arthritis Response Criteria (PsARC), • Duration of morning stiffness (minutes) during the previous week evaluated through week 24.

	Week 24 • Physical component summary score of the SF-36 at Week 14 • Additional secondary endpoints evaluated - efficacy, safety, and tolerability of golimumab and the pharmacokinetics/pharmacodynamics of golimumab dose groups.	disability index of the Health Assessment Questionnaire (HAQ DI) • The Short Form 36 (SF-36) health survey, also at weeks 12 and 24.			75) • Quality of life, as measured by the Short Form 36 (SF-36) Health Survey and function, evaluated using the Health Assessment Questionnaire (HAQ)	enthesitis and dactylitis, and • Psoriatic Arthritis Response Criteria score.	
Duration of follow-up	52 weeks	24 weeks	24 Weeks	12 weeks	48 weeks	50 weeks	24 weeks

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table B4: Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
GO REVEAL	• Men and women 18 years of age or older with diagnosis of PsA at least 6 months prior to first study agent administration and active PsA despite current or previous DMARD or NSAID therapy. • Diagnosis of active PsA must have included the presence of arthritis (characterized by 3 or more swollen joints and 3 or more tender joints) and psoriasis (defined as plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter and not on axilla, inframammary area, or groin). • Subjects must have had at least 1 of the PsA subsets (distal interphalangeal [DIP] joint arthritis, polyarticular arthritis with the absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, and spondylitis with peripheral arthritis). • Subjects with no evidence of active TB and no history of latent TB on TB screening. Subjects with latent TB newly detected at screening were eligible if they were started on treatment for latent TB prior to or simultaneously with first study agent administration.	• Subjects with other inflammatory diseases that could confound the evaluations of benefit from golimumab therapy. • Subjects who had previously been treated with anti-TNFα therapy, received systemic immunosuppressives, DMARDs other than MTX, or systemic corticosteroids within 4 weeks prior to the first study dose were excluded from participation. • Subjects who had received certain other drugs were also excluded. • Subjects who were pregnant, nursing, or planning pregnancy (including partners of male subjects) within 6 months after receiving the last administration of study agent were to be excluded. • Subjects who had a current serious infection or who, within 2 months prior to the first study dose, had had a serious infection, had been hospitalized for an infection, or had been treated with IV antibiotics for an infection. • Subjects with chronic or recurrent infectious diseases or certain other medical conditions were also to be excluded.

	• Subjects who had used or were currently using MTX, NSAIDS, oral corticosteroids, or topical or systemic psoriasis treatments were eligible for enrollment provided they met the treatment-specific requirements outlined in the protocol.	
ADEPT	• Patients at least 18 years old, with moderate to severe active PsA (defined as having at least 3 swollen joints and 3 tender or painful joints), • They needed to have either active psoriatic skin lesions or a documented history of psoriasis. • Patients were required to have a history of an inadequate response or intolerance to nonsteroidal anti inflammatory drug therapy for PsA.	• Treatment within 4 weeks of the baseline visit with cyclosporine, tacrolimus, DMARDs other than MTX, or oral retinoids • Topical treatments for psoriasis within 2 weeks of baseline, other than medicated shampoos or low-potency topical steroids • Concurrent treatment with MTX at dosages > 30 mg/week and/or corticosteroids in a prednisone-equivalent dosage of > 0 mg/day; and -anti-TNF therapy at any time. • History of neurologic symptoms suggestive of central nervous system demyelinating disease • History of active tuberculosis (TB) or listeriosis, or the presence of a severe infection requiring hospitalization or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days of study entry.
Genovese 2007	• Eligible patients were at least 18 years of age, in generally good health based on medical history, physical examination, laboratory profile, chest radiograph, and a 12-lead electrocardiogram. • Patients were required to have had ≥ 3 swollen joints and ≥ 3 tender or painful joints, and either an active cutaneous lesion of chronic plaque psoriasis or a documented history of chronic plaque psoriasis	• History of previous anti-TNF therapy • Intravenous infusions or intraarticular injections of corticosteroids within 4 weeks of baseline • Topical psoriasis therapies (e.g., keratolytics, coal tar, anthralin) within 2 weeks of baseline (although medicated shampoos and low potency topical steroid use on the palms, soles of the feet, axilla, and groin area were

	diagnosed by the investigator or a dermatologist. • All patients enrolled in the study were receiving concomitant DMARD therapy or had a history of DMARD therapy with an inadequate response, as defined by the investigator. - Oral corticosteroids dosage not exceeding equivalent of prednisone 10 mg/day. - MTX dosage not exceeding 30 mg/week.	allowed); ultravioletA(UVA) phototherapy, including psoralen and UVA, or use of a tanning booth within 2 weeks of the baseline visit; or oral retinoids within 4 weeks of the baseline visit, alefacept or siplizumab within 12 weeks, or any other biologic or investigational therapy within 6 weeks of the baseline visit. • Patients currently using or likely to need antiretroviral therapy. • Patients with persistent or severe infections or a history of active tuberculosis, or who had an active non-psoriatic skin disease that could interfere with the assessment of target lesions. • Significant history of cardiac, renal, neurologic, psychiatric, endocrinologic, metabolic, or hepatic disease • Neurologic symptoms suggestive of central nervous systemic demyelinating disease; and a history of malignancy other than carcinoma in situ of the cervix or adequately treated nonmetastatic squamous or basal cell skin carcinoma.
Mease 2000	• Eligible patients were adults between 18 and 70 years who had active psoriatic arthritis (defined as >3 swollen joints and >3 tender or painful joints) at the time of study enrolment. • Patients must have had an inadequate response to non-steroidal anti-inflammatory drugs and were thought candidates for immunomodulatory therapy. • Patients taking methotrexate (≤ 25 mg/week) were allowed to continue methotrexate if the dose was	• Patients with evidence of skin conditions other than psoriasis (such as eczema) • Topical therapies and oral retinoids for psoriasis were discontinued at least 2 weeks before the baseline evaluation and phototherapy was discontinued at least 4 weeks before treatment. • Patients on corticosteroids greater than 10 mg/day of prednisone.

	stable for 4 weeks before study start and remained stable throughout the study. • All patients were required to have hepatic transaminase concentrations no greater than twice the upper limit of normal, haemoglobin 85 g/L or higher, platelet count 125000 / mL or more, and serum creatinine 152•4 mmol/L or below.	
Mease 2004	• Eligible patients 18–70 years with active PsA, with at least 3 swollen and 3 tender joints at screening and a previous inadequate response to nonsteroidal anti-inflammatory drug therapy. • Patients had at least 1 of the following - clinical subtypes of PsA, distal interphalangeal (DIP) joint involvement, polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis), arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis–like arthritis. • Stable plaque psoriasis with a qualifying target lesion (at least 2 cm in diameter). • Concomitant methotrexate therapy, which had been stable for 2 months, could be continued at a stable dosage of ≤25 mg/week.	• Patients on disease-modifying antirheumatic drugs. • Patients on oral retinoids, topical vitamin A or D analog preparations, and anthralin.
IMPACT	• Patients 18 years and older with an established diagnosis of PsA of 6 months duration or longer. • Previous failure of treatment with ≥1 DMARDs. • At enrolment, patients were required to have active peripheral polyarticular arthritis, defined as the	• Patients testing positive for rheumatoid factor. • Patients with evidence of latent or active tuberculosis.

	presence of ≥ 5 swollen and tender joints in conjunction with at least 1 of the following criteria: erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour, C-reactive protein (CRP) level ≥ 115 mg/liter, and/or morning stiffness lasting 45 minutes or longer. • Negative results of serum tests for rheumatoid factor • Negative results for active or latent tuberculosis by purified protein derivative skin test and chest radiography.	
IMPACT 2	• Adult patients with active PsA diagnosed at least 6 months before the first infusion of study drug • Patients with active articular disease was defined as five or more swollen joints and five or more tender joints and either C reactive protein (CRP) levels of at least 15 mg/l and/or morning stiffness lasting 45 minutes or longer. • Patients with inadequate response to current or previous DMARDs or non-steroidal anti-inflammatory drugs (NSAIDs). • Active plaque psoriasis with at least one qualifying target lesion at least 2 cm in diameter. • Patients were required to have a negative test for rheumatoid factor in their serum.	• Patients with evidence of latent or active tuberculosis, chronic or clinically significant infection, malignancy, or congestive heart failure. • Patients who were on TNFa inhibitors previously.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table B5: Characteristics of participants in the RCTs across randomised groups (etanercept and infliximab)

	Etancercept				**Infliximab**			
	Mease 2000		**Mease 2004**		**IMPACT**		**IMPACT 2**	
	Etanercept (n=30)	Placebo (n=30)	Etanercept (n=101)	Placebo (n=104)	Infliximab (n=52)	Placebo (n=52)	Infliximab (n=100)	Placebo (n=100)
Age in years	46.0 (30.0-70.0)†	43.5 (24.0-63.0)†	47.6 (18-76)†	47.3 (21-73)†	[redacted]	[redacted]	[redacted]	[redacted]
Male (%)	53	60	57	45	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PsA (years)	9.0 (1-31)†	9.5 (1-30)†	9.0	9.2	[redacted]	[redacted]	[redacted]	[redacted]
Duration of psoriasis (years)	19.0 (4-53)†	17.5 (2-43)†	18.3	19.7	[redacted]	[redacted]	[redacted]	[redacted]
Mean number of prior DMARDS	1.5	2.0	1.6	1.7	-	-	-	-
Proportion of patients with numbers of previous DMARDs*	-	-	27% = 0 40% = 1 20% = 2	21%=0, 50% =1 19% =2	[redacted]	[redacted]	[redacted]	[redacted]

Concomitant therapies during study (%)								
Corticosteroids	20	40	19	15				
NSAIDs	67	77	88	83				
Methotrexate	47	47	42	41				
	-	-	-	-				
Hydroxycloroquine	-	-	-	-				
Sulfasalazine	-	-	-	-				
Leflunomide	-	-	-	-				
Other DMARD								
Type of PsA (%)								
DIP joints in hand and feet	-	-	51	50				
	-	-	1	2				
Arthritis mutilans	-	-	86	83				
Polyarticular arthritis	-	-	41	38				
	-	-	3	4				
Asymmetric peripheral arthritis	-	-	-	-				
Ankylosing arthritis								
Spondylitis with peripheral arthritis								
Tender Joint Count	22.5 (11, 32)*	19.0 (10, 39)*	20.4 (-)*	22.1 (-)*				

Swollen Joint Count	14.0 (8, 23)*	14.7 (7, 24)*	15.9 (-)*	15.3 (-)*	[redacted]	[redacted]	[redacted]	[redacted]
HAQ (0-3)	1.3 (0.9, 1.6)*	1.2 (0.8, 1.6)*	1.1 (-)*	1.1 (-)*	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of patients evaluable for PASI at baseline	19 (63%)♦	19 (63%)♦	Not available	Not available	[redacted]	[redacted]	[redacted]	[redacted]
PASI (0-72) at baseline among patients evaluable for PASI	10.1 (2.3-30.0)†	6.0 (1.5-17.7)†	Not available	Not available	[redacted]	[redacted]	[redacted]	[redacted]

†Median (Range); ‡Mean (SD); *Median (25th – 75th Percentile); ♦Patients with ≥3% psoriasis at baseline; **Patients with baseline PASI score of ≥ 2.5

Table B6: Characteristics of participants in the RCTs across randomised groups (golimumab and adalimumab)

	Golimumab			**Adalimumab**			
	GO REVEAL			**ADEPT**		**Genovese 2007**	
	[redacted]	[redacted]	[redacted]	Adalimumab (n=151)	Placebo (n=162)	Adalimumab (n=51)	Placebo (n=49)
Age in years‡	[redacted]	[redacted]	[redacted]	48.6 (12.5)	49.2 (11.1)	50.4 (11.1)	47.7 (11.3)
Male (%)	[redacted]	[redacted]	[redacted]	56	55	57	51
Duration of PsA (years)‡	[redacted]	[redacted]	[redacted]	9.8 (8.3)	9.2 (8.7)	7.5 (7.0)	7.2 (7.0)
Duration of psoriasis (years)‡	[redacted]	[redacted]	[redacted]	17.2 (12.0)	17.1 (12.6)	18.0 (13.2)	13.8 (10.7)
Number of prior DMARDS				1.5	1.5	1.7	2.1
Proportion of patients with numbers of previous DMARDs				-	-	-	

Concomitant therapies during study (%)	[redacted]	[redacted]	[redacted]	-	-	-	-
Corticosteroids	[redacted]	[redacted]	[redacted]	-	-	73	86
NSAIDs	[redacted]	[redacted]	[redacted]	51	50	47	47
Methotrexate	[redacted]	[redacted]	[redacted]	-	-	16	16
Hydroxycloroquine	[redacted]	[redacted]	[redacted]	-	-	8	14
Sulfasalazine	[redacted]	[redacted]	[redacted]	-	-	6	4
Leflunomide	[redacted]	[redacted]	[redacted]	-	-	2	6
Other DMARD			[redacted]				
Type of PsA (%)							
DIP joints in hand and feet	[redacted]	[redacted]	[redacted]	-	-	-	-
Arthritis mutilans	[redacted]	[redacted]	[redacted]	1	0	0	0
Polyarticular arthritis	[redacted]	[redacted]	[redacted]	64	70	82	84
Asymmetric peripheral arthritis	[redacted]	[redacted]	[redacted]	25	25	10	14
Ankylosing arthritis	[redacted]	[redacted]	[redacted]	1	0	2	2
Spondylitis with peripheral arthritis	[redacted]	[redacted]	[redacted]	-	-	-	-
Tender Joint Count‡	[redacted]	[redacted]	[redacted]	23.9 (17.3)	25.8 (18.0)	25.3 (18.3)	29.3 (18.1)
Swollen Joint Count‡	[redacted]	[redacted]	[redacted]	14.3 (12.2)	14.3 (11.1)	18.2 (10.9)	18.4 (12.1)
HAQ (0-3)‡	[redacted]	[redacted]	[redacted]	1.0 (0.6)	1.0 (0.7)	0.9 (0.5)	1.0 (0.7)

Number (%) of patients evaluable for PASI at baseline	[redacted]	[redacted]	[redacted]	70 (46%)♦	70 (43%)♦	-	-
PASI (0-72) at baseline among patients evaluable for PASI‡	[redacted]	[redacted]	[redacted]	7.4 (6.0)	8.3 (7.2)	-	-

‡Mean (SD); ♦Patients with ≥3% psoriasis at baseline;

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table B7: Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
GO REVEAL	• Proportion of subjects achieving an American College of Rheumatology (ACR) 20 response at Week 14 and Change from baseline in the PsA modified van der Heijde-Sharp (vdH-S) score at Week 24 (a radiographic indicator of disease progression).	Well established endpoint. Not widely used in clinical practice.	• ACR 20 response at Week 24 • Psoriasis Area and Severity Index (PASI) 75 improvement at Week 14 in a subset of subjects with ≥ 3% body surface area (BSA) psoriasis skin involvement at baseline; • Improvement from baseline in HAQ score at Week 24 • Physical component summary score of the SF-36 at Week 14 • Other endpoints include Psoriatic	PASI, HAQ, PsARC and SF-36 are widely used in clinical practice.

			Arthritis Response Criteria (PsARC), Disease Activity Score (DAS) 28, duration of morning stiffness, dactylitis and enthesitis assessments, target lesion assessments, Nail Psoriasis Severity Index (NAPSI), and Nail Physician Global Assessment (Nail PGA).	
ADEPT	• ACR 20 at week 12 and the change in modified TSS of structural damage on radiographs of the hands and feet at week 24.	Well established endpoint. Not widely used in clinical practice.	• ACR20 response rate at week 24, as well as ACR50 and ACR70 response rates at weeks 12 and 24. • Other secondary end points included response rates on the modified Psoriatic Arthritis Response Criteria (PsARC), the disability index of the Health Assessment Questionnaire (HAQ DI), and the Short Form 36 (SF-36) health survey, also at weeks 12 and 24. • Additional assessments included an evaluation of dactylitis (rated on a scale of 0–3 for each digit of the hand and toes) and enthesitis (defined as present or absent on the plantar fascia and insertion of the Achilles bilaterally), and scores on the fatigue scale of the Functional Assessment of Chronic Illness Therapy (FACIT-F).	HAQ, PsARC and SF-36 are widely used in clinical practice. Dactilytis, enthesitis and FACIT-F not widely used.
Genovese	• American College of Rheumatology 20% criteria for	Well established endpoint. Not	• Modified Psoriatic Arthritis Response Criteria (PsARC) and assessments of	HAQ, PsARC and SF-36 are

	improvement in rheumatoid arthritis (ACR 20) at week 12.	widely used in clinical practice.	disability, psoriatic lesions, and quality of life.	widely used in clinical practice.
Mease 2000	• The proportion of patients meeting the PsARC at 12 weeks.	Widely used in clinical practice and well established criterion.	• The proportion of patients meeting the American College of Rheumatology preliminary criteria for improvement (ACR20) at 12 weeks, which requires - ○ at least 20% reductions in tender and swollen joint counts and in at least three of the following: patient's assessment of pain, patient's global assessment, physician's global assessment, patient's assessment of disability, and acute phase reactant (C-reactive protein). ○ improvement of at least 50% in ACR50 and 70% in ACR70	Well established endpoint. Not widely used in clinical practice.
Mease 2004	• The proportion of patients meeting the ACR 20 at 24 weeks.	Well established endpoint. Not widely used in clinical practice.	• ACR50 and ACR70 responses • Psoriatic Arthritis Response Criteria (PsARC), • Dermatologist's static global assessment of psoriasis • Psoriasis Area and Severity Index (PASI 50 and PASI 75) • Quality of life, as measured by the Short Form 36 (SF-36) Health Survey and function, evaluated using the Health Assessment Questionnaire (HAQ)	PASI, HAQ, PsARC and SF-36 are widely used in clinical practice.

IMPACT	• American College of Rheumatology 20% criteria for improvement in rheumatoid arthritis (ACR 20) at week 16.	Well established endpoint. Not widely used in clinical practice.	• Psoriasis Area and Severity Index (PASI) score • ACR50 and ACR70 criteria • Disease Activity Score in 28 joints • Health Assessment Questionnaire • Ratings of enthesitis and dactylitis, and • Psoriatic Arthritis Response Criteria score.	PASI, HAQ, PsARC and SF-36 are widely used in clinical practice.
IMPACT 2	• American College of Rheumatology 20% criteria for improvement in rheumatoid arthritis (ACR 20) at week 14.	Well established endpoint. Not widely used in clinical practice.	• Psoriatic Arthritis Response Criteria (PsARC), • Duration of morning stiffness (minutes) during the previous week evaluated through week 24.	PsARC is widely used in clinical practice.

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table B8: Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
GO REVEAL	To assess the efficacy and safety of golimumab in patients with active psoriatic arthritis (PsA).	Treatment group differences were assessed with a 2-sided Cochran-Mantel-Haenszel test for discrete variables or 2-sided analysis of variance on van der Waerden normal scores for continuous parameters. All analyses included treatment and patients' use of MTX at baseline as factors and were performed at a 0.05 level of significance. **ITT analysis** The analyses were performed on an	The planned sample size (n = 396 [110 in the placebo group and 286 in the combined golimumab group]) provided > 98% power to detect a significant difference (α= 0.05) between the placebo and combined golimumab groups in the primary efficacy end point, assuming equal proportions of patients in each group received MTX at baseline and the following proportions of patients achieved an ACR20 response	**Placebo group** **Week 16**- Of 113 patients administered placebo, 52 completed study until week 16 while 51 patients crossed over to golimumab 50 mg group; 10 patients discontinued the study. **Week 24** – 51 out of 52 patients completed the study. **Golimumab 50 mg Group** **Week 16** – Of 146 patients on golimumab 50 mg , 111 completed the study upto week 16 while 28 crossed over golimumab 100 mg group; 7 patients discontinued the

		intention-to-treat basis	at week 14: 15% of patients receiving placebo, 25% of patients receiving placebo plus MTX, 42% of patients receiving both golimumab doses combined, and 42% of patients receiving both golimumab doses combined plus MTX.	study. **Week 24** – 109 patients completed the study; among the crossed over group, all the 28 patients completed the study. **Golimumab 100 mg Group** **Week 16** – Among 146 patients on golimumab 100 mg, 144 patients completed the study. **Week 24** – Among 144 patients who continued on golimumab 100 mg, 142 patients completed the study.
ADEPT	To evaluate the safety and efficacy of Adalimumab compared with placebo in the treatment of active psoriatic arthritis (PsA).	Proportions of patients' responding was compared using the Cochran-Mantel-Haenszel mean score test adjusted for the MTX use. Continuous data were analysed by ANOVA with factors of treatment, baseline, MTX use and extent of psoriasis. Nonresponder imputation was used, in which participants who discontinued or had missing data were counted as nonresponders. Patients who received rescue therapy were considered to be nonresponders at the time that rescue therapy was	Assuming that the effect size of anticipated change in the modified total Sharp score is 0.325, the sample size of 150 per treatment group gave 80% power to detect a significant difference between treatments on this primary outcome, with α=0.05 (two-sided).	Of 162 who received placebo, 149 completed the study. Of 151 who received adalimumab, 140 completed the study

		initiated. **ITT analysis** The analyses were performed on an intention-to-treat basis		
Genovese, 2007	To demonstrate the safety and efficacy of adalimumab for the treatment of active psoriatic arthritis (PsA) in patients with an inadequate response to disease modifying antirheumatic drugs (DMARD).	The proportions of patients' responding were compared using the Cochran-Mantel-Haenszel test, with baseline DMARD use as the stratification factor. ACR 20 at response rates at time points except for week 12 and ACR 50 and ACR 70 rates at all timepoints were analysed using Fisher's exact test, combining baseline DMARD use categories. Continuous data were analysed using ANOVA with factors of baseline DMARD use and treatment. Nonresponder imputation for missing data was used for analyses of ACR and PsARC responses, and last observation carried forward was used for all other efficacy measures. **ITT analysis -** The analyses were performed on an intention-to-treat basis	Assuming that a response rate of 25% on placebo and 60% on adalimumab, the sample size of 50 patients per groups gave 90% power to detect a significant difference between treatments on the primary outcome, with α =0.05 (two-sided).	Of 49 patients who received placebo, 46 patients completed the schedule of events through week 12. Of 51 patients who received adalimumab, 50 patients completed the schedule of events through week 12. Of 97 patients who entered the open-label extension week 12 to 24, 92 patients completed the open-label extension.

Mease, 2000	To assess the efficacy and safety of etanercept compared to placebo in patients with psoriatic arthritis and psoriasis.	Proportions of patients' responding were compared using the Mantel-Haenszel χ^2 test adjusted for the MTX use. Continuous variables were ranked and analysed by a general linear model with factors of treatment, MTX use and their interaction. The Breslow-Day test was used to test for heterogeneity of relative response between MTX use strata. The last observation carried forward (LOCF) approach was used for imputing missing data **ITT analysis -** All randomised patients included in the analysis	Assuming that a response rate of 30% on placebo and 75% on etanercept, the sample size of 30 patients per group gives 80% power to detect a significant difference between treatments in the primary outcome, with α=0.05 (two-sided).	Of 30 patients who received placebo, 26 completed the study. Of 30 patients who received etanercept, all 30 completed the study
Mease, 2004	To further evaluate the safety, efficacy, and effect on radiographic progression of etanercept in patients with PsA.	Binary response rates were compared using the Cochran-Mantel-Haenszel test or Fisher's exact test. Continuous variables were analysed by Wilcoxon's rank sum test, using LOCF for missing data or early termination. **ITT analysis** All randomised patients who received at least one dose of blinded	Assuming that an ACR 20 rate of 60% on etanercept and 30% on placebo, a sample size of 100 patients per group gives a power of 90% power to detect a significant difference between treatments in the primary outcome, with α =0.05 (two-sided).	Of 104 patients who received placebo, 72 completed 24 weeks of therapy. Of 101 patients who received etanercept, 93 completed 24 weeks of therapy.

		study drug were included in the analysis. Patients receiving MTX were randomised separately		
IMPACT	To investigate the efficacy and tolerability of infliximab therapy for the articular and dermatologic manifestations of active psoriatic arthritis (PsA).	Categorical outcomes (including ACR 20) were compared using the Chi-square test. The Mantel-haenszel test was conducted to estimate the odds ratios of the two treatment groups. Continuous outcomes were analysed using one-way ANOVA. **ITT analysis** The analyses were performed on an intention-to-treat basis	Assuming that an ACR 20 rate of 50% on infliximab and 20% on placebo, a sample size of 45 patients per group gave 80% power to detect a significant difference between treatments on the primary outcome, with α =0.05 (two-sided).	**Placebo group** *At week 0*- Of 52 patients assigned to placebo, 50 patients completed stage I of study until week 16. *At week 16* - Of 50 patients who crossed over to infliximab 5 mg/kg, 45 patients completed study until week 50. **Infliximab group** *Week 0* – Of 52 patients assigned to infliximab, 49 patients completed stage I of study until week 16. *Week 16* – Of 49 patients who continued with infliximab, 42 patients completed the study until week 50.
IMPACT 2	To evaluate further in a phase III, double blind trial the efficacy of infliximab in	Cochran-Mantel-Haenszel Chi-square test stratified by baseline MTX use was used to analyse categorical outcomes. A two-sided F test using ANOVA with baseline MTX as a factor was used to analyse continuous data. The LOCF	Assuming that an ACR 20 rate of 42% on infliximab and 20% on placebo, a sample size of 100 patients per group gives 90% power to detect a significant difference between treatments on the primary	**Placebo group** Of 100 patients who were assigned placebo, 47 entered early escape at week 16. Among the remaining 53 patients, 47 completed week 24. Furthermore, 45 out of 47 patients who entered early escape at week

	patients with active psoriatic arthritis (PsA), as observed in the smaller IMPACT trial.	approach was used for imputing missing data **ITT analysis** The analyses were performed on an intention-to-treat basis	outcome, with α =0.05 (two-sided).	16 completed week 24. **Infliximab group** Of 100 patients who were assigned infliximab, 9 entered early escape at week 16. Among the remaining 91 patients, 85 patients completed week 24. In the early escape group, 8 out of 9 patients completed week 24.

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

In the golimumab clinical trial (GO-REVEAL), the subgroup analyses were conducted based on demographic characteristics such as baseline disease, clinical characteristics, baseline PsA subtypes, baseline medications and prior therapies for PsA. These analyses were pre-planned. Separate post-hoc analyses were conducted comparing individual golimumab doses with placebo on some of the baseline demographics and disease characteristics.

Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

The patient flow for each of the included RCTs has been displayed below.

Figure B2: Patient flow in GO-REVEAL (golimumab)

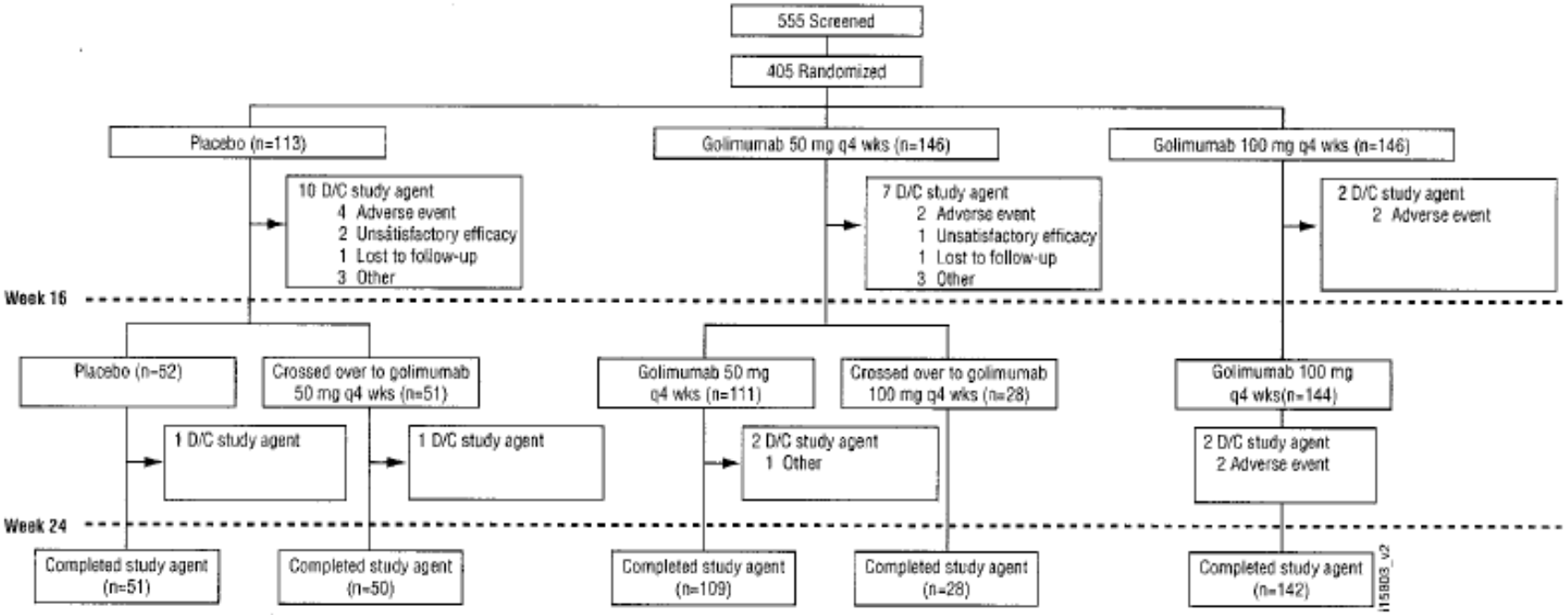
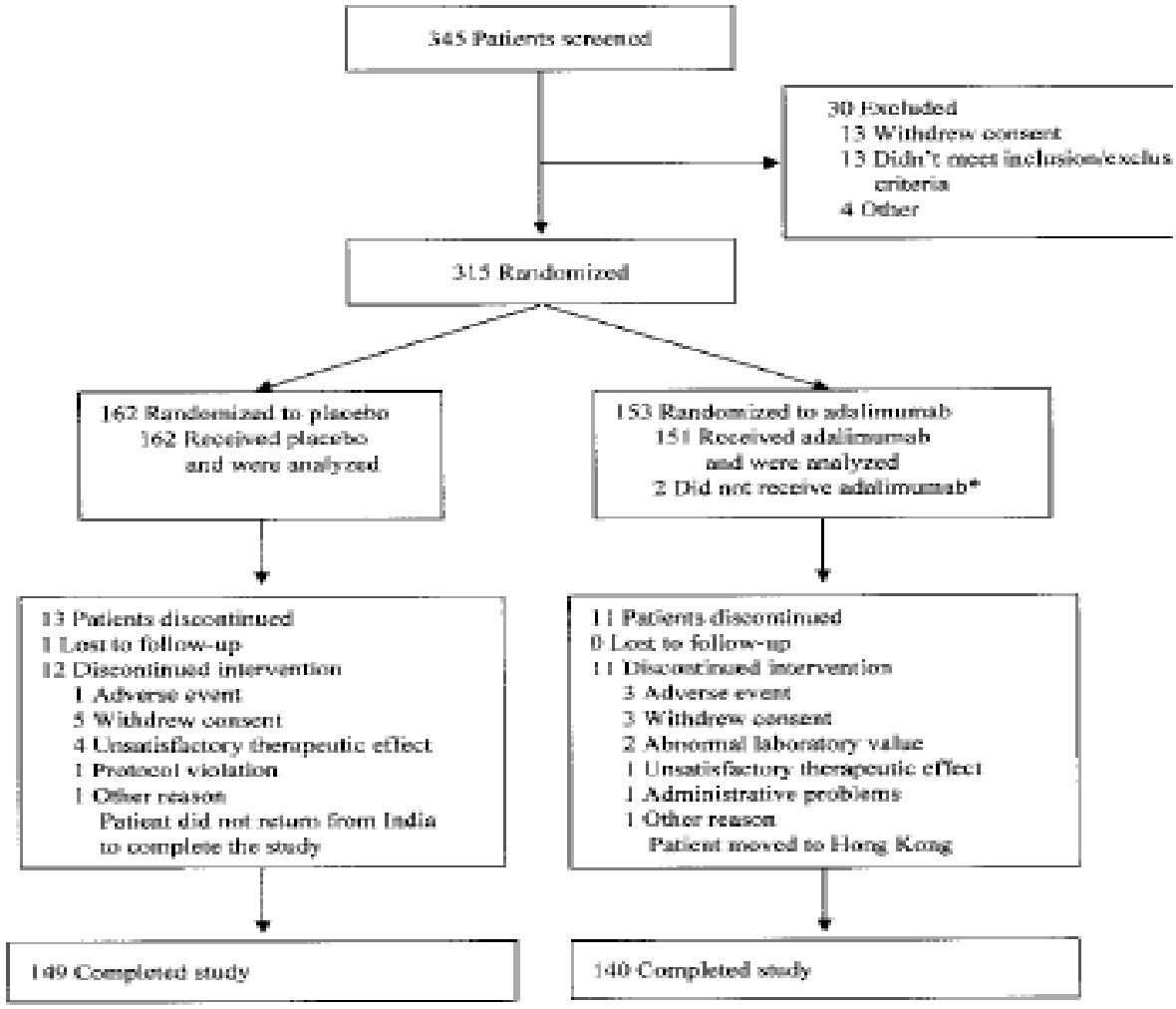


Figure B3: Patient flow in ADEPT (adalimumab)



* 1 patient refused prophylaxis for TB, 1 patient was admitted to hospital prior to first dose of study drug

Figure B4: Patient flow in Genovese 2007 (adalimumab)

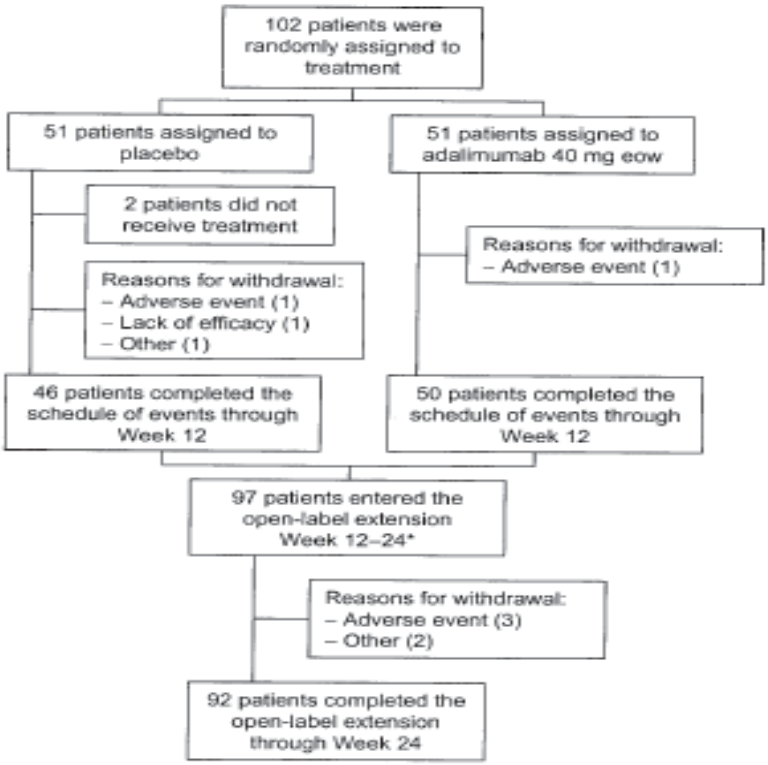
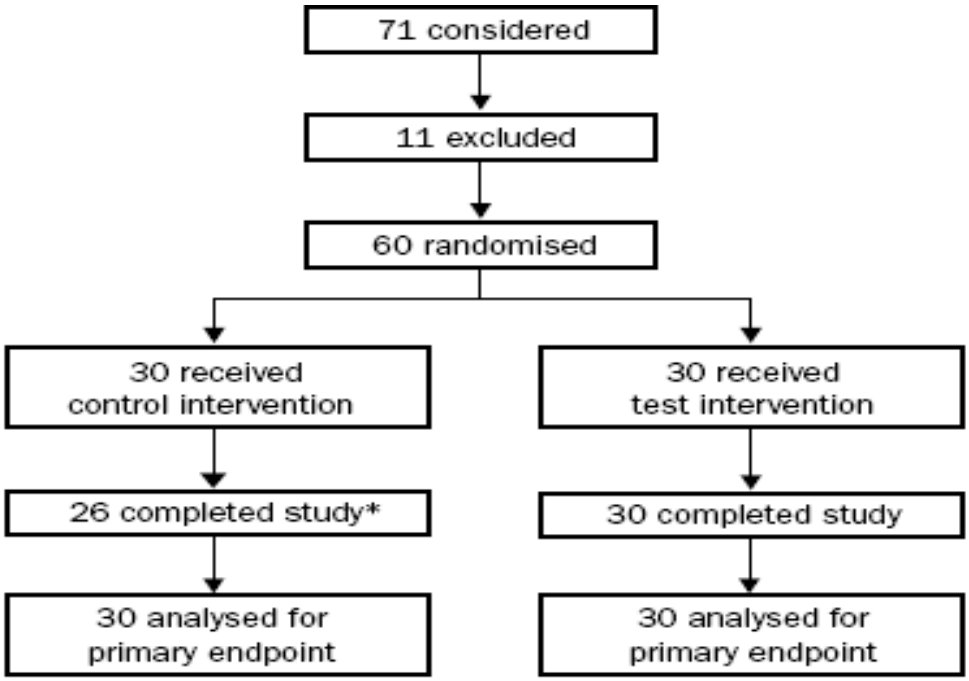
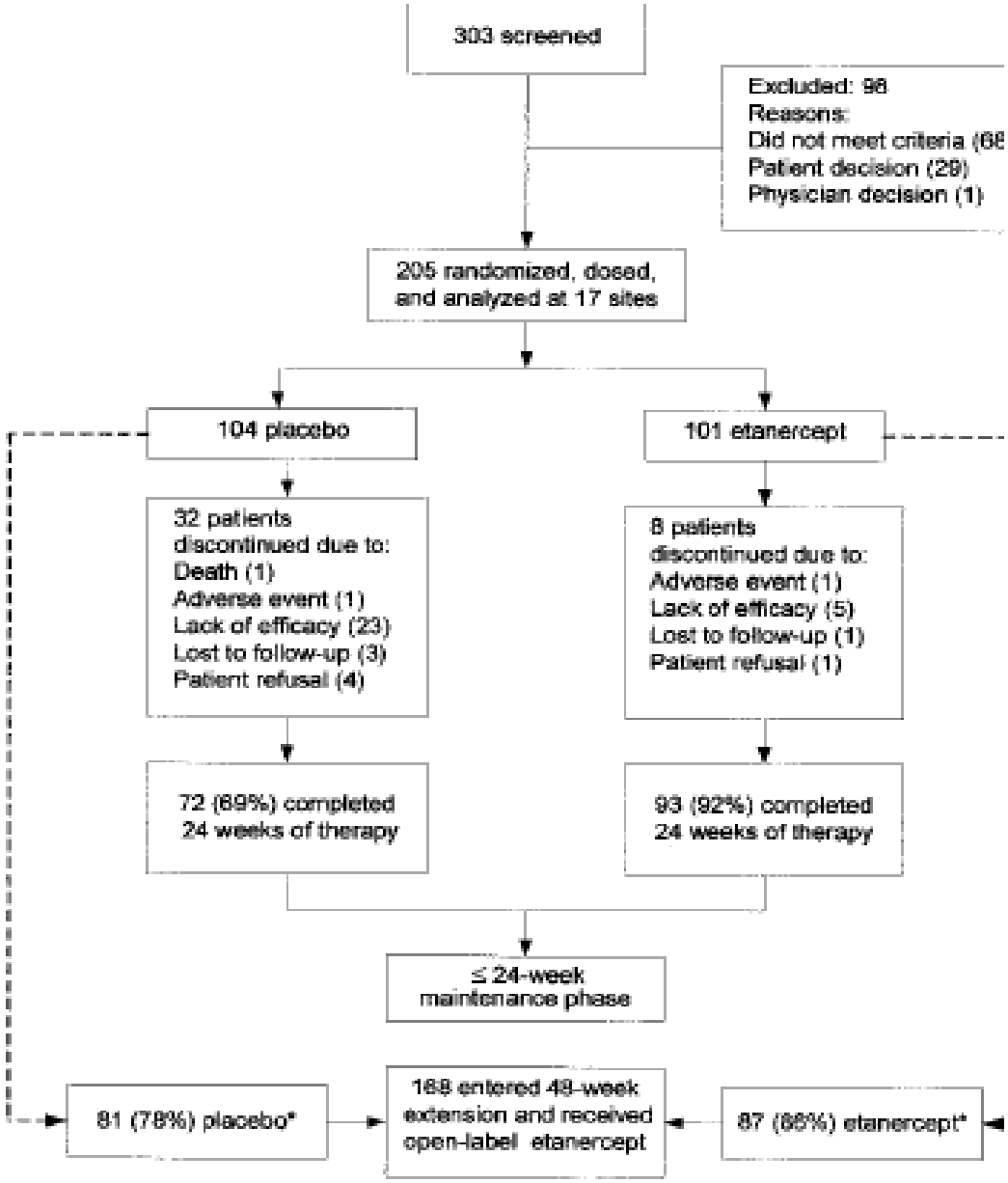


Figure B5: Patient flow in Mease 2000 (etanercept)



*LOCF for efficacy analysis

Figure B6: Patient flow in Mease 2004 (etanercept)



* Patients who completed 12 weeks of study drug in the 24-week placebo-controlle phase were eligible to enter the open-label extension.

Figure B7: Patient flow in IMPACT (infliximab)

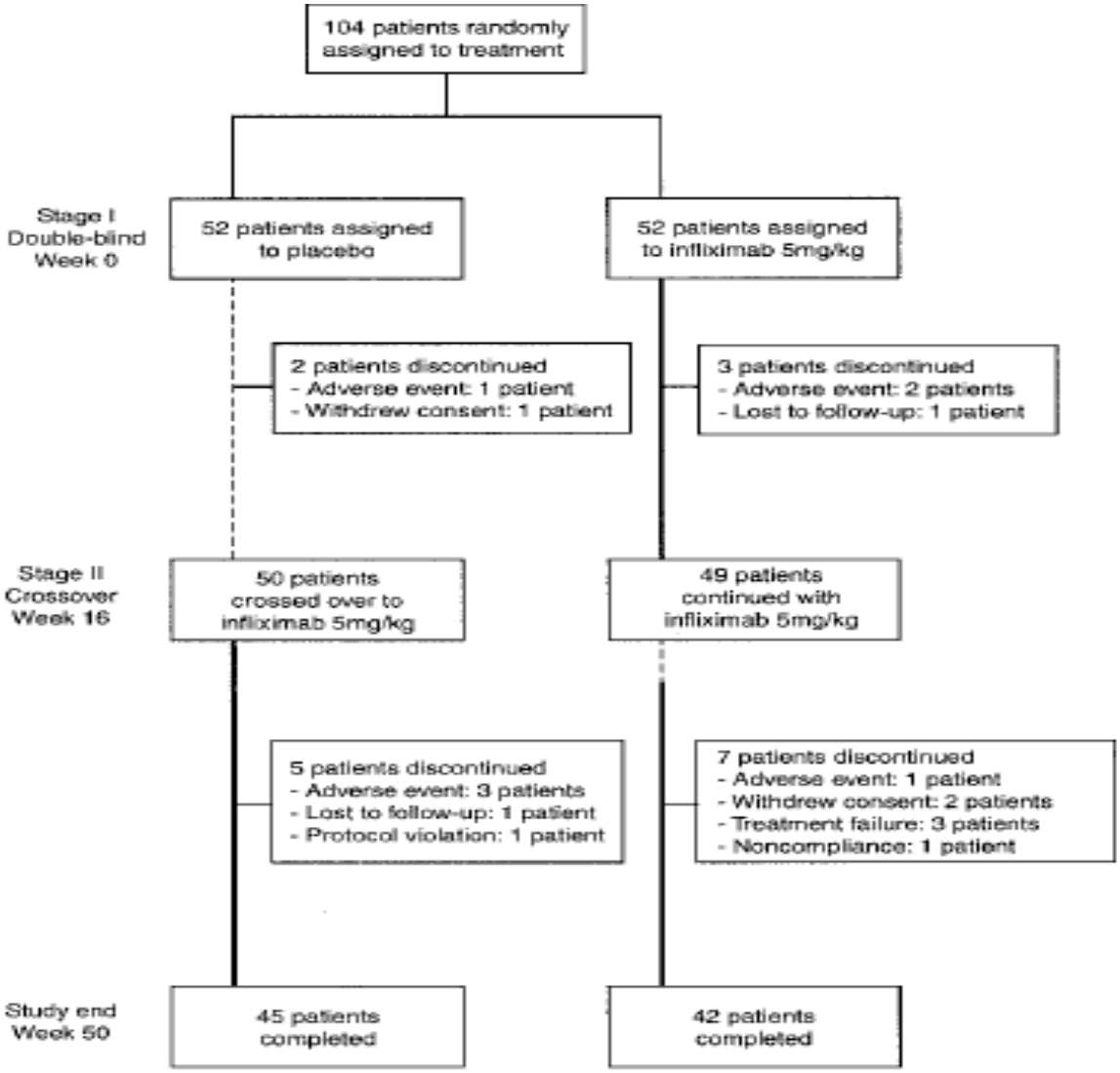
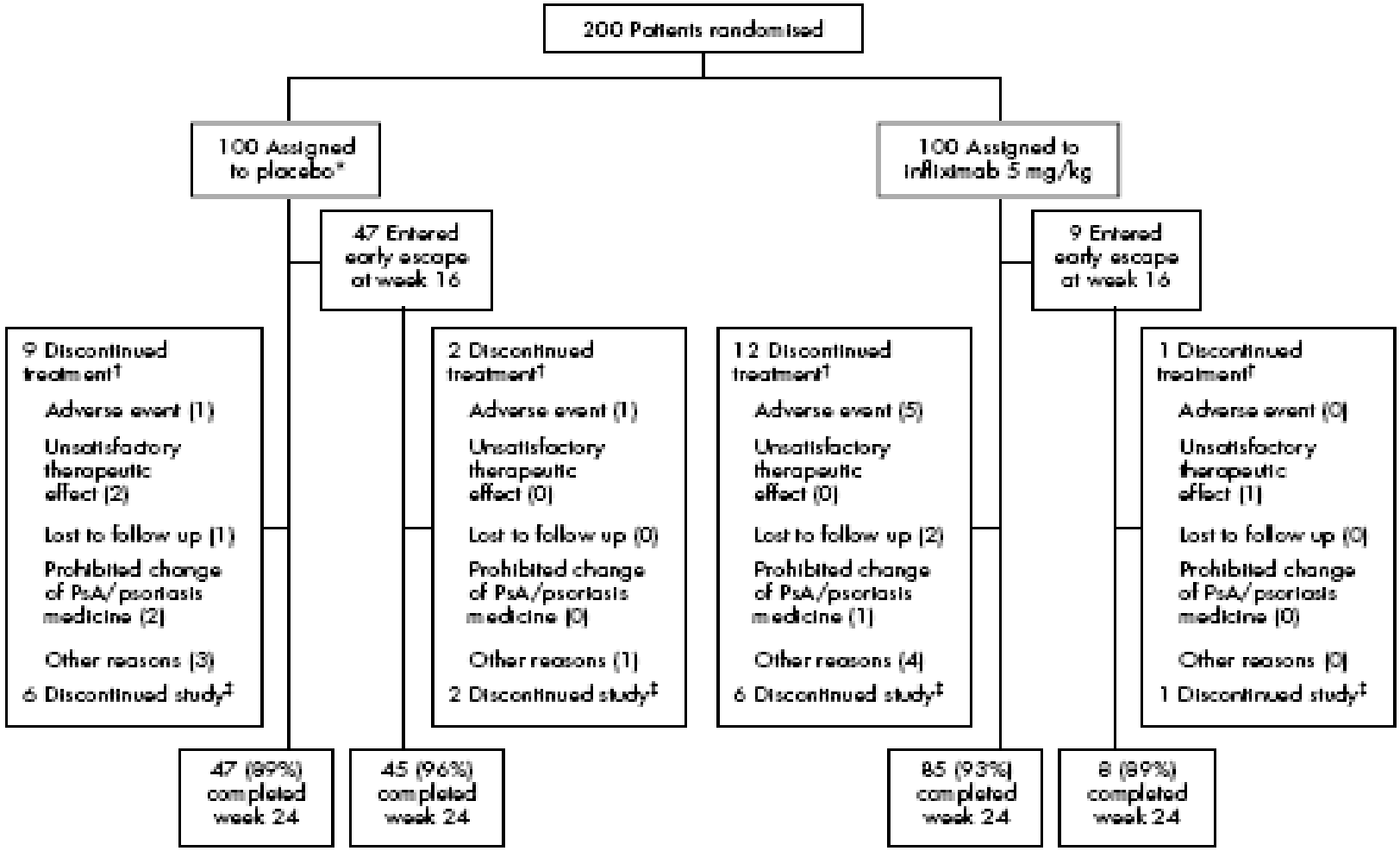


Figure B8: Patient flow in IMPACT 2 (infliximab)



5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

The quality assessment is available in Appendix 3, section 9.3.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table B9: Quality assessment results for RCTs

Trial no. (acronym)	GO-REVEAL	ADEPT	GENOVESE 2007	Mease 2000	Mease 2004	IMPACT	IMPACT 2
Was randomisation carried out appropriately?	YES	YES	YES	YES	YES	YES	YES
Was the concealment of treatment allocation adequate?	YES	NOT CLEAR	YES	YES	YES	YES	YES
Were the groups similar at the outset of the study in terms of prognostic factors?	YES	YES	YES	YES	YES	YES	YES
Were the care providers, participants and outcome assessors blind to treatment allocation?	YES	YES	YES	YES	YES	YES	YES
Were there any unexpected imbalances in drop-outs between groups?	YES	NO	NO	NO	NO	NO	NO
Is there any evidence to suggest that the authors measured more outcomes than they reported?	YES	NO	NO	NO	NO	NO	NO
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	YES	YES	YES	YES	YES	YES	YES
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination							

5.5 Results of the relevant RCTs

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

Please refer to 5.5.3

5.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

Not applicable

5.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Table B10: Study results for golimumab RCT

Trial	Duration	Outcomes	Golimumab 50 mg	Placebo	RR or mean difference (95% CI)
GO REVEAL	14 weeks	PsARC	103/138 (74.6%)	22/102 (21.6%)	3.5
		ACR 20			

		All pts	74/142 (52.1%)	9/105 (8.6%)	6.0
		+MTX	38/71 (53.5%)	8/55 (14.5%)	3.7
		-MTX	*36/72 (50%)*	2/52 (3.8%)	13.2
		ACR 50			
		All pts	44/142 (31%)	1/105 (1%)	31.0
		+MTX	*19/70 (27.1%)*	*1/53 (1.9%)*	14.3
		-MTX	*25/72 (34.7%)*	*0/52 (0%)*	-
		ACR 70			
		All pts	15/142 (10.6%)	1/105 (1%)	10.6
		+MTX	8/70 (11.4%)	*1/53 (1.9%)*	6
		-MTX	7/72 (9.7%)	*0/52 (0%)*	-
		HAQ change from baseline (mean (SD))	0.3	0.4	0.75
		PASI 50*			
		All pts	63/106 (59.4%)	7/73 (9.6%)	6.2
		+MTX	29/49 (59.2%)	*4/33 (12.1%)*	4.9
		-MTX	34/57 (59.6%)	*3/40 (7.5%)*	7.9
		PASI 75*			
		All pts	44/106 (41.5%)	1/73 (1.4%)	29.6
		+MTX	20/49 (40.8%)	1/33 (3%)	13.6
		-MTX	24/57 (42.1%)	0/40(0%)	-
		PASI 90*			
		All pts	22/106 (20.8%)	0 /73(0%)	-
		+MTX	11/49 (22.4%)	0/33 (0%)	-
		-MTX	11/57 (19.3%)	0/40 (0%)	-
	24 weeks	PsARC	100/137 (73%)	32/104 (30.8%)	2.4
		ACR 20			
		All pts	74/140 (52.9%)	14/105 (13.3%)	3.9
		+MTX	39/69 (56.5%)	*9/53 (17%)*	3.3
		-MTX	*35/71 (49.3%)*	*5/52 (9.6%)*	5.1
		ACR 50			
		All pts	45/140 (32.1%)	4/105 (3.8%)	8.4

		+MTX	27/69 (39.1%)	*3/53 (5.7%)*	6.9
		-MTX	*18/71 (25.4%)*	*52/145 (35.9%)*	0.7
		ACR 70			
		All pts	26/140 (18.6%)	1/105 (1%)	18.6
		+MTX	14/69 (20.3%)	*1/53 (9%)*	2.3
		-MTX	*12/71 (16.91%)*	*0/52 (0%)*	-
		HAQ change from baseline (mean (SD))	0.3	-0.03	-10
		PASI 50*			
		All pts	77/102 (75.5%)	6/73 (8.2%)	9.2
		+MTX	35/48 (72.9%)	3/33 (9.1%)	8.0
		-MTX	42/54 (77.8%)	3/40 (7.5%)	10.3
		PASI 75*			
		All pts	57/102 (55.9%)	1/73 (1.4%)	39.9
		+MTX	27/48 (56.3%)	0/33 (0%)	-
		-MTX	30/54 (55.6%)	1/40 (2.5%)	22.2
		PASI 90*			
		All pts	33/102 (32.4%)	0/ 73 (0%)	-
		+MTX	27/48 (56.3%)	0/33 (0%)	-
		-MTX	16/54 (29.6%)	0/40 (0%)	-
		vdH-S score (change from baseline)	0.27 ± 1.26	- 0.16 ± 1.31	-

Table B11: Study results for adalimumab RCTs

Trial	Duration	Outcomes	Adalimumab	Placebo	RR or mean difference (95% CI)
ADEPT	12 weeks	PsARC	94/151 (62%)	42/162 (26%)	2.40 (1.80, 3.20) p<0.05
		ACR 20			
		All pts	88/151 (58%)	23/162 (14%)	4.10 (2.75, 6.14) p<0.05

		+*MTX* -*MTX*	43/77 (55%) 45/74 (61%)		
		ACR 50 All pts +*MTX* -*MTX*	 54/151 (36%) 27/77 (36%) 27/74 (36%)	 6/162 (4%)	 9.66 (4.28, 21.79) p<0.05
		ACR 70 All pts +*MTX* -*MTX*	 30/151 (20%) 13/77 (17%) 17/74 (23%)	 1/162 (1%)	 32.19 (4.44, 233.11) p<0.05
		HAQ change from baseline (mean (SD))	-0.4(0.5)	-0.1(0.5)	-0.3 (-0.41, -0.19), p<0.001
		PASI 50* All pts +*MTX* -*MTX*	 50/69 (72%) 17/29 (76%) 28/40 (70%)	 10/69 (14%)	 5.00 (2.77, 9.03) p<0.05
		PASI 75* All pts +*MTX* -*MTX*	 34/69 (49%) 17/29 (59%) 17/40 (43%)	 3/69 (4%)	 11.33 (3.65, 35.17) p<0.05
		PASI 90* All pts +*MTX* -*MTX*	 21/69 (30%) 11/29 (38%) 10/40 (25%)	 0/69 (0%)	 43.00 (2.66, 696.04) p<0.05
	24 weeks	PsARC	91/151 (60%)	37/162 (23%)	2.64 (1.93, 3.60) p<0.05
		ACR 20			

		All pts +*MTX* -*MTX*	86/151 (57%) 42/77 (55%) 44/74 (59%)	24/162 (15%)	3.84 (2.59, 5.70) p<0.05
		ACR 50 All pts +*MTX* -*MTX*	 59/151 (39%) 28/77 (36%) 31/74 (42%)	 10/162 (6%)	 6.33 (3.34, 12.64) p<0.05
		ACR 70 All pts +*MTX* -*MTX*	 35/151 (23%) 17/77 (22%) 17/74 (23%)	 1/162 (1%)	 37.55 (5.21, 270.70) p<0.05
		HAQ change from baseline (mean (SD))	-0.4(0.5)	-0.1 (0.4)	-0.3 (-0.40, -0.20), p<0.001
		PASI 50* All pts +*MTX* -*MTX*	 52/69 (75%) 25/29 (86%) 27/40 (68%)	 8/69 (12%)	 6.50 (3.34, 12.64) p<0.05
		PASI 75* All pts +*MTX* -*MTX*	 41/69 (59%) 21/29 (72%) 20/40 (50%)	 1/69 (1%)	 41.00 (5.80, 289.75) p<0.05
		PASI 90* All pts +*MTX* -*MTX*	 29/69 (42%) 15/29 (52%) 14/40 (35%)	 0/69 (0%)	 59.00 (3.68, 946.75) p<0.05

		TSS mean change from baseline	-0.2 (n=144)	0.1 (n=152)	P<0.001
Genovese 2007	12 weeks	PsARC	26/51 (51%)	14/49 (24%)	1.78 (1.06, 3.00) p<0.05
		ACR 20	20/51 (39%)	8/49 (16%)	2.40 (1.17, 4.94) p<0.05
		ACR 50	13/51 (25%)	1/49 (2%)	12.49 (1.70, 91.90) p<0.05
		ACR 70	7/51 (14%)	0/49 (0%)	14.42 (0.85, 5.26) p=n.s
		HAQ change from baseline (mean (SD))	-0.3 (0.5)	-0.1 (0.3)	-0.2 (-0.36, -0.04), p=0.015
	24 weeks (open-label extension)	PsARC	38/51 (75%)	32/46 (70%)	-
		ACR 20	33/51 (65%)	26/46 (57%)	-
		ACR 50	22/51 (43%)	17/46 (37%)	-
		ACR 70	13/51 (27%)	10/46 (22%)	-
		HAQ change from baseline (mean (SD))	-0.3 (0.5)	-0.4 (0.4)	-

*reported for patients with at least 3% BSA psoriasis

Table B12: Study results for etanercept RCTs

Trial	Duration	*Outcomes*	Etanercept	Placebo	RR or mean difference (95% CI)
Mease 2000	12 weeks	*PsARC**	26/30 (87%)	7/30 (23%)	3.71 (1.91, 7.21)
		ACR 20	22/30 (73.0%)	4/30 (13%)	5.50 (2.15, 14.04)
		ACR 50	15/30 (50.0%)	1/30 (3%)	15.00 (2.11, 106.49)
		ACR 70	4/30 (13%)	0/30 (0%)	9.00 (0.51, 160.17)

	HAQ % change from baseline (mean (SD))	(n=29) 64.2 (38.7)	(n=30) 9.9 (42.9);	Not available
	PASI 50	8/19 (42%)	4/19 (21%)	2.00 (0.72, 5.53) p=0.295
	PASI 75	5/19 (26%)	0/19 (0%)	11.00 (0.65, 186.02) p=0.0154
Mease 2004 12 weeks	*PsARC*			
	All pts	73/101 (72%)	32/104 (31%)	2.35 (1.72, 3.21) p<0.001
	+MTX	32/42 (76%)	14/43 (33%)	2.34 (1.47, 3.72)
	-MTX	41/59 (69%)	18/61 (30%)	2.35 (1.54, 3.60)
	*ACR 20**			
	All pts	60/101 (59%)	16/104 (15%)	3.86 (2.39, 6.23) p<0.001
	+MTX	26/42 (62%)	8/43 (19%)	3.33 (1.70, 6.49)
	-MTX	34/59 (58%)	8/61 (13%)	4.39 (2.22, 8.7)
	ACR 50			
	All pts	38/101 (38%)	4/104 (4%)	9.78 (3.62, 26.41) p<0.001
	+MTX	17/42 (40%)	1/43 (2%)	17.40 (2.42, 124.99)
	-MTX	21/59 (36%)	3/61 (5%)	7.24 (2.28, 22.98)
	ACR 70			
	All pts	11/101 (11%)	0/104 (0%)	23.68 (1.41, 396,53) p<0.001
	+MTX	4/42 (10%)	0/43 (0%)	9.21 (0.51, 165.93)
	-MTX	7/59 (12%)	0/61 (0%)	15.5 (0.91, 265.46)
	HAQ % change from baseline (mean (SD))	(n=96) 53.5 (43.4)	(n=99) 6.3 (42.7)	Not available
24 weeks	*PsARC*			
	All pts	71/101 (70%)	24/104 (23%)	3.05 (2.10, 4.42) p<0.001
	+MTX	31/42 (74%)	11/43 (26%)	2.89 (1.68, 4.95)
	-MTX	40/59 (68%)	13/61 (21%)	3.18 (1.90, 5.32)
	ACR 20			

	All pts	50/101 (50%)	14/104 (13%)	3.68 (2.17, 6.22) p<0.001
	+MTX	23/42 (55%)	8/43 (19%)	2.94 (1.49, 5.83)
	-MTX	27/59 (46%)	6/61 (10%)	4.73 (2.10, 10.63)
	ACR 50			
	All pts	37/101 (37%)	4/104 (4%)	9.52 (3.52, 25.75) p<0.001
	+MTX	16/42 (38%)	3/43 (7%)	5.46 (1.72, 17.37)
	-MTX	21/59 (36%)	1/61 (2%)	21.71 (3.02, 156.30)
	ACR 70			
	All pts	9/101 (9%)	1/104 (1%)	9.27 (1.20, 71.83) p=0.009
	+MTX	2/42 (5%)	0/43 (0%)	5.12 (0.25, 103.50)
	-MTX	7/59 (12%)	0/61 (0%)	15.50 (0.91, 265.46)
	HAQ % change from baseline (mean (SD))	(n=96) 53.6 (55.1)	(n=99) 6.4 (49.6)	47.20 (32.47, 61.93) p<0.001
	PASI 50	31/66 (47%)	11/62 (18%);	2.65 (1.46, 4.80) p<0.001
	PASI 75	15/66 (23%)	2/62 (3%)	7.05 (1.68, 29.56) p=0.001
	PASI 90	4/66 (6%)	2/62 (3%)	1.88 (0.36, 9.90) p=0.681
	TSS Mean (SD) annualised rate of progression			
	All pts	(n=101) –0.03 (0.73)	(n=104) 0.53 (1.39)	-0.56 (-0.86, -0.26) p=0.0006
	+MTX	(n=42) 0.06 (0.76)	(n=43) 0.48 (1.00)	-0.42 (-0.80, -0.04) p=0.12345
	-MTX	(n=59) -0.09 (0.71)	(n=61) 0.57 (1.62)	-0.66 (-1.11, -0.21) p=0.0014

Note* Primary outcome variable in the respective trials

Table B13: Study results for infliximab RCTs

Trial	Duration	Outcomes	Infliximab	Placebo	RR or mean difference (95% CI)

IMPACT	14 weeks	PsARC	40/52 (76.9%)	7/52 (13.5%)	5.71 (2.82, 11.57)
		ACR 20 All pts *+MTX* *-MTX*	 35/52 (67.3) NR NR	 6/52 (11.5%) NR NR	 5.83 (2.68, 12.68) - -
		ACR 50	19/52 (36.5%)	1/52 (1.9%)	19.00 (2.64, 136.76)
		ACR 70	11/52 (21.2%)	0/52 (0%)	23.00 (1.39, 380.39)
	16 weeks	PsARC	39/52 (75.0%)	11/52 (21.2%)	3.55 (2.05, 6.13) p<0.01.
		ACR 20			
		All pts *+MTX* *-MTX*	34/52 (65.4%) 15/24 (62.5%) 19/28 (67.9%)	5/52 (9.6%) 4/34 (11.8%) 1/18 (5.6%)	6.80 (2.89, 16.01) p<0.01. 5.31 (2.01, 14.03) p<0.01. 12.21 (1.79, 83.46) p<0.01
		ACR 50	24/52 (46.2%)	0/52 (0%)	49.00 (3.06, 785.06) (p<0.01
		ACR 70	15/52 (28.8%)	0/52 (0%)	31.00 (1.90, 504.86)p<0.01
		HAQ mean (SD) % change from baseline	(n=48) –49.8 (56.8)	(n=47) 1.6 (56.9)	–51.4 (–74.5, -28.3); p<0.01.
		PASI 50*	22/22 (100%)	0/16 (0%)	33.26 (2.17, 510.71)
		PASI 75*	15/22 (68.2%)	0/16 (0%)	22.91 (1.47, 356.81)
		PASI 90*	8/22 (36.4%)	0/16 (0%)	12.57 (0.78, 203.03)
		PASI mean (SD) change from baseline**	(n=42) -4.1 (3.9)	(n= 38) 0.9 (3.7)	–5 (–6.8, -3.3); p<0.01
IMPACT 2	14 weeks	PsARC	77/100 (77%)	27/100 (27%)	2.85 (2.03, 4.01)
		ACR 20			

		All pts +*MTX* -*MTX*	58/100 (58%) NR NR	11/100 (16%) NR NR	5.27 (2.95, 9.44) - -
		ACR 50	36/100 (36%)	3/100 (3%)	12.00 (3.82, 37.70)
		ACR 70	15/100 (15%)	1/100 (1%)	15.00 (2.02, 111.41)
		HAQ mean (SD) % change from baseline	(n=100) -48.6 (43.3)	(n=100) 18.4 (90.5)	-67.00 (-86.66, -47.33)
		PASI mean (SD) % change from baseline	NR	NR	-
	24 weeks	PsARC	70/100 (70%)	32/100 (32%)	2.19 (1.60, 3.00)
		ACR 20 All pts +*MTX* -*MTX*	 54/100 (54%) NR NR	 16/100 (16%) NR NR	 3.38 (2.08, 5.48) - -
		ACR 50	41/100 (41%)	4/100 (4%)	10.25 (3.81, 27.55)
		ACR 70	27/100 (27%)	2/100 (2%)	13.5 (3.30, 55.26)
		HAQ mean (SD) % change from baseline	(n=100) -46.0 (42.5)	(n=100) 19.4 (102.8)	-65.40 (-87.20, -43.60)
		PASI mean (SD) % change from baseline	NR	NR	-

*PASI 50/75/90 outcomes are for subgroup of patients with PASI scores ≥2.5 at baseline

**two sites did not perform baseline PASI measurements

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Meta-analysis was conducted and the details have been explaned in section 5.7.

5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Not applicable

5.7 *Indirect and mixed treatment comparisons*

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

The search strategy used was identical to that used in the clinical section. For details, please refer to section 5.1 and 5.2.

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Please refer to quality assessment data presented in earlier sections (section 5.1 to 5.5)

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Table B14: Summary of the trials used to conduct the indirect comparison

No. trials	References of trials	Placebo	Golimumab	Adalimumab	Etanercept	Infliximab
1	GOREVEAL	✓	✓			
2	ADEPT	✓		✓		
3	Genovese	✓		✓		
4	Mease 2000	✓			✓	
5.	Mease 2004	✓			✓	

6	IMPACT	✓				✓
7	IMPACT 2	✓				✓
Adapted from Caldwell et al. (2005) Simultaneous comparison of multiple treatments combining direct and indirect evidence. BMJ 331: 897–900						

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

Table B15: Summary of the data used in indirect comparison

Study	Treatment	Data
Woolacott et al 2006 (includes data on PsARC and 12-wk HAQ for IMPACT 1, Mease 2000, Mease 2004)	Infliximab, Etanercept	Not using PsARC from meta-analysis
		HAQ: Infliximab resp. -0.6667 (SE 0.0905) HAQ: Infliximab nonresp. -0.2169 (SE 0.0901) HAQ: Etanercept resp. -0.7214 (SE 0.0551) HAQ: Etanercept nonresp. -0.2414 (SE 0.0719) Placebo: mean -0.2827 (SE 0.0553) * We address differences in the handling of natural progression and placebo non-responders
		PASI: None
IMPACT, Antoni 2005a	Infliximab	Using CIC data instead of study publication.
IMPACT data request C-I-C data	Infliximab	[redacted]
		HAQ: Woolacott et al 2006 report
		[redacted]

Study	Treatment	Data
		[redacted]
IMPACT 2, Antoni 2005	Infliximab	Using CIC data instead of study publication
IMPACT 2 data request C-I-C data	Infliximab	[redacted]
		[redacted]
		[redacted]
Mease 2000	Etanercept	PsARC: eta 26/30 vs plac 7/30
		HAQ: Woolacott et al 2006 report
		PASI: Placebo n=19, median 6.0, range (1.5-17.7). Etanercept n=19, median 10.1, range (2.3-30.0) Improvement: 46.2% (N=19) in etanercept, 8.7% (N=19) in placebo
Mease 2004	Etanercept	PsARC: eta 73/101 vs plac 32/104
		HAQ: Woolacott et al 2006 report
		PASI baseline: Not reported. PASI 24wk: Placebo +8.1% (SE 9.0 N=62), Etanercept -42.0% (SE

Study	Treatment	Data
		6.0 N=66)
GO-REVEAL C-I-C data	Golimumab 50mg	[redacted]
		[redacted]
		[redacted]
Genovese 2007	Adalimumab	PsARC wk 12: Placebo 12/49 Adalimumab 26/51
		HAQ wk 12: Placebo -0.1 (SD 0.3 N=49)

Study	Treatment	Data
		Ada -0.3 (SD 0.5 N=51)
		PASI: No data
ADEPT, Mease 2005	Adalimumab	PsARC 12wk: Ada 62% of 151, Placebo 26% of 162.
		HAQ 24wk: Plac -0.1 SD0.4 N=162, Ada -0.4 SD0.5 N=151
		PASI: Figure 2B Plac N=69 PASI50=12% PASI75=1% PASI90=0 Ada N=69 PASI50=75% PASI75=59% PASI90=42%

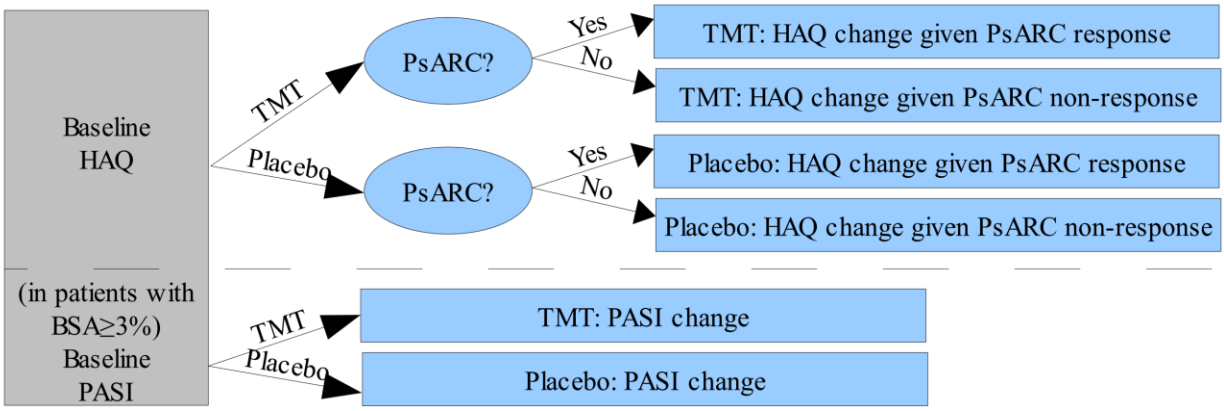
5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

The patient outcomes of interest were PsARC response to treatment, the effect on HAQ score and, in the subgroup of patients with BSA≥3% at baseline, the effect on PASI score.

Clinical effectiveness model structure

The change in HAQ from baseline was modelled conditional on PsARC response. After investigating the relationship between PsARC response and change in PASI in the subgroup of patients with BSA≥3% at baseline, it was decided to model change in PASI without conditioning on PsARC. This structure is illustrated below.

Figure B9: Clinical effectiveness model structure



Here, the modelled outcomes are shaded in light blue. Using the commercial-in-confidence (CIC) data on infliximab and golimumab, the relation between baseline HAQ and PASI scores and the magnitude of HAQ change or PASI change was verified, as well as patient-level correlations between these quantities. It was found that both HAQ and PASI change are best modelled on the natural scale of absolute change: i.e. a HAQ change from 1.5 to 0.75 expressed as -0.75 was statistically more robust and less correlated with other quantities, than the same HAQ change expressed as -50%. The evidence synthesis model thus uses absolute changes in HAQ and PASI (as in Woolacott et al 2006).

Respecting the RCT nature of the available data, all outcomes were modelled relative to placebo. In particular, the probability of PsARC response with treatment was modelled as composed of the probability of PsARC response with placebo and a treatment-related increment, this being on the log-odds scale. The HAQ change given PsARC response with treatment was modelled as composed of the HAQ change given PsARC response with placebo plus a treatment-related increment. A similar approach was adopted for the HAQ change in non-responders and the PASI change.

For PsARC, the data used was response data at week 12 or week 14, depending on the study. For HAQ, the data used included

- week 12 and 24 for adalimumab,
- week 14 or 16 for infliximab,
- week 12 for etanercept and
- week 14 for golimumab.

For PASI, the data used included

- week 24 for adalimumab,
- week 14 or 16 for infliximab,
- week 24 for etanercept, and

- week 14 for golimumab.

Previous evidence synthesis by Woolacott et al. 2006

The evidence synthesis in the previous appraisal (Woolacott et al.) had access to commercial-in-confidence data on etanercept (Mease et al 2000 and 2004). This allowed Woolacott and colleagues to estimate the changes in HAQ conditional on PsARC response for etanercept and infliximab, and these quantities are critical to the long-term health economic model. Despite shortcomings in the structure of the equations and in particular, inconsistent distinction between placebo effects and the natural progression, we used the results of this precursor study for etanercept. Because those results already include data on PsARC and HAQ change relating to Antoni et al 2005a, Mease et al 2000 and 2004, double-counting was avoided by not using these data sources again for the same quantities.

Reporting of endpoint data

For HAQ and PASI, the reporting in the different studies appears not to be standardised. Whereas PsARC was always expressed as a number of respondents out of the total, HAQ was sometimes expressed as an absolute change or as a relative change in % from baseline. PASI was often reported as a relative change in % from baseline, but sometimes instead reported as a proportion of patients who achieve 50% PASI improvement, 75% PASI improvement.

From a health economic viewpoint, absolute changes in the HAQ and PASI scores matter. Both costs and quality of life can be related to these. An average % change across a group of patients can only be evaluated in absolute terms when the individual patient baseline values are known. Therefore, for trials that only report these relative outcomes, we assumed a homogeneous baseline patient population (i. e. mean baseline PASI times mean percentage change gives mean absolute change). For studies that report the proportion of patients beyond a certain level of relative PASI change, these were first transformed into % PASI changes using CIC data from the GO-REVEAL study and then transformed to the absolute scale as above.

The details of the assumptions used in the indirect comparison and the Winbugs code used in the analysis is available in section 9.17, Appendix 17.

5.7.6 Please present the results of the analysis.

Table B16: Results of the indirect comparison

Outcome	Placebo	Infliximab	Etanercept	Adalimumab	Golimumab
PsARC response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ change from baseline, PsARC responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ change from baseline, PsARC non-responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI change from baseline, BSA≥3% subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In terms of PsARC response at 12 weeks, while infliximab has a slightly superior rate in terms of its central estimate of [redacted] compared to etanercept with [redacted] the difference of only [redacted] between them is marginal with the 95% confidence intervals for the two being almost the same. The gap between etanercept and golimumab with [redacted] is smaller at [redacted] and again the 95% confidence intervals are similar, though those for golimumab are slightly narrower.

The PsARC response at 12 weeks for adalimumab is somewhat worse at [redacted]. While the upper bound of the 95% confidence interval for adalimumab crosses over the lower bound of the 95% confidence interval for golimumab, it is below the lower bound of the 95% confidence intervals of both infliximab and etanercept. The 95% confidence intervals for all treatments for the PsARC response at 12 weeks all lie above the upper bound of the 95% confidence interval for placebo.

For the average HAQ change among responders etanercept with [redacted] shows a somewhat better central estimate than infliximab with [redacted] a difference of [redacted]. The 95% confidence intervals overlap to a large degree, with that of etanercept being around a [redacted], or around one standard error, leftwards shift of that of infliximab. The average HAQ changes among responders for both adalimumab and golimumab are worse at [redacted] and [redacted] respectively. Adalimumab shows considerably more uncertainty having a standard error of [redacted], which causes its 95% confidence interval to overlap those of the other three treatments. Golimumab, with a standard error of [redacted] has a 95% confidence interval that falls slightly below that of etanercept, but that creeps into the lower bound of the 95% confidence interval for infliximab. The 95% confidence intervals for the HAQ change among responders for both etanercept and infliximab lie above the upper bound of the 95% confidence interval for placebo, but those for adalimumab and golimumab both cross the upper bound of the 95% confidence interval for placebo.

The estimates of the changes in PASI among those with clinically significant psoriasis at baseline were not differentiated by PsARC response. Infliximab was estimated to have the largest effect upon PASI with a reduction of [redacted], coupled with a standard error of [redacted]. Etanercept and golimumab were somewhat worse, with estimates of [redacted] and [redacted] respectively and standard errors of similar magnitude of around [redacted] causing their 95% confidence intervals to overlap that of infliximab. The central estimate for adalimumab was -[redacted] around which there was considerable uncertainty, the standard error of [redacted] causing its 95% confidence interval to encompass all those of the other treatments. The 95% confidence intervals for the PASI change for etanercept, infliximab and golimumab lie above the upper bound of the 95% confidence interval for placebo, but that for adalimumab strays well into the 95% confidence interval for placebo.

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

The data available on common endpoints was limited and was reported inconsistently. Therefore, no formal assessment of heterogeneity was undertaken.

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

The trials included here have also been critically evaluated by Rodgers *et al* in the publication titled - Etanercept, Infliximab and Adalimumab for the Treatment of Psoriatic Arthritis: a Systematic Review and Economic Evaluation (Rodgers et al, 2009).

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

No non-RCT evidence was used.

5.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

There are no trials designed to assess the safety outcomes of the interventions discussed herein. Please refer to earlier sections for relevant information.

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Table B17: Adverse events across randomised groups for golimumab (GO-REVEAL trial)

System organ/ class/adverse events	16 weeks					24 Weeks				
	Golimumab 50 mg % of patients (n = 146)	Golimumab 100 mg % of patients (n = 146)	Placebo % of patients (n = 113)	Relative risk (95% CI) Golimumab 50 mg	100 mg	Golimumab 50 mg % of patients (n = 146))	Golimumab 100 mg % of patients (n = 146)	Placebo % of patients (n = 113)	Relative risk (95% CI) Golimumab 50 mg	100 mg
Upper respiratory tract infection	[redacted]									
Nasopharyngitis	[redacted]									
Headache	[redacted]									
Diarrhea	[redacted]									
Hypertension	[redacted]									
Infections and Infestations	[redacted]									

CI, confidence interval

Adapted from European Public Assessment Reports published by the European Medicines Agency

Table B18: Published systematic reviews of adverse events of biologics excluding golimumab

Study details	Intervention and patients	Analyses	Outcomes
Bongartz 2006	Infliximab & Adalimumab 5014 RA patients	Studies were combined using a fixed-effects model of Mantel-Haenszel method. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, with a continuity correction method for sparse data. The effects for high and low doses of antiTNFs were estimated separately. The number-needed-to-harm with 95% CI was also calculated. Statistical heterogeneity was assessed using I2 statistic. Sensitivity analyses were performed with exclusion of trials of moderate or high risk of bias, omission of malignancies diagnosed within the first 6 weeks of a trial, and omission of malignancies that were classified as non-melanoma skin cancers.	The pooled OR for malignancy was 3.3 (95% CI: 1.2, 9.1) and for serious infection was 2.0 (95% CI: 1.3, 3.1). Malignancies were significantly more common in patients received higher doses of anti-TNFs compared with patients received lower doses of anti-TNFs. For patients with anti-TNF treatment in included RCTs, the number needed to harm was 154 (95% CI: 91, 500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (95% CI: 39, 125) within a treatment period of 3 to 12 months.
Bongartz 2009	Etanercept 3316 RA patients	Studies were combined using a random-effects model of DerSimonian and Laird model. Pooled hazard ratios (HRs) with 95% CIs were calculated using individual patient data (IPD). A survival analysis of time-to-first-event using the Cox's proportional hazards model stratified by trial and assuming a fixed treatment effect was conducted. Sensitivity analyses were performed by omitting cancers diagnosed within 6 weeks of trial entry and omitting all non-melanoma skin cancers (NMSC) from case definition. Subgroup analyses were performed	The pooled HR for malignancies based on IPD data was 1.84 (95% CI: 0.79, 4.28) in patients using etanercept compared with controls. The random effects model resulted in a similar estimate of an HR of 1.82 (95% CI: 0.78, 4.22). When using Mantel–Haenszel methods, the pooled OR for malignancies in patients using etanercept compared with patients receiving control treatment was 1.93 (95% CI: 0.85, 4.38). When using a random-effects DerSimonian and Laird model, the pooled HR malignancies in patients receiving etanercept compared

		for three non-overlapping periods of follow-up time (<6 months, 6–12 months, >24 months). In addition, pooled odds ratios (ORs) with 95% CIs were calculated using the Mantel–Haenszel model with a continuity correction method.	with patients receiving control treatment was 1.71 (95% CI: 0.73, 4.01). With the exclusion of four malignancies that were diagnosed during the first 6 weeks after the first treatment dose , the HR for malignancies in patients treated with etanercept compared with the non-etanercept group was 1.87 (95% CI: 0.75, 4.62). With the exclusions of all NMSC from analyses, similar results were found (HR 1.86, 95% CI: 0.62, 5.59). When the data were stratified according to three different time points: 0–6 months; 6–12 months and more than 12 months, it did not show a particular time period in which the risk of cancer was significantly increased.
Brimhall 2008	Etanercept & Infliximab 7931 patients with moderate to severe psoriasis	Studies were combined in meta-analyses using the Mantel–Haenszel method, with a constant continuity correction. The synthesis results from the random-effects models were also reported. Bioequivalent or equivalent FDA-approved doses were pooled for each biological agent. The safety of biological agents was assessed by relative risk of one or more adverse events and serious adverse events for all doses. All dosages were combined for comparison. The number needed-to -treat (NNT) and the number needed- -to-harm (NNH), with 95% CIs, were calculated. Statistical heterogeneity was measured using Q statistic.	Etanercept: The pooled RR of one or more AEs was not significantly increased for patients receiving etanercept (RR 1.05, 95% CI: 0.96, 1.16, p=0.28). Similar results were observed for the incidence of SAEs (RR 1.17, 95% CI: 0.59, 2.33, p=0.66). The most common reported AEs reported were injection-site reaction, headache and upper respiratory tract infection. The most common SAEs were malignancy (n=10), serious infection (n=4) and worsening psoriasis (n= 3). Both AEs and SAEs were evaluated cumulatively over 12–24 weeks of the treatment.. Infliximab: The pooled RR for one or more AEs was significantly associated with an increased one or more AEs compared with placebo (RR1.18, 95% CI: 1.07, 1.29, P <0.001), with NNH of 9 (95% CI: 5.99, 19.61). The most

			common reported AEs were upper respiratory tract infection, headache, increased hepatic enzymes and infection. Infliximab was not associated with a significant increase in SAEs (RR 1.26, 95% CI: 0.56, 2.84, p =0.58). The most common SAEs reported were malignancy (n =12), serious infection (n =6), serious infusion reaction (n =4) and lupus-like syndrome (n =4). Both AEs and SAEs were evaluated across 10–30 weeks of the treatment.
Gartlehner 2006	Etanercept , Infliximab and Adalimumab The review included RA patients who have failed to respond to traditional DMARD therapy. For indirect comparison, the authors pooled data for 2354 patients receiving adalimumab (five studies), for 1151 patients	Studies were combined in meta-analyses using random-effects models. Subgroup analyses were conducted for the population who had remained symptomatic despite the methotrexate treatment. Subgroup analyses were also performed by only including data to FDA approved dosage ranges to achieve better equivalency across drugs. Statistical heterogeneity was measured using I2 statistic and meta-regression. Publication bias was assessed using funnel plots and Kendall's tests. Where there were no direct head-to-head studies comparing an antiTNF with another, an indirect comparison was undertaken using placebo as the common comparator. For the adverse event data, the evidence was summarised qualitatively.	When the studies were pooled, adalimumab was associated with weighted mean incidence of diarrhoea (8.16, 95% CI: 4.44, 11.88), headache (18.23, 95%CI: 6.51, 29.95), infection site (18.98, 95% CI: 9.21, 28.76), nausea (8.84, 95% CI: 5.55, 12.13), rhinitis (14.8, 95% CI: 7.26, 22.35), and upper respiratory tract infection (17.05, 95% CI: 9.5, 24.59). Etanercept was associated with weighted mean incidence of diarrhoea (18.14, 95% CI: 3.45, 32.84), headache (17.54, 95%CI: 1.9, 33.18), infection site (24.67, 95% CI: 11.21, 38.13), nausea (20.86, 95% CI: 2.65, 39.08), rhinitis (18.42, 95% CI: 6.97, 35.71), and upper respiratory tract infection (20.89, 95% CI: 6.97, 34.82). Infliximab was associated with weighted mean incidence of diarrhoea (9.31, 95% CI: 7.94, 10.68), headache (17.7, 95% CI: 3.03, 33.36), rhinitis (7.77, 95% CI: 0, 18.12), upper respiratory tract infection (24.05, 95% CI: 0, 49.81).

	receiving etanercept (five studies), and for 704 patients receiving infliximab (four studies). The total number of patients in the review was not reported.		In addition, rare but serious adverse events (e.g. serious infections, lymphoma or neutropenia) were of concern in the included trials but could not be reliably assessed.
Ravindran 2008	Etanercept , Infliximab & Adalimumab 2039 PsA patients in total receiving the treatment of antiTNFs, Sulfasalzaine, gold salts, Leflunomide and DMARDs. (882 PsA patients receiving antiTNFs)	Studies were combined in meta-analyses using random-effects models. The pooled risk ratios (RRs) with 95% CIs for dichotomous outcomes were calculated. The pooled Peto odds ratios (ORs) with 95% CIs were calculated for the outcome of overall toxicity based on withdrawals due to side-effects. Sensitivity analyses were performed based on agents used and outcome measured. The ratio of number-needed-to- treat (NNT) to number-needed-to harm (NNH) was calculated to assess the benefit versus risk of each treatment.	When the studies (2 RCTs of etanercept, 2 RCTs of infliximab and one RCT of adalimumab) were pooled, antiTNF treatment was associated with a non-significant increase of withdrawal rate due to toxicity compared with placebos (RR 2.2, 95%CI; 0.82, 5.91, p=0.12; 5 RCTs). AntiTNFs were associated with a high ratio (0.25) of numbers needed to treat (NNT) to numbers needed to harm (NNH).

Saad 2008	Etanercept , Infliximab & Adalimumab 982 PsA patients	Studies were combined in meta-analyses using random-effects models. The pooled relative risks (RRs) and risk differences (RDs) for dichotomous outcomes, with 95% CIs, were calculated. The weighted mean differences (WMDs) for continuous outcomes, with 95%CIs were also calculated. Statistical heterogeneity was measured using Chi^2 and I^2 statistics. Where there were no direct head-to-head studies comparing an antiTNF with another, an indirect comparison was undertaken using placebo as the common comparator.	There were no significant differences between biologics and placebos in the proportion of patients experiencing withdrawals for any reason (RR 0.48, 95% CI: 0.20, 1.18), withdrawal due to adverse events (RR 2.14, 95% CI: 0.73, 6.27), serious adverse events (RR 0.98, 95% CI: 0.55, 1.77), and upper respiratory tract infections (RR 0.91, 95% CI: 0.65, 1.28). The pooled rate for injection site reactions were significantly higher for adalimumab and etanercept compared with placebos (RR 2.48, 95% CI: 1.16, 5.29). There was no significant difference in the proportion of patients experiencing infusion reactions with infliximab compared with placebos (RR 1.03, 95% CI: 0.48, 2.20). Significant heterogeneity was only observed in the outcome of withdrawal for any reason (I^2=53.1%, p=0.07). Indirect analyses did not show any significant differences between these biologics in the proportion of patients experiencing serious adverse events. Five RCTs (n=922) monitored the incidence of malignancies during treatment; only one patient in the placebo group developed a basal cell carcinoma of the skin.

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The safety profile of golimumab in PsA is consistent with that of other anti-TNF agents. Injection-site reactions occurred in a small proportion of patients and were mild in most cases. Malignancies were reported for 3 patients receiving golimumab 100 mg (2 cases of basal cell malignancies and 1 case of prostate cancer) through week 24. Certain safety events reported after week 24, after which all patients switched from the control arm to receive active treatment, are important to note, including 2 deaths (a climbing accident and a case of small cell lung cancer) and 1 report of liver histoplasmosis. One-year golimumab efficacy and safety data are forthcoming.

Elevations of the transaminase level were more common in the golimumab groups compared with the placebo group; patients with elevated transaminase levels were generally asymptomatic. These findings are consistent with observations with other biologic agents.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Golimumab is a TNF-α inhibitor with superior efficacy compared to standard care. The efficacy of golimumab is comparable to other TNF-α inhibitors including infliximab, adalimumab and etanercept. The clinical trial, GO-REVEAL has demonstrated golimumab to be a safe treatment option similar to other TNF-α inhibitors.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths of the clinical-evidence base include – Inclusion of RCTs for analysis, the large number of parameters considered, TNF-α inhibitors considered safe and efficacious based on earlier data.

Weakness – Golimumab is a relatively new drug hence long-term data is awaited. In addition, there are no non-RCTs or observational studies either at this point of time.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The evidence laid out relates to the usefulness of golimumab in treatment of psoriatic arthritis. In this regard, the intervention has been indirectly compared with other TNF-α inhibitors. Furthermore, clinical and safety benefits of the interventions have been compared on parameters such as – PSARC, HAQ and PASI, all of which are of high clinical significance.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Golimumab has been reviewed on the basis of an RCT for this appraisal (GO-REVEAL); this may influence the ability to generalise the findings.

In the RCT considered, golimumab has been considered as the first line of treatment; however in clinical practice patients exposed to other TNF-α inhibitors may be offered golimumab.

In the RCT considered, golimumab has been administered for a period of 24 weeks before the non-responders switched to a higher dose; however, as per the current NICE guidance TNF-α inhibitors are discontinued in the event of inadequate clinical response by the end of week 12.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A systematic search of the economic literature was conducted. The objective of the search was to identify published cost-effectiveness studies of therapies used in the treatment of psoriatic arthritis. The search strategy and the summary of identified articles are outlined in section 9.10, Appendix 10.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Table B19: Summary list of other cost-effectiveness evaluations

	Bravo Vergel et al.	ERG/submission for Adalimumab [TAG 125]	Bansback et al.	SP submission for Infliximab [TAG 104]	Rodgers et al. [Currently ongoing MTA
Time horizons	Lifetime, plus shorter	Lifetime, plus shorter	10 year, 5 year, 1 year & 6 months	Two models: Active joint model (AJM) Chronic joint model (CJM) AJM 2, 5, 10 and 30 years CJM 5, 10, 30 and 45 years	Lifetime, plus shorter
Discount rate: Benefits Costs	 1.5% 6.0%	 3.5% 3.5%	 3.5% 3.5%	 3.5% 3.5%	 3.5% 3.5%
Model type	Cost utility decision tree framework Both deterministic and probabilistic	Micro simulation, probabilistic at individual patient level	Micro simulation, probabilistic at individual patient level	Micro simulation, probabilistic at individual patient level	Cost utility decision tree framework Both deterministic and probabilistic
Comparators	Infliximab Etanercept	Adalimumab 40mg eow	Etanercept, with CSA with MTX or leflunomide 2nd line	Infliximab vs Placebo	Infliximab Etanercept

	Palliative care	Infliximab 4 vials Etanercept plus range of other DMARDS 2nd line	CSA with MTX or leflunomide Those withdrawing experiencing palliative care		Adalimumab Palliative care as 2nd line drawn from MTA
Model description	Patients trialled on active treatment. Those not showing PsARC response at 12 weeks come off treatment and experience natural progression in terms of HAQ. Responders have 12 week HAQ effect, differentiated by treatment. Long term withdrawal from treatment also differentiated by treatment probabilistically, but not in terms of functional form. QoL and non-drug costs a function of HAQ score.	Patients trialled on single TNF-α inhibitor Non-responders move onto sequence of up to 5 DMARDs [ERG concerned at high cost of these and that the more costly would have been tried prior to TNF-α inhibitors] Patient progression in terms of HAQ modelled, together with PASI. HAQ and PASI scores determine Quality of Life and Cost.	PsARC12 for response assessment. Rebound equal to gain and rebound to baseline both modelled. The difference between these varies only for the DMARD arm for whom PSARC12 response does not halt HAQ progression.	AJM patients remain on infliximab until 3 consecutive cycles in worst health state of 10+ active joints: active 0: zero active joints active 1: 1-4 active joints active 2: 5-9 active joints active 3:>=10 active joints Note that the submission appears to switch between states being defined over 0-3 and over 1-4.	Essentially the same as Bravo Vergel, but with PASI also modelled. Patients trialled on TNF-α inhibitor PsARC response determines continued treatment. Responders have 12 week HAQ effect, differentiated by treatment. Responders have 12 week PASI effect, differentiated by treatment. Possibility of including 24 week HAQ and PASI effects among responders. QoL a function of HAQ and PASI.

	Those on palliative care have annual HAQ progression (0.07) 12 week initial cycle. Variable cycle thereafter of 1/39th of time horizon	Those on DMARDs have annual HAQ progression (0.07) [ERG note Bansback used 0.028 for DMARD reponders] 6 monthly cycle		16 week cycles	Non-drug costs a function of HAQ and PASI, these being seen as independent Equal likelihood of long term withdrawal from treatment among responders drawn from Bravo Vergel. Rebound equal to gain and equal to natural history Annual HAQ progression among non-responders as per Bravo Vergel Annual PASI progression among non-responders zero 12 week initial cycle. Annual cycle with half cycle correction thereafter.
Assumptions	Responders see no HAQ progression	Responders see no HAQ progression	Etanercept responders see no HAQ progression, but other active treatment		Responders see no HAQ progression

	Rebound equal to gain, or equal to natural history Non-responders revert to natural history	Responders see no PASI worsening Rebound equal to gain Those receiving DMARDs revert to natural history	responders do experience annual HAQ progression.		Responders see no PASI worsening Rebound equal to gain, or equal to natural history Non-responders revert to natural history
Clinical effectiveness:	IMPACT I, Mease 2000, Mease 2004 HAQ changes conditional upon PSARC12 were estimated directly from manufacturer submitted data.	4 trials for adalimumab: M02-570 12 week RCT for those failing on DMARDs 51%-61% failed on min 2 DMARDs M02-518 24 week RCT for those failing on NSAIDs [ADEPT] 40%-43% failed on min 2 DMARDs Meta analysis of M02-570 and M02-518 presented for arthritis component M02-537 Open label	2 trials for Etanercept: Phase II 16-0612 Phase III 16-0030 But economics base case based upon Mease 2004 Leflunomide Kaltwasser et al 2004 trial report paper of leflunomide vs placebo in PsA Cyclosporin Fraser et al 2003 trial report paper of CSA+MTX against MTX in PsA	IMPACT I for infliximab. The Toronto Psoriatic Arthritis Research Programme beyond 50 weeks for the placebo arm.	IMPACT I and II for infliximab. ADEPT and Genovese for adalimumab. Mease 2000 and Mease 2004 for etanercept. PSARC12 response based on indirect comparison HAQ conditional on PsARC at 12 week PASI conditional on PsARC at 12 week

		follow-up of: M02-570 [12 week] and M02-518 [24 week] M04-724 Non-RCT prospective of those failing on DMARDs			
Clinical effectiveness estimates	Response status by PsARC 12 week HAQ change at 12 weeks given response / no response	Response status by PsARC 12 week HAQ change given response PASI change given response Estimates of response status may also have been disaggregated by ACR response type ARC20, ARC50 and ARC75. ARC responses appear to be used to predict the change in PASI for the non-adalimumab patients as in table 5.2 of the ERG report for infliximab. Also see appendix 5 of Abbott	Response status by PsARC 12 week HAQ change given response Annual HAQ progression based upon open label extension of Mease 2004 etanercept trial [for non etanercept treatments? But open label so used to justify etanercept no progression assumption?]	IMPCT I response effectively not having 3 consecutive cycles of the worst health state.	Response status by PsARC 12 week HAQ change at 12 week given response / no response PASI 50, PASI 75 and PASI 90 response at 12 week given response / no response

		STA submission. Excluded trials of less than 24 weeks as unrepresentative of TNF-α inhibitor effectiveness; i.e. excluded M02-570. For TNF-α inhibitors relied on: M02-518 for adalimumab Mease et al for Etanercept IMPACT II for Infliximab Note that M02-570 also did not measure PASI. M02-518 results used to derive 12 week responses from 24 week data across treatments: PsARC at 12wks 80% 24wk value.			

		ARC20 at 12wks 78% 24wk value ARC50 at 12wks 71% 24wk value PASI75 at 12wks 70% 24wk value Response likelihood/type split by baseline BSA at 3% Given correction for proportion of patients BSA<3% and BSA>3%, indirect comparison treat results as if from single study. Correlations between response types for patients with an without skin disease from M02-518 assumed to apply to other TNF-α inhibitors. Based upon type of response and ACR and PASI, regression of M02-518 used to			

		predict 24 week HAQ and PASI changes for patient baseline characteristics and ARC and PASI.			
Adverse events	Not explicitly modelled	Not explicitly modelled	Not explicitly modelled		Not explicitly modelled.
Mortality multiplier	Wong 2002		Almost same as in York Model, same as S-P submission: 1.59 as opposed to 1.60 York 1.65 as opposed to 1.66 York	The Toronto Psoriatic Arthritis Research Programme 1.59 as opposed to 1.60 York 1.65 as opposed to 1.66 York	Wong 2002
Long term withdrawal	Geborek, Crnkic et al. 2002. 3-20 month data Pooled results between etanercept and infliximab to arrive at single distribution, but draw separate rates for etanercept and infliximab for each	Observational study from Spanish Registry BioBadaser 2005 [only TNF-α inhibitors?] Sensitivity analysis using Flendrie Common annual withdrawal rate for all TNF-α inhibitors	Swedish observational study among RA patients for etanercept "The literature" for other treatments		As per Bravo Vergel

<table>
<tr><td></td><td>iteration</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Natural history/palliative care</td><td>TAR meta analysis</td><td></td><td>24 Leeds PsA patients data</td><td>The Toronto Psoriatic Arthritis Research Programme</td><td>TAR meta analysis</td></tr>
<tr><td>QoL estimates</td><td>EQ-5D as function of HAQ score 0.82 – 0.3HAQ
Probabilistic relationship
As reported in the Wyeth submission. No published evidence.</td><td>ADEPT trial SF36 data converted using Brazier SF-6D
Also SF-6D converted to EQ-5D according to Gray et al

Separately modelled for those with and without skin disease:
BSA>3% QoL a function of HAQ and PASI
BSA<3% QoL a function of HAQ
Much greater QoL effect under EQ-5D than SF-36 from both HAQ and PASI changes.

Confusing in that ERG report also mentions</td><td>EQ-5D as function of HAQ score 0.82 – 0.3HAQ
Probabilistic relationship
No published evidence</td><td>Toronto PsA database patient subset, EQ-5D values. Note that this was poorly correlated with PASI, and as a consequence it appears that only the arthritic component was included.

For the AJM
<table><tr><td>Active State</td><td>QoL</td><td>STD</td></tr><tr><td>0</td><td>0.75</td><td>0.30</td></tr><tr><td>1</td><td>0.67</td><td>0.26</td></tr><tr><td>2</td><td>0.50</td><td>0.29</td></tr><tr><td>3</td><td>0.29</td><td>0.37</td></tr></table>
For the CJM
<table><tr><td></td><td colspan="2">Chronic State</td></tr><tr><td>Active</td><td></td><td></td></tr></table></td><td>Analysis provided by manufacturers and selected by TAR.

EQ-5D as a function of both HAQ and PASI.</td></tr>
</table>

		that Menter el al 2005 was used to estimate QoL impact of psoriasis aspect		State	1(0?)	2(1?)		3(2?)	4(3?)
				0	0.92	0.84		0.76	0.69
				1	0.75	0.68		0.60	0.52
				2	0.59	0.51		0.44	0.36
				3	0.43	0.39		0.27	0.19
Cost estimates									
Direct drug and monitoring	BNF for dosing and cost Expert opinion for administration BSR guidelines for monitoring PSSRU and Reference costs for unit costs of most others Lab costs mainly from York NHS Trust	MIMS for dosing and cost Expert opinion for administration BSR guidelines for monitoring PSSRU and Reference costs for unit costs of most others Lab Costs based upon Barton et al 2004	MIMS for dosing and cost PSSRU and Reference costs for unit costs of most others	£451 per vial, with 4 vial dosing £100 per infusion based upon NHS reimbursement rates.				As per Bravo Vergel coupled with SPCs.	
HAQ score related [HAQDI? 0-3]	Kobelt et al 2002 [Rheumatoid arthritis]	Kobelt et al 1999 [Rheumatoid arthritis] Sensitivity analysis using Yelin et al 1999 [Rheumatoid arthritis]	Kobelt et al 2002 [Rheumatoid arthritis]	n.a.				Kobelt et al 2002 [Rheumatoid arthritis]	
PASI score related	n.a.	Expert opinion for 4 PASI states	n.a.	n.a.				Manufacturer estimates	

<table>
<tr><td></td><td></td><td>Linear regression for interpolation between PASI states</td><td></td><td></td><td></td></tr>
<tr><td>Other</td><td></td><td></td><td></td><td>Non-infliximab costs from the Toronto Psoriatic Arthritis Research Programme. Canadian health resource utilisation was assigned UK based costs on a unit per unit basis using MIMS and unit costs from Charing Cross Hospital.

Other costs were converted to £ based on OECD purchasing power parity table for 2003. How these were applied is unclear though the mean 2003 non infliximab costs appear to be:<table><tr><td>State</td><td>Active</td><td>Chronic</td></tr><tr><td>0</td><td>£341</td><td>£400</td></tr><tr><td>1</td><td>£440</td><td>£332</td></tr><tr><td>2</td><td>£416</td><td>£440</td></tr><tr><td>3</td><td>£514</td><td>£494</td></tr></table></td><td></td></tr>
<tr><td>Other</td><td>Only 85% of Kobelt</td><td>ERG concerned at</td><td>ERG concerned about</td><td>ERG found submission</td><td>Only 85% of Kobelt costs</td></tr>
</table>

comments	costs applied, seemingly as an ad hoc adjustment to avoid double counting	clinical effectiveness estimates maintaining absolute relative risks across indirect comparisons, rather than relative to placebo.	HAQ progression for DMARD responders but not etanercept responders Some double counting in terms of uncritical application of Kobelt costs	poorly documented and opaque	applied, seemingly as an ad hoc adjustment to avoid double counting

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

The quality assessment for each identified study is available in section 9.11, Appendix 11 as per the format of Drummond and Jefferson (1996).

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The patient group studied included individuals with active and progressive psoriatic arthritis who have responded inadequately to previous DMARDs. This reflects the licensed patient group studied in the golimumab clinical trial (GO-REVEAL) as well as patient group included in the scope of this appraisal. Hence, there are no specific implications of the available evidence base to the specifications of the decision problem.

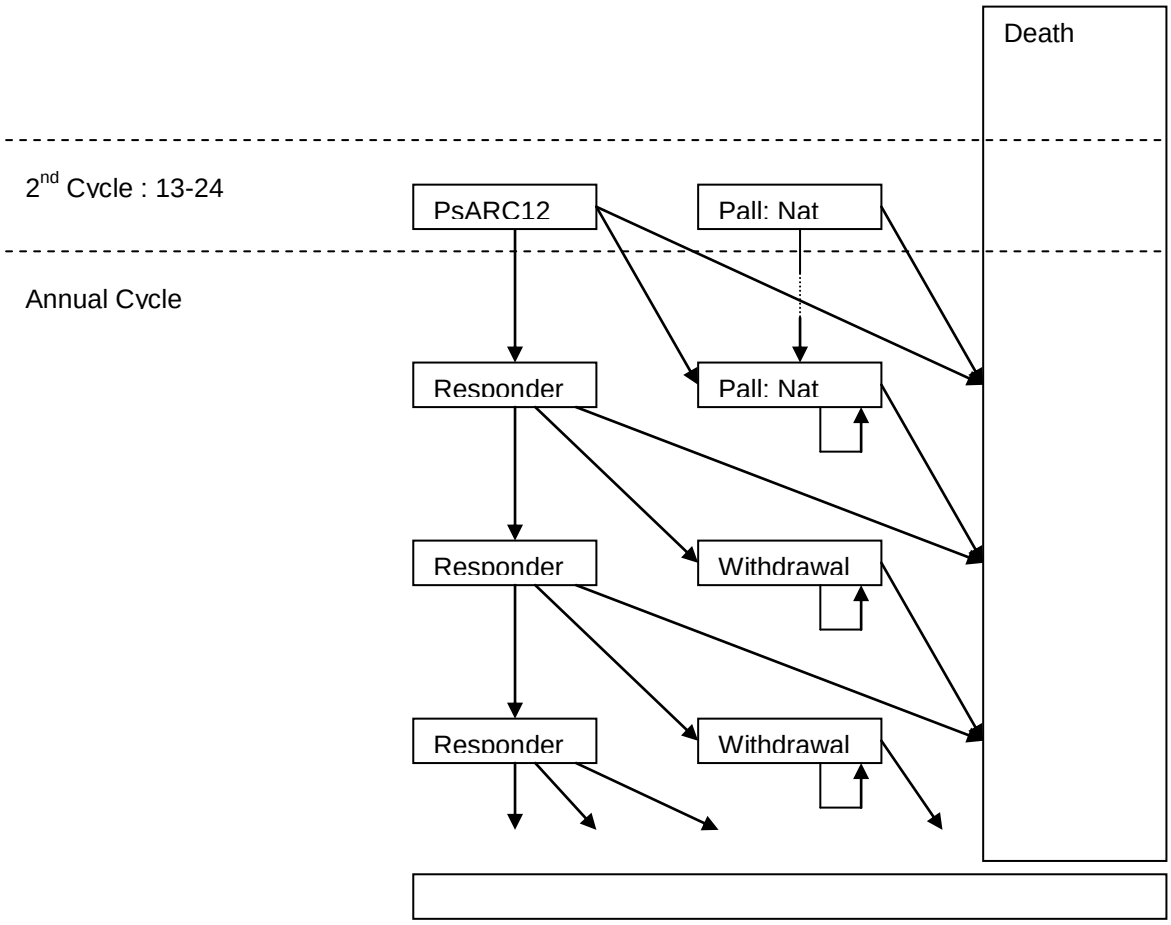
[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

Figure B10: Cost effectiveness model structure



6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The model structure in terms of the cohort flow is presented diagrammatically in section 6.2.2. This can be briefly summarised as having a 1st cycle of 0-12 weeks, a 2nd cycle of 13-24 weeks, and thereafter annual cycles. The model has been developed based on previous work of Bravo Vergel and colleagues (Bravo Vergel et al, 2007). The current NICE guidance recommends TNF-α inhibitor treatment (Etanercept and adalimumab) for 12 weeks until assessment of response and only responders are allowed to continue treatment on TNF-α inhibitor (TAG 104 & TAG 125). On the contrary, the current BSR guidelines recommend TNF-α inhibitor treatment for at least 6 months before the continuation decision (Kyle et al, 2005). Our market research suggested that the current clinical practice is split between the NICE guidance and BSR guidelines and therefore we selected the model with first two 12-week cycles to allow flexibility of incorporating either in the decision rule.

Subsequent to this the mixed treatment comparison

- has retained the analysis of the PsARC at 12 weeks or the nearest time point thereafter across comparators

- has taken the last available data point with randomised control for the HAQ and PASI for each of the comparators, rather than impose a common time point.

Therefore, for a given treatment the economic modelling applies the same HAQ and PASI change among responders for both the first and the second cycle of the model. Similarly, for a given treatment the HAQ and PASI change among non-responders is applied but due to the model structure this is only applied during the first cycle.

The sequential treatment with a 2nd TNF-α inhibitor was not considered for the following reasons.

- No evidence is available currently for sequential use of TNF-α inhibitors in psoriatic arthritis. Although NICE appraisal committee in a previous appraisal (TA 104)

concluded that such evidence should be considered in future reviews, our literature search did not identify any such evidence.

- There is currently data available on sequential use of TNF-α inhibitors in RA but not in psoriasis. PsA being a condition with a significant proportion of psoriasis patients, the available evidence may not be sufficient to capture the true benefit of TNF-α inhibitors.

- The analysis of BSRBR data conducted in RA patients for a separate NICE appraisal in sequential use of TNF-α inhibitors revealed that the relative treatment effect of a 2nd TNF-α inhibitor relative to DMARDs would be similar or even better to their use as first line treatments. The resulting ICERs are therefore likely to be similar to those presented in the current analysis.

6.2.4 Please define what the health states in the model are meant to capture.

The health states in the model capture response to treatment estimated using PsARC. Patients deemed as responders have achieved PsARC response at week 12 and move to 'PsARC12' health state. PsARC response was defined as improvement in at least two of the following four parameters, one of which is either the tender or swollen joint count, with no worsening of the other parameters.

- At least 30% reduction in tender joint count

- At least 30% reduction in swollen joint count

- At least one point reduction in clinician's assessment

- At least one point reduction in patient assessment

Patients who do not achieve PsARC response deemed as non-responders and switch to 'Not PsARC12' health state.

After assessment of primary response (week 12/24), patients continuing to respond switch to 'Responder t0/t1/t2' health states and patients losing response and withdrawing from

treatment switch to 'Withdrawal t0/t1/t2' health states. All patients entering the model can die and move to 'Death.'

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model captures the benefit of treatment on the rheumatic component of the condition using HAQ score and on the psoriatic component of the condition using PASI score. Patients' baseline HAQ and PASI scores were estimated to reduce on response to treatment and the magnitude of HAQ and PASI reduction was estimated using data from clinical trials compared using mixed treatment comparisons.

Within the base case, the model assumes that disease progression does not occur for patients responding to treatment. This was assumed in the analysis conducted by Bravo Vergel and others due to the fact that no differential deterioration was found between etanercept and infliximab, and that HAQ progression was found to be halted in patient who continued to receive etanercept or infliximab for 48 and 34 weeks respectively after the break of randomisation (Bravo Vergel, 2007). However the uncertainty around this assumption is addressed in the one way sensitivity analysis where the HAQ of responders is assumed to progress at the same rate as natural history after the initial HAQ improvement.

The treatment pathway assumed that patients withdrawing from TNF-α inhibitor treatment move to palliation and not placebo. In common with the Bravo Vergel model, palliation was assumed to experience natural progression.

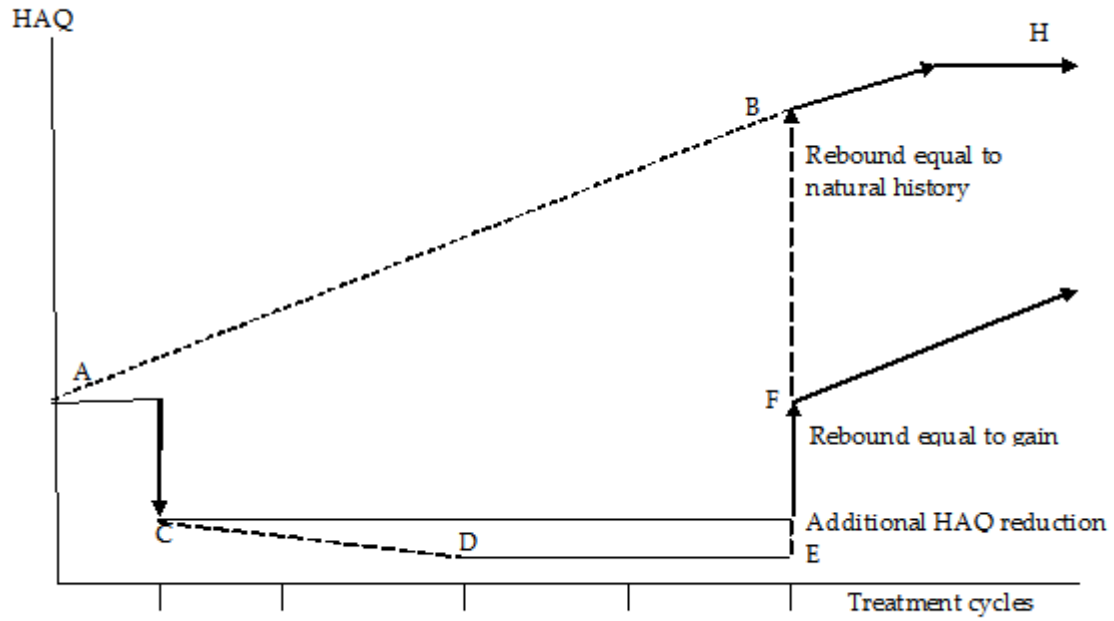
The analysis assumed continued HAQ reduction for patients responding to treatment for the first three cycles (12, 12 and 52 months). This has been schematically displayed by the dotted line between points C and D in Figure B11 below. After first three cycles HAQ was assumed to remain constant represented by a solid line between points D and E. The assumption was based on the analysis of IMPACT, IMPACT 2 and GO-REVEAL trials and has been presented in section 9.14, Appendix 14. In addition to the initial HAQ reduction estimated

using indirect comparison, the HAQ reductions used in the 2nd and 3rd cycles were -0.0628 and -0.0313 respectively.

For patients withdrawing from treatment, rebound was modelled under two scenarios: rebound equal to gain with natural history disease progression thereafter, and rebound equal to the natural history disease progression as would have occurred from baseline with only palliative care. The natural history disease progression for HAQ was assumed to be as per the Bravo Vergel model and has been represented by a dotted line between A and B. The HAQ progression was subject to the constraint of a maximum value for HAQ of 3 represented by H in Figure B11.

An example of the evolution of the HAQ score for a patient withdrawing from treatment at the end of the 5th cycle of the model; i.e. at the end of the third full annual cycle, is depicted below. Therefore, for a patient coming off treatment at the start of the 6th cycle, if rebound is equal to natural history it is assumed that the patient will experience an average HAQ score of B for the 6th cycle whilst for a patient rebounding equal to gain the average HAQ score will be F.

Figure B11: HAQ reduction and rebound effect



The natural history disease progression for PASI was assumed to flat, based upon expert opinion.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B20: Key features of the cost effectiveness analysis

Factor	Chosen values	Justification	Reference
Time horizon	40 years	Lifetime model with patient starting age of 45 years	
Cycle length	First two cycles of 12 weeks followed by annual cycle	Clinical practice and previous NICE guidance	
Half-cycle correction	Yes		
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case	
Discount of 3.5% for utilities and costs	Yes	NICE reference case	
Perspective (NHS/PSS)	NHS/PSS	NICE reference case	
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

In the economic analysis four treatment alternatives were compared. These included maintenance treatment with a TNF-α inhibitor (infliximab, adalimumab or etanercept) followed by a sequence of DMARDs. The comparator was palliative care comprising of DMARDs. All the TNF-α inhibitor treatments were implemented as per their marketing

authorisation and therefore the evidence directly relates to the dose used in this analysis. The doses modelled included

- Golimumab: 50 mg given once a month, on the same date each month.
- Infliximab: 5 mg/kg given as an intravenous infusion over a 2 hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.
- Adalimumab: 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.
- Etanercept: 25 mg administered twice weekly, or 50 mg administered once weekly.

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The model assumes continued treatment for patients responding to golimumab (assessed using PsARC response criteria) after week 12. This is in accordance with the SPC which states "available data suggest that clinical response is usually achieved within 12 to 14

weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period." This also is in line with the SPCs of other TNF-α inhibitors and current NICE guidance (TAG 104 & TAG 125). Patients not exhibiting PsARC response discontinued treatment and switched to palliative care.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

The relative treatment effects were estimated using indirect comparison techniques. The details are available in Section 5.7.

The results of the mixed treatment comparison, coupled with an assumption of no disease progression while remaining on treatment, enabled the evolution of HAQ and PASI scores to be modelled as a single step function for those remaining on treatment. However, due to the half cycle correction, among responders only half the HAQ and PASI benefit is experienced during the first cycle with the full benefit being experienced from the second cycle onwards.

As stated in section 6.2.5, the treatment pathway assumed that patients withdrawing from TNF-α inhibitor treatment move to palliative care and not placebo, and experience natural disease progression. Therefore, in line with the Bravo Vergel model, the placebo effect needed to be subtracted from treatment effect estimated using the mixed treatment comparison. This was achieved by subtracting the product of the probability of PsARC response under placebo with the absolute placebo effect upon; e.g. the HAQ. It is important to note that this primarily affects the comparison of the TNF-α inhibitors with palliative

care. Assuming that a common placebo effect is observed across treatments this will have a minimal impact upon the comparisons between TNF-α inhibitors.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Not applicable

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

All the trials identified during the systematic review have cross over designs. Therefore, there is no randomised controlled evidence for long term transition probabilities for PsARC response. The long term extension trials of TNF-α inhibitors suggest continued treatment effects (in terms of HAQ benefit) and comparable transitions beyond the initial trial period. Therefore, instead of using transition probabilities for response beyond the first cycle, the model uses a constant withdrawal rate in the base case.

There were two estimates for withdrawal rates available in literature. We used the more recent estimate of 16.5% in the base case (Rodgers et al, 2009) and used the other estimate 11.14% in the sensitivity analysis (Geborek et al, 2002).

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The intermediate outcomes of change in HAQ and PASI were linked to the final outcome of QALYs. The detailed methods of elicitation are available in section 6.4.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The values were estimated using published estimates. No expert opinion was used.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table B21: Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Time horizon	40 years	Range (5 – 40 years)	
Proportion of females	40%	-	-
Mortality Females	1.60	Beta	

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

(SMR)			
Mortality Males (SMR)	1.66	Beta	
Age	47 years	-	
Weight	[redacted]		
Baseline HAQ	[redacted]		
Baseline PASI	[redacted]		
Proportion with psoriasis	[redacted]		
Treatment withdrawal rate	16.5%	Beta	
Vial Optimisation for infliximab	Yes		
Base year (costs)	2009		
Different placebo responses for TNF-α inhibitors	No		
PASI costs	Include phototherapy		
HAQ rebound assumption	Equal to gain		
PASI rebound assumption	Equal to gain		
HAQ rebound for non-responders	Equal to gain		
PASI rebound for non-responders	Equal to gain		
PsARC 12 Response Golimumab Infliximab Etanercept Adalimumab Placebo	 [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted] [redacted]	
HAQ change for PsARC responders Golimumab Infliximab	 [redacted] [redacted]	 [redacted] [redacted]	

Etanercept Adalimumab Placebo	[redacted]	[redacted]	
HAQ change for PsARC non-responders Golimumab Infliximab Etanercept Adalimumab Placebo	[redacted]	[redacted]	
PASI change from baseline Golimumab Infliximab Etanercept Adalimumab Placebo	[redacted]	[redacted]	
Natural history HAQ change	0.0719	Normal	
Drug cost /cycle (Including monitoring) 1st Cycle Golimumab Infliximab Etanercept Adalimumab 2nd Cycle Golimumab Infliximab Etanercept Adalimumab Annual Cycle Golimumab Infliximab Etanercept Adalimumab	 £ 2,658.00 £ 5,826.15 £ 2,658.12 £2,658.00 £ 2,308.81 £ 3,863.92 £ 2,308.92 £ 2,308.81 £ 9,608.30 £ 12,601.45 £ 9,608.82 £ 9,608.30		

Other costs while on TNF-α inhibitors Intercept Slope Incremental costs as a function of PASI Intercept Slope	 £ 1,186.59 £ 358.93 - £ 167.00	Normal	
Other costs while OFF TNF-α inhibitors Intercept Slope Incremental costs as a function of PASI Intercept Slope	 £ 1,395.99 £ 422.28 - £ 167.00	Normal	
QoL as a function of HAQ and PASI Intercept Slope HAQ Slope PASI	 0.897 - 0.298 - 0.004		
CI, confidence interval			

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

The clinical effectiveness estimated using 12-16 week trial data was extrapolated to the model time horizon of 40 years. Following assumptions have been made.

- Patients responding to treatment at 12 weeks were assumed to continue with their current treatment with an annual probability of withdrawing from treatment and moving onto palliative care.

- Patients not responding to treatment at 12 weeks were assumed to withdraw treatment and move to palliative care.

- A proportion of patients were assumed to have no clinically significant psoriatic component to their disease at baseline, within the trials this typically being the proportion of patients with a BSA < 3% and being around 1/3rd of those recruited to the trial. For these patients only the impact upon the HAQ is modelled.

- The treatment benefit in terms of the HAQ reduction is assumed to continue for 2nd and 3rd cycle (24 weeks & annual cycle, respectively) after which TNF-α inhibitor treatment was assumed to offer no additional HAQ reduction. Fourth cycle onwards, the HAQ score for responders was assumed to remain constant as long as they were on TNF-α inhibitor treatment.

- For patients withdrawing from treatment, the HAQ was assumed to return to baseline and then follow decrement equal to natural history thereafter.

- The treatment benefit in terms of the PASI reduction is assumed only in the 1st cycle after which TNF-α inhibitor treatment was assumed to offer no additional PASI reduction.

- For patients withdrawing from treatment, the PASI was assumed to return to baseline and then follow decrement equal to natural history thereafter.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Following assumptions were used in the economic analysis

Assumptions related to clinical effectiveness

- PASI is only modelled for the subset of patients with initial BSA ≥ 3%.

- The relevant PASI outcome is the absolute change in PASI score as quality of life and costs are influenced by the absolute PASI score, rather than any percentage change. Where trials only report the relative change in PASI (e. g. average 54% improvement) or "response criteria" such as PASI50, PASI75, etc., the absolute changes have to be inferred.

- PASI is modelled as an aggregate across patients with or without a PsARC response. The provided golimumab QoL data indicates that PASI improvement is not greater in the group of patients achieving PsARC response. In the absence of data on the other comparators, it is assumed that this also applies to all other drugs.

- All patients with BSA >3% are assumed to have identical PASI baseline values equal to the mean PASI baseline score reported for this subgroup in the trial. Absolute PASI change can be inferred accurately from relative PASI change when the patient-level values are available. But in trial reports there are only aggregate results on this. If the trial does not report the baseline PASI for this group, it is assumed to be equal to the average score reported in the other trials. These assumptions are necessary to extract relevant absolute PASI change from a relative change in PASI. Alternatives to this assumptions are: (a) to use patient-level data, (b) to extract absolute changes in PASI score, (c) to ignore PASI, but these alternatives are not available.

- Where PASI change is reported as proportion of patients with PASI50, PASI75 etc., to translate this into an average relative change in PASI score, the mean relative change in PASI for patients with PASI50 etc. is required. Based on a weighted mean analysis of the GO-REVEAL additional data, the mean relative PASI change in patients achieving PASI25 (and no higher improvement) was 38.2%, for PASI50 it was 60.4%, for PASI75 it was 82.5%, and for PASI90 it was 96.9%. It is assumed that similar relationships hold for the patient groups in the other trials. Without individual patient-level data, this is the best that can be achieved. The PASI50 etc outcomes by themselves do not quantify PASI change in a quantifiably meaningful way.

- The PASI change is not correlated with the PASI baseline score. The golimumab aggregate data suggest this assumption is reasonable, given that there is not access to patient level data to test this, nor to the patient-level PASI baseline values to represent this correlation even if it were known.

- The PASI change and HAQ change are not correlated in the BSA > 3% group, an assumption supported by the golimumab aggregate data.

- The HAQ change is conditional on PsARC response. Though data availability conditional on PsARC is scarce, this information is essential to the health-economic model.

- Where trials do not report the HAQ outcomes separately by PsARC response group, it has been assumed that the HAQ change for the PsARC non-responders is equivalent to the average HAQ change in non-responders seen in other trials, and the HAQ change for the PsARC responders is inferred to match the reported mean HAQ change. Alternatives to this assumption include different calculation models for the inference: e.g. the ratio between the HAQ changes in the two groups is the same across trials, but this is unfavourable due to possible division by zero Other alternatives, such as not to model HAQ conditional on PsARC, were also discarded.

- The HAQ change from baseline to the last RCT controlled data point up to week 24 is the main outcome of interest and is the main determinant of the outcomes of the economic model.

- The HAQ change is not correlated with baseline HAQ score. Patient-level data would be needed to test this thoroughly, but the golimumab extraction suggests that this assumption holds. On a technical level, there must be some relationship because the HAQ scale is bounded by 0 and 3, so patients with extremely low or high values cannot show the same amount of absolute change as patients in the centre of the range. But empirically there is no evidence that this matters.

- The HAQ change is assumed identical for the subgroups with or without BSA ≥ 3% at baseline. This is suggested by the golimumab data, and is a model simplification.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Psoriatic arthritis (PsA) is a chronic, debilitating spondylarthropathy characterized by inflammatory arthritis that affects the joints and connective tissue and is associated with psoriasis of the skin or nails. The rheumatic characteristics of PsA include stiffness, pain, swelling, and tenderness of the joints and surrounding ligaments and tendons, although the severity of symptoms can range from mild to very severe. The course of PsA can be variable and unpredictable, ranging from mild and nondestructive disease to erosive and deforming arthritis (seen in 40% to 60% of PsA patients). Untreated PsA patients may have persistent inflammation, progressive joint damage, severe physical limitations, disability, and increased mortality. The number of actively inflamed joints may contribute to declining physical function in patients with PsA. In addition to skin and joint involvement, PsA may be associated with other inflammatory conditions, including autoimmune disorders and cardiovascular disease. Patients with psoriasis are at greater risk of developing Crohn's disease and ulcerative colitis than the general population, and are also at increased risk of cardiovascular disease which may further decrease their HRQL. Nail psoriasis is seen in up to 80% of the patients with PsA. Nail psoriasis is a frequent and cosmetically disfiguring presentation of PsA, often causing functional impairment, pain, and emotional distress for many patients.

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Assessment of physical function in PsA is commonly evaluated using the Health Assessment Questionnaire Disability Index (HAQ-DI; score range, 0 to 3 where 0 indicates no physical disability). Physical function generally worsens as the number of inflamed joints increases (eg, from 1-5 joints to 6-20 joints) and as disease activity worsens (using the

Psoriasis Area and Severity Index [PASI]). Nail psoriasis is difficult to treat successfully, requiring either long duration of therapy (ie, application of topical steroids and vitamin D analogues for 3 months or longer) or painful and invasive procedures (ie, intralesional injections of steroids).

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

In the clinical trial of Golimumab (GO-REVEAL), the HRQL data was collected using SF-36 at weeks 14 and 24. This is not consistent with the reference case and was therefore not used in the base case.

In the base case, an algorithm estimating the utilities based on HAQ and PASI used in a previous NICE appraisal was used (Rodgers et al, 2009). The algorithm used has been reproduced below.

Expected utility = 0.897 – 0.298 X HAQ – 0.004 X PASI

The assessment group report (Rodgers et al, 2009) investigated three separate algorithms submitted by the three manufacturers (Abbott, Schering-Plough and Wyeth) in that appraisal and concluded that three algorithms based on three separate datasets were consistent and would have non-significant impact on the results. Therefore, the algorithm chosen by Rodgers et al was selected in the base case.

A separate algorith based on mapping of SF-36 data on to EQ-5D using patient level data from golimumab clinical trial (GO-REVEAL) was used in the sensitivity analysis. The derivation of the regression model used to estimate the utilities is explained in section 9.15, Appendix 15.

This algorithm henceforth referred as Gray algorith analyses the model of natural-scale QoL was again, much better than the logarithmic-scale QoL model. All coefficients with the exception of the sHAQ squared coefficient were significant at the 95% level. The coefficients and their standard errors are presented in Table B22 below.

Table B22: Gray algorithm coefficient means and standard errors

	Gray Algorithm	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The correlation matrix for the coefficient estimates is given below in Table B23.

Table B23: The correlation matrix for the Gray algorithm

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

The above central estimates in Table B23 can be combined with the central estimates of effectiveness (not adjusted for placebo effect) among patients with a significant degree of

psoriasis who are PsARC responders to yield the following coefficient values shown in Table B24.

Table B24: Gray algorithm coefficients for patients with psoriasis who are PsARC responders

Gray	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The algorithm results in etanercept being very marginally superior to infliximab among patients with psoriasis. But note that this is among PsARC responders, and does not take into account the higher PsARC response rate for infliximab. Golimumab is noticeably inferior to all other treatments among PsARC responders, but again this does not take into account the considerably better PsARC response rate for golimumab as compared to adalimumab.

While the Gray algorithm results in somewhat higher quality of life values in general among responders, the impact of this among PsARC responders is somewhat greater for infliximab and etanercept, and is negligible for golimumab.

Within the modelling given the assumptions outlined in subsequent sections, progression of the HAQ will lead some patients off anti-TNF treatment to have a HAQ score of 3 and a PASI score of 11. The Gray algorithm estimates these patients as having a QoL of 0.04. As avoiding natural progression in the HAQ is the main benefit from anti-TNF treatments in general, the movement towards these QoL values has a major impact upon cost effectiveness results. For patients without psoriasis who are PsARC responders the corresponding figures are shown in Table B25.

Table B25: Gray algorithm coefficients for patients without psoriasis who are PsARC responders

Gray	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

The details of the mapping exercise are available in section 6.4.3.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

In the ongoing appraisal of TNF-α inhibitors, Rodgers and collegues conducted a systematic literature search of HRQoL data. We updated this search but did not find any addiitonal HRQoL related information. We have therefore selected to use their algorithm in our base case.

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.

- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

HRQL was measured in the clinical trial of golimumab in PsA (GO-REVEAL). The details of the trial are available in section 5.2 through section 5.5.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The algorithm taken from a previous NICE appraisal (Rodgers et al, 2009) was based on a similar methodology to our analysis. Therefore, the algorithms are comparable. The actual values derived using these algorithms differ slightly due to the inclusion of PsARC response criteria which is further derived from the indirect comparison.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

In the economic analysis, the adverse events were included only to the extent that they affect the initial response and the long term withdrawal rates. Due to unavailability of data, impact of serious adverse events leading to co-morbidities or adverse events leading to temporary withdrawal from treatment and the associated disutility were not considered.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table B26: Summary of quality of life values for cost effectiveness analysis

State	Regression estimate	SE	Reference in submission	Justification
Intercept	0.897	0.006	Section 6.4.3	
sHAQ	-0.298	0.006	Section 6.4.3	
sPASI	-0.004	0.0003	Section 6.4.3	
sHAQ*PASI	0.0000	0.00001	Section 6.4.3	

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Clinical experts were not used in the estimation of HRQL values.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The HRQL in a particular health state is determined by the HAQ and the PASI. The algorithm used in the economic analysis uses both the clinical assessment indicators (HAQ and PASI) to estimate the HRQL of the patient. Therefore, the potential variances in the disease activity and the resultant HRQL are captured by HAQ and PASI and are reflected in the utility values over the course of the treatment.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Based on our literature search, no health effects identified in the literature and the clinical trials have been excluded.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline quality of life is determined by the baseline HAQ and PASI scores and has been presented in section 6.4.3.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Patients' HRQL changed depending on the change in HAQ and PASI. It was assumed that PASI remains constant after the first cycle whereas HAQ remains constant from the 4th cycle onwards. Therefore, for responders, the HRQL changed until the 3rd cycle and then remained constant. For non-responders a constant HAQ decrement was assumed throughout the analysis time horizon. Therefore, for non-responders or patients losing response the HRQL changed over time.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The values in sections 6.4.3 through 6.4.8 have not been amended.

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The current clinical management of this condition requires patients to have a regular contact with the specialist rheumatology or dermatology centres in the UK. This involves regular attendance at an outpatient clinic and face to face consultation with a consultant or non-consultant in rheumatology or dermatology department. Patients with moderate to severe symptoms may also be hospitalised occasionally. The reference costs used in PsA are presented in the tables below.

Table B27: Reference costs used in this appraisal

Regular admissions								
Elective inpatient HRG data								
Service Code	Regular Day / Night Admissions	No. of Admissions	National Average Unit Cost £	Interquartile Range of Unit Costs 2		No of bed days	Avg length of stay	No. of Data Submissions
				Lower Quartile £	Upper Quartile £			
HD23A	Inflammatory Spine, Joint or Connective Tissue Disorders with Major CC	586	£3,244	£1,603	£4,826	5,469	9.33	173
HD23B	Inflammatory Spine, Joint or Connective Tissue Disorders with CC	1,786	£2,077	£905	£2,981	8,738	4.89	310
HD23C	Inflammatory Spine, Joint or Connective Tissue Disorders without CC	1,786	£1,225	£619	£1,738	4,513	2.53	255
Non-elective inpatient (long stay) HRG data								
HD22B	Inflammatory Spine, Joint or Connective Tissue Disorders 70 years and over with CC	6	£1,913	£1,913	£1,913	38	6.33	1
HD23A	Inflammatory Spine, Joint or Connective Tissue Disorders with Major CC	3,082	£2,675	£1,574	£3,081	29,705	9.64	704
HD23B	Inflammatory Spine, Joint or Connective Tissue Disorders with CC	5,061	£1,646	£1,064	£1,965	28,786	5.69	869
HD23C	Inflammatory Spine, Joint or Connective Tissue Disorders without CC	1,968	£1,442	£804	£1,640	8,271	4.20	585

Non-elective inpatient (short stay) HRG data								
HD23A	Inflammatory Spine, Joint or Connective Tissue Disorders with Major CC	1,238	£383	£248	£446	1,238	1.00	394
HD23B	Inflammatory Spine, Joint or Connective Tissue Disorders with CC	4,307	£349	£237	£406	4,307	1.00	666
HD23C	Inflammatory Spine, Joint or Connective Tissue Disorders without CC	3,816	£361	£230	£417	3,816	1.00	604

Day Cases						
HRG Code	HRG Label	No. of FCEs	National Average Unit Cost £	Interquartile Range of Unit Costs 2		No. of Data Submissions
				Lower Quartile £	Upper Quartile £	
HD23A	Inflammatory Spine, Joint or Connective Tissue Disorders with Major CC	480	£447	£337	£478	72
HD23B	Inflammatory Spine, Joint or Connective Tissue Disorders with CC	8,006	£494	£235	£524	333
HD23C	Inflammatory Spine, Joint or Connective Tissue Disorders without CC	21,598	£462	£226	£496	470

Adult OP First attendance						
Specialty Code	Specialty	No. of First Attendances	National Average Unit Cost	Interquartile Range of Unit Costs 2		No. of Data Submissions
				Lower Quartile	Upper Quartile	

			£	£	£	
410	Consultant led: Face to face - Rheumatology	267,760	£203	£146	£239	162
410	Consultant led: Non face to face - Rheumatology	30	£140	£114	£192	8
410	Non consultant led: Face to face - Rheumatology	20,914	£126	£107	£152	68
410	Non consultant led: Non face to face - Rheumatology	2,316	£17	£17	£17	1
330	Consultant led: Face to face - Dermatology	716,931	£113	£90	£131	168
330	Consultant led: Non face to face - Dermatology	7,037	£30	£22	£38	10
330	Non consultant led: Face to face - Dermatology	44,578	£74	£48	£99	110
330	Non consultant led: Non face to face - Dermatology	14	£79	£50	£104	3
	Average		133.690			

Adult OP Follow-up attendance						
Specialty Code	Specialty	No. of First Attendances	National Average Unit Cost £	Interquartile Range of Unit Costs 2		No. of Data Submissions
				Lower Quartile £	Upper Quartile £	
410	Consultant led: Face to face - Rheumatology	972,253	£115	£88	£137	161
410	Consultant led: Non face to face - Rheumatology	7,579	£50	£17	£50	14
410	Non consultant led: Face to face - Rheumatology	169,434	£81	£65	£99	86
410	Non consultant led: Non face to face - Rheumatology	965	£46	£38	£44	7
330	Consultant led: Face to face - Dermatology	1,311,205	£76	£57	£86	166
330	Consultant led: Non face to face - Dermatology	2,174	£35	£34	£34	9
330	Non consultant led: Face to face - Dermatology	395,074	£50	£33	£63	111
330	Non consultant led: Non face to face - Dermatology	1,060	£46	£45	£45	7
	Average		£86			

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The NHS reference costs cover a wide variety of conditions related to rheumatology and dermatology and also have wider geographical coverage. Due its generalisability, NHS reference costs are appropriate for costing the TNF-α inhibitor treatments within NHS.

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A recent systematic search for the information on resource use was conducted by Rodgers and colleagues (Rodgers et al, 2009). We updated the systematic review but did not find any additional information. Therefore, the resource use infromation used in the ongoing appraisal (Rodgers et al, 2009) was used.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts were used to estimate the resource use based on PASI. The information was collected using an internet based survey of 22 clinical experts. All the experts were dermatologists specialising in treatment of PsA patients and requiring experience of using TNF-α inhibitors in the past. In total 35 clinical experts from UK's leading dermatology centres were approached. Experts were selected based on their geographical location, size of their practice, previous experience of treating PsA patients and using TNF-α inhibitors. Of these 22 responded to the PASI resource use questionnaire presented in Appendix 16. The resource use estimates thus derived were the means of the resource use estimated by the individual respondent.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Table B28: Unit costs associated with the technology in the economic model

Items	Golimumab	Infliximab	Etenercept	Adalimumab	Ref in submission
Technology cost	£774.58	£419.62	£178.75	£357.50	

Mean cost of technology treatment					
Cycle 1	£2,145.00	£5,363.37	£2,145.12	£2,145.00	
Cycle 2	£2,145.00	£3,575.58	£2,145.12	£2,145.00	
Annual cycle	£9,295.00	£11,620.64	£9,295.52	£9,295.00	
Administration cost					
Cycle 1	£330.71	£372.00	£330.71	£330.71	
Cycle 2	£91.50	£248.00	£91.50	£91.50	
Annual cycle	£0.00	£806.00	£0.00	£0.00	
Monitoring cost (including tests)					
Cycle 1	£182.28	£90.78	£182.28	£182.28	
Cycle 2	£72.30	£40.34	£72.30	£72.30	
Annual cycle	£313.30	£174.81	£313.30	£313.30	
Total					
Cycle 1	£2,658.00	£5,826.15	£2,658.12	£2,658.00	
Cycle 2	£2,308.81	£3,863.92	£2,308.93	£2,308.81	
Annual cycle	£9,608.30	£12,601.45	£9,608.82	£9,608.30	

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

The health state costs were estimated as a function of HAQ and PASI

Costs as a function of HAQ

The ongoing costs were estimated as a function of HAQ. They were derived from the Kobelt et al 2002 study. In common with the Bravo Vergel model, patients remaining on treatment

only incur 85% of these costs while those withdrawing from treatment and moving on to palliative care incur 100% of these costs. These have been updated for inflation by applying the index. The resultant costs as a function of PASI are displayed in Table B22.

Table B29: Cost as a function of HAQ

	Mean	SE
constant	£1325	£466
slope	£401	£259

Within the probabilistic modelling these have been implemented as normal distributions subject to the constraint of the value being non negative i.e. a minimum value of £0 being applied. The model also allows for restricting the slope of the function to being non-negative, which has been assumed for the base case of the probabilistic modelling.

Costs as a function of PASI

A literature search was conducted in order to identify any sources in the literature which related PASI scores with resource use which would be in addition to that associated with rheumatology component. As outlined in Appendix 16, while some papers were identified that explored resource use and PASI, none of the estimates provided the required information. Therefore, a separate data collection exercise was initiated and a short resource use questionnaire as outlined in Appendix 16 was administered to 35 dermatologists. The responses of 22 dermatologists who responded were used to estimate the resource use costs including the inpatient, consultant led outpatient, nurse led outpatient and phototherapy costs associated with different PASI scores. The resultant analysis indicated an additional cost of £167 per PASI point increase in additon to the cost associated with the HAQ score change. However, this estimate of £167 is driven by the estimated additional costs of phototherapy of £275. Excluding phototherapy costs would result in a cost of only £53 per PASI point increase. The uncertainty around the use of phototherapy was further explored within sensitivity analyses.

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

No additional cost for adverse events was included in the analysis. It was assumed that patients suffering from serious adverse events would withdraw from treatment and the cost of minor adverse events was included in the hospitalisation costs.

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No additional miscellaneous costs were considered.

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The uncertainty around structural assumptions has been investigated. Following assumptions were changed in Scenario analysis.

Rebound equal to natural history HAQ progression:

The base case assumed rebound equal to gain. Therefore, patients withdrawing from treatment were assumed to return to baseline HAQ score and have natural history progression thereafter. In this scenario, it was assumed that patients withdrawing from treatment would return to HAQ score equal to natural history of primary non-responders.

This is a pessimistic assumption as it assumes that patients lose all the benefit of TNF-α inhibitor immediately following treatment withdrawal.

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Following variables were subjected to deterministic sensitivity analysis.

Table B30: Variables used in the sensitivity analyses

Variable	Base case	Parameter change	Rationale
Time horizon	40 years	5 years / 20 years	Shorter time horizon as limited long term data available
Discount rate	3.5%	0 - 6%	NICE reference case
Females	40%	0 – 100%	
Age	47 yrs	30 – 60 yrs	
Mean weight	[redacted]	60 - 80 kg	
Baseline HAQ score	[redacted]	± 50% change	
Baseline PASI score	[redacted]	± 50% change	
Placebo HAQ responses	Common	Individual from TNF-α inhibitor trials	
Withdrawal rates	16.5%	11.14%	Bravo Vergel Model
Psoriasis Costs	Included	Excluded	A proportion of patients do not have significant psoriasis
Phototherapy costs	Included	Excluded	Some psoriasis patients do not require phototherapy
QoL data	Rodgers et al.	Algorithm based on golimumab trial data	
Golimumab annual acquisition cost	£9,294.96	± 20%	

HAQ change for responders	Continued up to 3 cycles	No HAQ benefit beyond the first cycle	Consistent with the previous NICE appraisals
HAQ change for non-responders	Trial based HAQ benefit in cycle 1	No HAQ benefit for non-responders	
PASI change for non-responders	Trial based PASI benefit in cycle 1	No PASI benefit for non-responders	
Natural history HAQ progression	0.0719	0.1018	Current evidence synthesis (Placebo HAQ change for non-responders)
PsA management cost on TNF-α inhibitors	85% of costs for patients on palliative care	± 15%	

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was undertaken with 10,000 simulations. The details of the distributions and their sources have been outlined in section 6.3.6.

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.

- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table B31: Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
PsARC response		
• Golimumab 50mg @ 14 weeks	73% (GO-REVEAL)	73.3%
• Adalimumab eow @ 12 weeks	62% (ADEPT)	54.8%
	51% (Genovese 2007)	54.8%
• Etanercept @ 12 weeks	87% (Mease 2000)	74.8%
	72% (Mease 2004)	74.8%
• Infliximab @ 16 weeks	75% (IMPACT)	76.8%§
• Infliximab @ 14 weeks	77% (IMPACT2)	76.8%§
Patients still on treatment at the end of 2nd annual model cycle (128 weeks)		
• Adalimumab @ 144 weeks	84.5%# (Mease 2009)	79.5%§§
• Infliximab @ 98 weeks	70.4%# (Antoni 2008)	80.0%§§
• Etanercept @ 96 weeks	73.8%# (Mease 2006)	79.8%§§

eow – Every other week; §The response @ 12 weeks; #Of the patients who completed first 24 weeks and then entered the open label trial; §§End of 2nd annual model cycle is 128 weeks

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The markov traces are available in the MS Excel model accompanying this submission.

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The markov traces are available in the MS Excel model accompanying this submission.

6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

The model calculates the QALYs based on two pivotal intermediate outcomes; HAQ and PASI using an algorithm outlined in section 6.4.3. Therefore, it has not been possible to present disaggregated results.

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Not applicable

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table B32: Base-case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Palliation (QALYs)	ICER (£) incremental vs TNF-α inhibitors (QALYs)
Palliation	£62,224	5.44				
Adalimumab	£86,410	6.97	£24,186	1.53	£15,820	£15,820
Golimumab	£94,151	7.34	£7,740	0.37	£16,811	£20,901
Etanercept	£94,578	7.69	£428	0.35	£14,402	£1,232
Infliximab	£100,691	7.69	£6,112	0.00	£17,149	Dominated

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

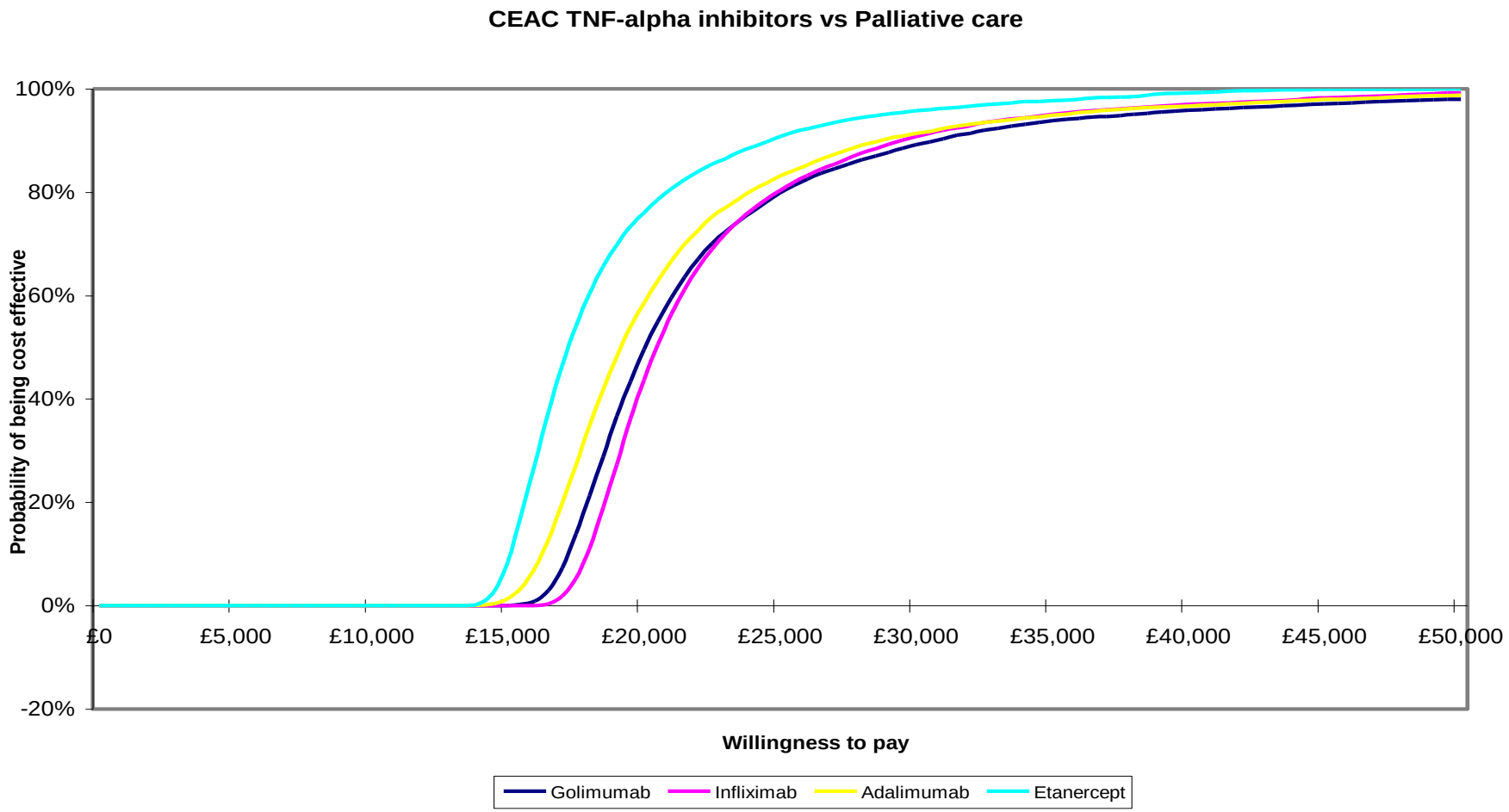
Table B33: Results of deterministic sensitivity analysis

Variable	Base case	Parameter change	ICER vs Palliative care
Time horizon	40 years	5 years 20 years	£41,799 £20,446
Discount rate	3.5%	0% costs & 0% outcomes 0% costs & 3.5% outcomes 3.5% costs & 0% outcomes	£12,396 £39,978 Dominant
Females	40%	All males All females	£17,095 £16,367
Age	47 yrs	30 yrs 60 yrs	£15,478 £20,348
Baseline HAQ score	[redacted]	+ 50% change - 50% change	£18,802 £16,014
Baseline PASI score	[redacted]	+ 50% change - 50% change	£16,939 £16,807
Placebo HAQ responses	Common	Individual from TNF-α inhibitor trials	£16,864
Withdrawal rates	16.5%	11.14%	£17,311
Psoriasis Costs	Included	Excluded	£18,043
Phototherapy costs	Included	Excluded	£17,652
QoL data	Rodgers et al.	Algorithm based on previous NICE appraisal (Bravo Vergel, 2007)	£19,218
Golimumab annual acquisition cost	£9,294.96	+ 20% change - 20% change	£20,617 £13,004
HAQ change for responders	Continued up to 3 cycles	No HAQ benefit beyond the first cycle	£18,642
HAQ change for non-responders	Trial based HAQ benefit	No HAQ benefit for non-responders	£16,819

	in cycle 1		
PASI change for non-responders	Trial based PASI benefit in cycle 1	No PASI benefit for non-responders	£16,839
Natural history HAQ progression	0.0719	0.1018	£14,825
PsA management cost on TNF-α inhibitors	85% of costs for patients on palliative care	+ 15% change - 15% change	£17,317 £16,305

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Figure B12: CEAC of TNF-α inhibitors compared to palliative care



6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table B34: Results of the structural sensitivity analysis (rebound equal to natural history)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Palliation	ICER (£) incremental vs TNF-α inhibitors
Palliation	£62,224	5.44				
Adalimumab	£87,533	6.20	£25,309	0.76	£33,514	£33,514
Golimumab	£95,577	6.36	£8,044	0.16	£36,402	£49,942
Etanercept	£96,028	6.69	£451	0.33	£27,090	£1,359
Infliximab	£102,173	6.67	£6,145	-0.03	£32,693	Dominated

6.7.10 What were the main findings of each of the sensitivity analyses?

The structural sensitivity analysis had a significant impact on the results. Changing the assumption from 'rebound equal to gain' to 'rebound equal to natural history' significantly increased the ICERs. In the previous appraisals of TNF-α inhibitors, the committee has acknowledged that the true rebound effect would lie somewhere between gain and natural history and in absence of any evidence have accepted 'rebound equal to gain' as the base case assumption.

One way sensitivity analyses identified the key variables affecting ICERs. Reducing the model time horizon had a significant impact with increased ICERs for shorter time horizons. Changing the other parameters such as age, baseline HAQ & PASI scores, withdrawal rates, QoL algorithm, and natural history HAQ progression had less significant impact on ICERs.

The probabilistic sensitivity analysis suggested that golimumab was a cost effective treatment alternative with the probability of it being cost effective to be 50% and 89% compared to palliative care at a willingness to pay of £20,000 per QALY and £30,000 per QALY, respectively. The ICER for golimumab compared to palliative care also was comparable to other TNF-α inhibitors.

6.7.11 What are the key drivers of the cost-effectiveness results?

The key drivers for cost effectiveness analyses were PsARC response rates and the magnitude of HAQ and PASI change for PsARC responders. Among the TNF-α inhibitors, both infliximab and etanercept showed numerically higher PsARC response rates and higher magnitude of HAQ response. It is however important to note that the clinical trials of infliximab and etanercept included patients with more active and longer duration of disease (section 5.3.4) compared with golimumab and hence the magnitude of treatment effect observed in indirect comparison thus resulting in significant impact on cost effectiveness results should be viewed with caution.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

We validated our methods and results with those available in literature. Our model was based on the model by Bravo Vergel and colleagues which has been used in a previous NICE appraisal. We also compared our model with an ongoing NICE appraisal which has used analysis by Rodgers and colleagues. Our model and analysis closely resembles both these models and thus conforms to the analyses used in previous NICE appraisals. Some variations exist such as method of elicitation of PASI response wherein we estimated PASI response status on a continuous scale instead of PASI50, PASI75 and PASI90 cut-off points used in analysis by Rodgers and others. However we do not anticipate it having a significant impact. This assessment has also been confirmed by a similar comparison by Rodgers and colleagues in the assessment report for the ongoing PsA appraisal.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.

- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

The base case assumed a proportion of patients (66%) having significant psoriatic component BSA ≥ 3%. This proportion was estimated from the clinical trials (GO-REVEAL, IMPACT and IMPACT2) of infliximab and golimumab to which we had access.

However the remaining patients (34%) would predominantly have rheumatic disease. The impact of TNF-α inhibitors on these patients was estimated in the subgroup analysis. For these patients only the impact upon their rheumatic component was modelled, estimated using HAQ. No impact on the dermatological component on the quality of life was assumed and therefore the PASI impact on utility was not modelled.

Conversely, a separate subgroup of patients with significant psoriasis (66% in base case) also was modelled in the subgroup analysis.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

The subgroups have been defined in section 6.9.1.

6.9.3 Please describe how the statistical analysis was undertaken.

No separate indirect comparison was undertaken. The primary reason was unavailability of subgroup data for other TNF-α inhibitors. The results of the base case indirect comparison were assumed to be applicable to both the above subgroups.

The model structure and assumptions were identical to those in the base case. In the subgroup analysis

- Patients with rheumatic condition only: For these patients no impact on psoriatic component was assumed. Therefore, no costs and benefits related to psoriasis were included in the calculations.

- Patients with psoriatic and rheumatic conditions: For these patients impact on both rheumatic and psoriatic component was assumed. Costs and benefits related to psoriasis as well as arthritis were included in the analysis.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

Table B35: Results of the subgroup analysis (rheumatic patients only)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Palliation	ICER (£) incremental vs TNF-α inhibitors
Palliation	£40,275	5.85				
Adalimumab	£66,377	7.35	£26,102	1.50	£17,405	£17,405
Golimumab	£74,542	7.71	£8,165	0.36	£18,378	£22,378
Etanercept	£74,767	8.06	£225	0.35	£15,557	£638
Infliximab	£81,990	8.04	£7,223	-0.03	£19,069	Dominated

Table B36: Results of the subgroup analysis (rheumatic patients with significant psoriasis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Palliation	ICER (£) incremental vs TNF-α inhibitors
Palliation	£70,342	5.30				
Adalimumab	£93,820	6.83	£23,478	1.54	£15,249	£15,249
Golimumab	£101,403	7.21	£7,583	0.37	£16,245	£20,366
Etanercept	£101,906	7.55	£503	0.35	£13,982	£1,456
Infliximab	£107,608	7.56	£5,702	0.01	£16,462	£912,114

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

None of the obvious subgroups were excluded.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results from this economic submission are consistent with the results presented in the assessment report for the recent NICE appraisal for TNF-α inhibitors in PsA (Rodgers et al, 2009). Compared to other published studies in literature (Bravo Vergel, 2007; Bansback 2006; Olivieri, 2008), our results indicate lower ICERs for TNF-α inhibitors compared to palliation. We believe this can be attributable to the incorporation of psoriatic benefit into the analysis which none of the previous studies, with the exception of Rodgers et al, had included. Our model closely resembles that used by Bravo Vergel and Rodgers, both of which were used in previous NICE appraisals.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

The economic evaluation covers all the licensed patient populations for golimumab in PsA. Similar to the existing TNF-α inhibitors, golimumab may potentially be used as a 2nd line treatment option for patients already exposed to TNF-α inhibitors. However, golimumab has no specific licence in this population and do not have any evidence of 2nd line use. Therefore, this subgroup was intentionally excluded from this submission.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The primary strength of this analysis is that it is based on the previous work in this area. Our model was based on models used in Bravo Vergel and Rodgers analyses, both of which

have been used in previous NICE appraisals and formed the basis of existing NICE recommendations.

The analyses have several limitations. A number of parameters such as QoL algorithm, withdrawal rates, resource use estimates were derived from literature and were based on non-randomised evidence. There was no evidence available for some of the structural assumptions such as rebound assumptions. In addition, some of the data were gathered based on expert opinion. This adds significant uncertainly to the findings but can only be attributed to the significant limitations in the available evidence.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The number of patients eligible to receive treatment has been outlined in the table below.

Table B37: Patients eligible to receive golimumab

Population	2010	2011	2012	2013	2014	2015
UK	55,219,919	55,608,985	56,000,816	56,395,430	56,792,847	57,193,089
England	52,203,692	52,579,558	52,958,131	53,339,430	53,723,474	54,110,283
Wales	3,016,227	3,029,427	3,042,684	3,056,000	3,069,374	3,082,806
Prevalence	82,830	83,413	84,001	84,593	85,189	85,790
Patients currently receiving treatment with biologics	1,988	2,002	2,016	2,030	2,045	2,059
New patients	9,227	9,292	9,358	9,424	9,490	9,557
New patients eligible for biologics	221	223	225	226	228	229
Total patients receiving treatment	**2,209**	**2,225**	**2,241**	**2,256**	**2,272**	**2,288**

7.2 *What assumption(s) were made about current treatment options and uptake of technologies?*

In line with the EMEA licensed approval received 1st October 2009, golimumab is assumed to be prescribed to DMARD experienced PsA patients. Comparators within the budget impact model included TNF-α inhibitors who have:

- Market authorisation within England and Wales for treatment of PsA, and
- Positive NICE guidance for use within DMARD experienced PsA patients.

Based on these criteria, the following comparators were included within the budget impact model:

- Adalimumab
- Etanercept
- Infliximab

Golimumab is primarily assumed to replace subcutaneous biologics.

For calculation of eligible patients, following assumptions have been used.

- Prevalence of PsA in UK – 0.15%
- Incidence of PsA in UK – 0.017%
- 2.4% of all PsA patients are eligible for treatment
- PsARC response rates at 12 weeks are 73.4% for golimumab, 76.8% for infliximab, 74.8% for etanercept and 54.8% for adalimumab
- Annual withdrawal rate is 11% for all TNF-α inhibitors

7.3 *What assumption(s) were made about market share (when relevant)?*

The estimated market shares are displayed in Table below

Table B38: Estimated market shares of current and future treatments

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

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Apart from the cost of acquiring golimumab, no costs in addition to the other subcutaneous TNF-α inhibitors are expected.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The unit costs assumed is identical to that used in the economic analysis.

7.6 Were there any estimates of resource savings? If so, what were they?

The estimated resource savings are listed below.

Table B39: Estimated resource savings due to use of golimumab

	2011	2012	2013	2014	2015
Golimumab	-£1,181	-£3,958	-£8,565	-£15,333	-£23,886
Infliximab	-£55,439	-£53,151	-£49,893	-£46,030	-£42,088
Etanercept	-£231,527	-£227,826	-£222,899	-£216,898	-£209,996
Adalimumab	-£158,877	-£160,286	-£161,472	-£161,845	-£161,335
Total	**-£447,024**	**-£445,221**	**-£442,829**	**-£440,106**	**-£437,306**

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The total costs to the NHS are listed below.

Table B40: Total costs following recommendation of golimumab in PsA

	2011	2012	2013	2014	2015
Golimumab	£46,873	£147,998	£310,115	£544,648	£834,344
Infliximab	£1,326,355	£1,259,500	£1,171,206	£1,072,099	£976,531
Etanercept	£5,906,460	£5,803,408	£5,671,170	£5,512,187	£5,331,122
Adalimumab	£4,587,318	£4,630,630	£4,662,948	£4,667,231	£4,645,569
Total	**£11,867,005**	**£11,841,535**	**£11,815,439**	**£11,796,166**	**£11,787,566**

Assuming the savings listed in section 7.6, the net budget impact to NHS is outlined below.

Table B41: Estimated budget impact of golimumab

	2011	2012	2013	2014	2015
Golimumab	£45,628	£143,998	£301,652	£529,698	£811,323
Infliximab	£1,291,064	£1,225,769	£1,139,636	£1,043,045	£949,996
Etanercept	£5,738,188	£5,637,990	£5,509,457	£5,354,948	£5,178,994
Adalimumab	£4,457,688	£4,499,799	£4,531,186	£4,535,289	£4,514,174
Total	**£11,532,567**	**£11,507,556**	**£11,481,932**	**£11,462,980**	**£11,454,487**

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Patient-focused aspects of golimumab have been identified as a potential resource savings as they may assist patients in achieving greater compliance, which in turn will improve treatment outcomes, reduce drug wastage, and reduce payer costs. The following features of golimumab treatment are difficult to quantify at this early stage:

Convenient, monthly dosing

Golimumab is self-administered by patients via a once-monthly subcutaneous injection. The auto injector has been specifically developed in response to patient needs; its features

include an ergonomically designed barrel for easy handling, a large side button for ease of activation that does not require thumb strength, a safety sleeve to avoid accidental firing, a large observation window, audible clicks for initiation and completion of golimumab administration, and a needle which auto-injects and auto-retracts whilst remaining out of sight of patients.

Reduction in injection site reactions

Golimumab differs in its molecular make-up and compound formulation compared to other TNFα inhibitors. The buffered solution (without citric acid monohydrate & low injection volume 0.5 ml) correlates with a lower incidence of injection site reactions.

Patient Support Programme

Schering-Plough will provide a golimumab patient support programme, designed to encourage patients to stay on their treatment as directed, and remind them when their next monthly treatment is due. It will also assist in managing treatment expectations, and provide simple and relevant information and timely practical help so that patients feel comfortable with self-injection.

8 References

Please use a recognised referencing style, such as Harvard or Vancouver.

Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of psoriatic arthritis: a systematic review. *J Rheumatol.* 2008;35:1354-1358.

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RAISE study

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9 Appendices

9.1 Appendix 1

9.1.1 SPC/IFU, scientific discussion or drafts.

SPC provided as a separate document along with the submission.

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The databases searched included Medline, Embase, Medline (R) In-Process and the Cochrane Library.

9.2.2 The date on which the search was conducted.

Searches were conducted on 25th January 2010.

9.2.3 The date span of the search.

All the searches were conducted as an update of the search strategy used by Rodgers and colleagues except for golimumab searches were conducted for the entire period.

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategies used for the RCT searches are outlined below.

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

1 randomized controlled trial.pt. (279847)
2 controlled clinical trial.pt. (79924)
3 randomized.ab. (196338)
4 placebo.ab. (117755)
5 drug therapy.fs. (1343325)
6 randomly.ab. (145366)
7 trial.ab. (203152)
8 groups.ab. (977161)

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (2518054)

10 (animals not (humans and animals)).sh. (3333697)

11 ((randomized controlled trial or controlled clinical trial or randomized or placebo or drug therapy or randomly or trial or groups) not (animals not (humans and animals))).af. (1546933)

12 Arthritis, Psoriatic/ (2352)

13 (psoria$ adj2 (arthrit$ or arthropath$)).ab,ti. (3882)

14 12 or 13 (4451)

15 (etanercept or enbrel).ab,rn,ti. (2436)

16 (infliximab or remicade).ab,rn,ti. (5372)

17 (adalimumab or humira).ab,rn,ti. (1451)

18 15 or 16 or 17 (7287)

19 11 and 14 and 18 (238)

20 (golimumab or simponi).ab,rn,ti. (52)

21 11 and 14 and 20 (5)

22 (200906$ or 200907$ or 200908$ or 200909$ or 200910$ or 200911$ or 200912$ or 2010$).ed. (476080)

23 19 and 22 (12)

24 21 or 23 (17)

25 from 24 keep 3,10,14,16 (4)

26 from 24 keep 11-17 (7)

EMBASE <1988 to 2010 Week 03>

1 psoriatic arthritis/ (4152)

2 (psoria$ adj2 (arthrit$ or arthropath$)).ti,ab. (3059)

3 1 or 2 (4797)

4 *Etanercept/ (2176)

5 (etanercept or enbrel).ti,ab. (2443)

6 *Infliximab/ (3792)

7 (infliximab or remicade).ti,ab. (4406)

8 *Adalimumab/ (1054)

9 (Adalimumab or humira).ti,ab. (1142)

10 (2009$ or 2010$).em. (692611)

11 4 or 5 or 6 or 7 or 8 or 9 (7293)

12 10 and 11 (1149)

13 3 and 12 (114)

14 random$.tw. (390544)

15 clinical trial$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (617969)

16 exp health care quality/ (860177)
17 14 or 15 or 16 (1489427)
18 13 and 17 (64)
19 *Golimumab/ (29)
20 (golimumab or simponi).ti,ab. (39)
21 19 or 20 (46)
22 3 and 18 and 21 (17)

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

No additional searches were conducted.

9.2.6 The inclusion and exclusion criteria.

Following inclusion and exclusion criteria were used.

Study design

- Randomised controlled trials (RCTs) (including any open-label extensions of these RCTs)
- Non randomised trials only when the information was not available in RCTs

Interventions

- Etanercept
- Infliximab
- Adalimumab
- Golimumab
- Palliative care which included NSAIDs and DMARDs

Participants

Active and progressive PsA with an inadequate response to previous standard therapy (including at least one DMARD).

Outcomes

- PsARC
- PASI

- HAQ
- Quality of life assessments including DLQI, EQ-5D, SF-36 etc.

9.2.7 The data abstraction strategy.

The strategy outlined in Rodgers et al. was adopted. Data on study and participant characteristics, efficacy outcomes, adverse effects, costs to the health service, and cost-effectiveness were extracted. Baseline data were extracted where reported. Data were extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus, or consulting a third reviewer if necessary. Data from studies with multiple publications were extracted and reported as a single study. In the rare case of minor discrepancies for the same data between published and unpublished data, data from published sources were used except in case of golimumab where data from the CSR was preferred.

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

A suggested format for the quality assessment of RCT(s) is shown below.

GO REVEAL		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate sample size Number randomised was stated True randomisation carried out Subjects were randomized in a 1:1.3:1.3 ratios to 1 of 3 treatment groups: placebo, golimumab 50 mg, and golimumab 100 mg. Relatively even treatment balance within sites was ensured, within baseline MTX usage and within the study overall, using an adaptive stratified randomization design.	Yes
Was the concealment of treatment allocation adequate?	Randomized treatment allocation was done using a centralized IVRS.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Demographic characteristics of subjects at baseline were generally well balanced across treatment groups: • majority of subjects were men (60.2%) • most subjects were Caucasian (97.0%) • median age was 47.0 years • median weight was 84.0 kg	Yes

Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Randomization files containing treatment assignments for individual subjects were maintained in limited-access directories within the electronic data filing system at the central randomization centre. Personnel having contact with study sites, including the medical monitor, remained blinded to the treatment assignment of individual subjects until the 24-week database lock. Furthermore, all site monitors, site personnel, and subjects remained blinded to treatment assignment until the last subject completes Week 52 evaluations and the database is locked.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	> 80% patients were part of follow-up assessment	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No such reference in the publication	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

9.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

No additional data searches were conducted. This information was expected to be available from the search strategy in Appendix 3 (section 9.3).

9.4.2 The date on which the search was conducted.

Identical to section 9.2.2.

9.4.3 The date span of the search.

Identical to section 9.2.3.

9.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Identical to section 9.2.4.

9.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

9.4.6 The inclusion and exclusion criteria.

Identical to section 9.2.6.

9.4.7 The data abstraction strategy.

Identical to section 9.2.7.

9.5 *Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)*

9.5.1 The quality assessment of comparator RCT(s) is shown below.

ADEPT		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate sample size Number randomised was stated True randomisation carried out	Yes
Was the concealment of treatment allocation adequate?	Not reported in trial publications	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The demographic characteristics and measures of disease severity in the patients at baseline were comparable between treatment groups. The mean age of all study patients was 49 years; slightly more than half (55.6%) were men. Overall, the duration of psoriasis in patients at entry was about twice as long as the duration of PsA. The subtypes of PsA reported and the percentage of patients with any spondylitis were similar in each group. Patients had moderately or severely active arthritis, and the mean numbers of tender and swollen joints were 24.9 and 14.3, respectively. The degree of psoriasis was similar among those patients with > 3% BSA skin involvement in both groups. Approximately half (50.5%) of the patients were reported to be taking MTX at baseline.	Yes

Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Not reported	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	≥80% patients in follow-up assessment	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No such reference int the publication	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Genovese 2007		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate sample size Number randomised was stated True randomisation carried out	Yes
Was the concealment of treatment allocation adequate?	Not reported in the trial publications.	Not Clear

Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline demographic data, medication usage, and disease severity characteristics were similar between treatment groups and representative of long-standing, predominantly polyarticular PsA.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Not reported in the trial publications.	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	≥ 80% patients in follow-up assessment	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No such reference in the publications	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Mease 2000		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate sample size Number randomised was stated True randomisation carried out	Yes

Was the concealment of treatment allocation adequate?	Block randomisation was used; within each group of four patients enrolled, two were assigned at random to the placebo group and two to etanercept group. Etanercept was supplied as a sterile, lyophilised powder in vials containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1•2 mg tromethamine per vial. Placebo was identically supplied and formulated except that it contained no etanercept.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Clinical and laboratory assessments done at screening and baseline consisted of physical examination, vital signs, measures of disease activity (arthritis and psoriasis), concomitant medications, laboratory studies (haematology, serum chemistry, urinalysis), and monitoring of adverse events. Arthritis disease-activity measures included assessments of 78 joints for tenderness and 76 joints for swelling (graded 0–3), patient's and physician's global assessments (on a 0–5 Likert scale), patient's assessment of pain, patient's assessment of disability as indicated by responses on the Health Assessment Questionnaire (HAQ), erythrocyte sedimentation rate, and serum concentration of C-reactive protein.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Placebo was identically supplied and formulated except that it contained no etanercept.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	> 80% patients were part of follow-up assessment	No

Is there any evidence to suggest that the authors measured more outcomes than they reported?	No such reference in the study publications.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Mease 2004		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate sample size Number randomised was stated True randomisation carried out	Yes
Was the concealment of treatment allocation adequate?	Study drug administration was done by self-administered subcutaneous injection. Etanercept was supplied to patients in syringes, each containing the contents of 1 reconstituted vial of etanercept or otherwise identically furnished placebo.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline characteristics demonstrate that the trial populations are similar and are likely to be representative of a population with PsA requiring DMARD or biologic therapy.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Eligible patients were randomly assigned to receive placebo or etanercept at a dosage of 25 mg subcutaneously twice weekly in an initial 24-week blinded phase. Patients continued to receive blind-labeled therapy in maintenance phase until all patients had completed the 24-week blinded phase and the database was locked.	Yes

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	> 80% patients were part of follow-up assessment	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No such reference in the study publications.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

IMPACT		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate sample size Number randomised was stated True randomisation carried out	Yes
Was the concealment of treatment allocation adequate?	Infliximab was supplied in 20-ml vials containing 100 mg of the lyophilized concentrate, while placebo was identically formulated but did not contain infliximab. Infusions were administered over 2 hours by blinded personnel using an infusion set through a peripheral venous access site.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The trial populations are broadly similar, likely to be representative of a population with quite severe PsA requiring further DMARD or biologic therapy and that the treatment and placebo groups were well balanced.	Yes

Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Based on reference in the trial publication	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	≥ 80% patients were part of follow-up assessment	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	None such reported in the trial publication	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

IMPACT 2		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate sample size Number randomised was stated True randomisation carried out	Yes
Was the concealment of treatment allocation adequate?	The study drug was prepared by an unblinded research pharmacist, administered by blinded investigators. Infliximab was supplied in single-use 20 ml vials containing 100 mg of the lyophilised powder, placebo was identically formulated except that it did not contain infliximab.	Yes

Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The trial populations are broadly similar, likely to be representative of a population with quite severe PsA requiring further DMARD or biologic therapy and that the treatment and placebo groups were well balanced.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	To maintain the blinding, patients randomised to infliximab who had 10% improvement received additional placebo infusions at weeks 16 and 18. Patients who were assigned early escape (< 10% improvement from baseline in both swollen and tender joint counts) using a blinded procedure were part of an interactive patient allocation algorithm so that the option or early escape was not at the discretion of the patient or the physician.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	≥ 80% patients were part of follow-up assessment	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No such reference in the study publications	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

The following information should be provided.

9.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

No additional data searches were conducted. This information was expected to be available from the search strategy in Appendix 3 (section 9.3).

9.6.2 The date on which the search was conducted.

Identical to section 9.2.2.

9.6.3 The date span of the search.

Identical to section 9.2.3.

9.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Identical to section 9.2.4.

9.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

9.6.6 The inclusion and exclusion criteria.

Identical to section 9.2.6.

9.6.7 The data abstraction strategy.

Identical to section 9.2.7.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

9.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

No non-RCT evidence was used.

9.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

The following information should be provided.

9.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The databases searched included Medline, Embase, Medline (R) In-Process and the Cochrane Library.

9.8.2 The date on which the search was conducted.

Searches were conducted on 25th January 2010.

9.8.3 The date span of the search.

All the searches were conducted as an update of the search strategy used by Rodgers and colleagues except for golimumab searches were conducted for the entire period.

9.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategies used to identify adverse events are outlined below.

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

1 (etanercept or enbrel).ab,ti. (2439)
2 (infliximab or remicade).ab,ti. (4327)
3 (adalimumab or humira).ab,ti. (1135)
4 (gomimumab or simponi).ab,ti. (2)
5 1 or 2 or 3 or 4 (6191)
6 Safety/ (27578)
7 (safe or safety).ab,ti. (296803)
8 (side effect or side effects).ab,ti. (136384)
9 emergency treatment.ab,ti. (2773)

10 undesirable effect$.ab,ti. (1538)
11 tolerability.ab,ti. (21310)
12 Drug Toxicity/ (3176)
13 toxicity.ab,ti. (183499)
14 Adverse Drug Reaction Reporting Systems/ (4034)
15 adrs.ab,ti. (1095)
16 (adverse adj3 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ab,ti. (160529)
17 (undesire$ adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ab,ti. (1034)
18 Drug Hypersensitivity/ (17890)
19 (hypersensit$ or hyper sensit$).ab,ti. (46875)
20 harm$.ab,ti. (64460)
21 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (809777)
22 5 and 21 (1923)
23 exp infection/ci [Chemically induced] (2951)
24 exp urinary tract infections/ci [Chemically induced] (62)
25 exp respiratory tract infections/ci [Chemically induced] (3720)
26 exp skin diseases, infectious/ci [Chemically induced] (458)
27 exp bone diseases, infectious/ci [Chemically induced] (137)
28 exp arthritis, infectious/ci [Chemically induced] (57)
29 exp neoplasms/ci [Chemically induced] (50719)
30 exp tuberculosis/ci [Chemically induced] (323)
31 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (57199)
32 22 and 31 (67)
33 (2009$ or 2010$).ed. (799061)
34 32 and 33 (18)
35 from 34 keep 2,11 (2)
36 from 35 keep 1-2 (2)
37 from 36 keep 1-2 (2)

EMBASE <1988 to 2010 Week 03>

1 (etanercept or enbrel).ab,ti. (2443)
2 (infliximab or remicade).ab,ti. (4406)
3 (adalimumab or humira).ab,ti. (1142)
4 (golimumab or simponi).ti,ab. (39)
5 1 or 2 or 3 or 4 (6303)
6 (safe or safety).ti,ab. (242470)
7 side effect$.ti,ab. (106920)

8 emergency treatment.ti,ab. (1439)
9 undesirable effect$.ti,ab. (1269)
10 toxicity.ti,ab. (147110)
11 adrs.ti,ab. (1223)
12 (adverse adj3 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab. (142027)
13 safety/ or drug safety/ (190216)
14 side effect/ (99926)
15 adverse drug reaction/ (7122)
16 drug tolerability/ (58872)
17 toxicity/ or drug toxicity/ (21491)
18 drug surveillance program$/ (7548)
19 adverse outcome/ (2097)
20 hypersensit$.ti,ab. (29136)
21 harm$.ti,ab. (44607)
22 drug hypersensitivity/ (21245)
23 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (771311)
24 5 and 23 (2793)
25 etanercept/ae, to [adverse drug reaction, drug toxicity] (2375)
26 infliximab/ae, to [adverse drug reaction, drug toxicity] (3859)
27 adalimumab/ae, to [adverse drug reaction, drug toxicity] (1283)
28 golimumab/ae, to [adverse drug reaction, drug toxicity] (40)
29 25 or 26 or 27 or 28 (5104)
30 24 or 29 (5888)
31 Urinary tract infection/si [side effects] (2320)
32 Lower respiratory tract infection/si [side effects] (172)
33 skin infection/si [side effects] (547)
34 bone infection/si [side effects] (30)
35 infectious arthritis/si [side effects] (64)
36 neoplasm/si [side effects] (549)
37 tuberculosis/si [side effects] (1406)
38 31 or 32 or 33 or 34 or 35 or 36 or 37 (4644)
39 30 and 38 (1230)
40 (2009$ or 2010$).dp. (104802)
41 39 and 40 (36)
42 from 41 keep 1-36 (36)
43 from 42 keep 1-36 (36)

9.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

9.8.6 The inclusion and exclusion criteria.

Following inclusion and exclusion criteria were used.

Study design

- Randomised controlled trials (RCTs) (including any open-label extensions of these RCTs)
- Non randomised trials only when the information was not available in RCTs

Interventions

- Etanercept
- Infliximab
- Adalimumab
- Golimumab
- Palliative care which included NSAIDs and DMARDs

Participants

Active and progressive PsA with an inadequate response to previous standard therapy (including at least one DMARD).

Outcomes

- Malignancies
- Severe infections (i.e. those that require IV antibiotic therapy and/or hospitalisation or cause death)
- Reactivation of latent tuberculosis.

9.8.7 The data abstraction strategy.

Identical to section 9.2.7.

9.9 Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

9.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

No studies specific to the adverse events of TNF-α inhibitors were identified.

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The databases searched included Medline, Embase, Medline (R) In-process and NHS EED. Due to unavailability of access EconLIT was not searched.

9.10.2 The date on which the search was conducted.

The search was conducted on 14th April 2010.

9.10.3 The date span of the search.

The searches spanned from beginning of 2004 until 14th April 2010.

9.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>		
#	**Search Statement**	**Results**
1	Arthritis, Psoriatic/	2467
2	(psoria$ adj2 (arthrit$ or arthropath$)).ab,ti.	4004
3	1 or 2	4591
4	(etanercept or enbrel).ab,rn,ti.	2526
5	(infliximab or remicade).ab,rn,ti.	5571
6	(adalimumab or humira).ab,rn,ti.	1550
7	(golimumab or simponi).ab,rn,ti.	60
8	Economics/	25769

9	exp "Costs and cost analysis"/	148742
10	"Value of Life"/	5111
11	(econom$ or cost$ or price$ or pricing or pharmacoeconom$).ab,ti.	354220
12	(expenditure$ not energy).ab,ti.	13659
13	(value adj1 money).ab,ti.	17
14	budget$.ab,ti.	14157
15	(letter or editorial or historical article).pt.	1199962
16	4 or 5 or 6 or 7	7610
17	(2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$).ed.	4738739
18	3 and 16 and 17	504
19	8 or 9 or 10 or 11 or 12 or 13 or 14	449781
20	19 not 15	427193
21	(animals not (animals and humans)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	3354227
22	20 not 21	397850
23	18 and 22	29

EMBASE <1988 to 2010 Week 14>		
#	**Search Statement**	**Results**
1	Arthritis, Psoriatic/	4339
2	(psoria$ adj2 (arthrit$ or arthropath$)).ab,ti.	3173
3	1 or 2	5007
4	(etanercept or enbrel).ab,rn,ti.	2570
5	(infliximab or remicade).ab,rn,ti.	4630
6	(adalimumab or humira).ab,rn,ti.	1232
7	(golimumab or simponi).ab,rn,ti.	48
8	Economics/	7905
9	exp "Costs and cost analysis"/	131525
10	"Value of Life"/	34157
11	(econom$ or cost$ or price$ or pricing or pharmacoeconom$).ab,ti.	247001
12	(expenditure$ not energy).ab,ti.	9471
13	(value adj1 money).ab,ti.	6
14	budget$.ab,ti.	8256

15	(letter or editorial or historical article).pt.	699967
16	4 or 5 or 6 or 7	6640
17	8 or 9 or 10 or 11 or 12 or 13 or 14	346726
18	17 not 15	320627
19	(animals not (animals and humans)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	251697
20	18 not 19	316962
21	(2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$).em.	3865300
22	3 and 16 and 21	608
23	20 and 22	57
24	from 23 keep 1-57	57

NHS Economic Evaluation Database (NHS EED) http://www.crd.york.ac.uk/CRDWeb/

The NHS EED was searched for economic evaluations. The search was carried out on 14th April 2010 and identified 17 records.

1 MeSH Arthritis, Psoriatic 17

9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

	Study name – Bravo Vergel	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	Yes	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	

20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

	Study name – Adalimumab submission [TAG 125]	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	

3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	Yes	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	

27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

	Study name – Bansback et al.	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	

9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	Yes	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	

33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

	Study name – Infliximab submission [TAG 104]	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	

14. Were productivity changes (if included) reported separately?	Yes	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

	Study name – Rodgers et al. [Ongoing MTA]	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	Yes	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	

21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.12 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

The search strategy was updated from searches conducted by Rodgers et al, 2009.

9.12.2 The date on which the search was conducted.

14th April 2010

9.12.3 The date span of the search.

01 January 2009 – 14 April 2010

9.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Please refer to Rodgers et al, 2009.

9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

9.12.6 The inclusion and exclusion criteria.

Please refer to Rodgers et al, 2009.

9.12.7 The data abstraction strategy.

Please refer to Rodgers et al, 2009.

9.13 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

9.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

The search strategy was updated from searches conducted by Rodgers et al, 2009.

9.13.2 The date on which the search was conducted.

14th April 2010

9.13.3 The date span of the search.

01 January 2009 – 14 April 2010

9.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Please refer to Rodgers et al, 2009.

9.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

9.13.6 The inclusion and exclusion criteria.

Please refer to Rodgers et al, 2009.

9.13.7 The data abstraction strategy.

Please refer to Rodgers et al, 2009.

9.14 Appendix 14: HAQ reduction estimation

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9.15 Appendix 15: Quality of Life regression

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9.16 *Appendix 16: Psoriasis Area and Severity Index (PASI) and Resource Use*

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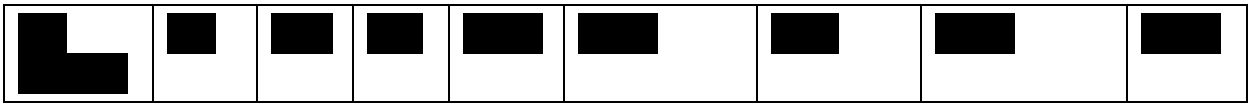

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9.17 Appendix 17: Assumptions used in the indirect comparison and the Winbugs code

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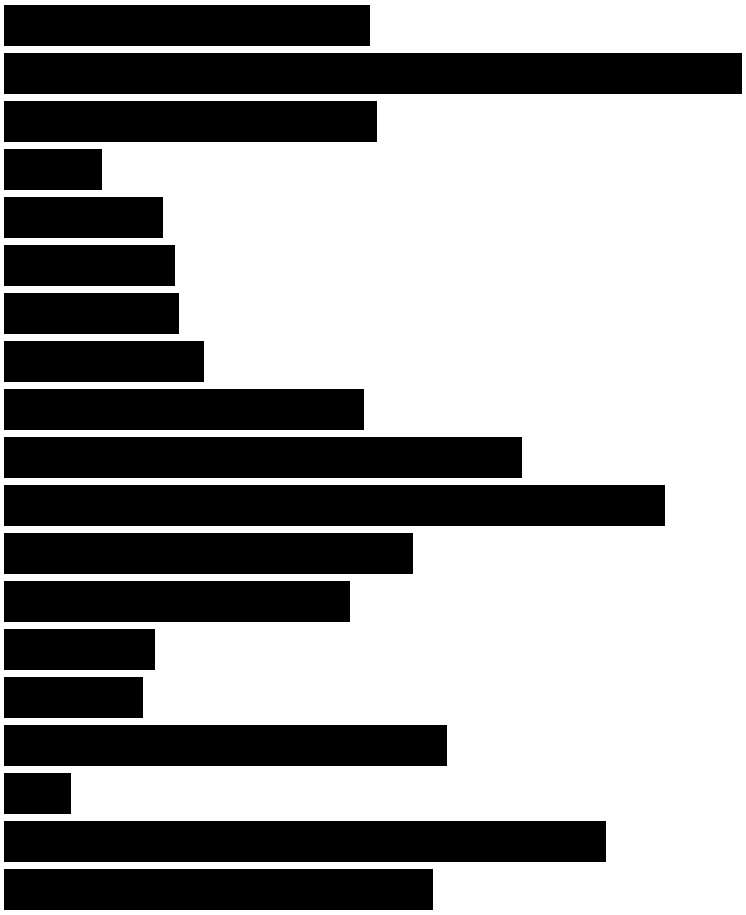

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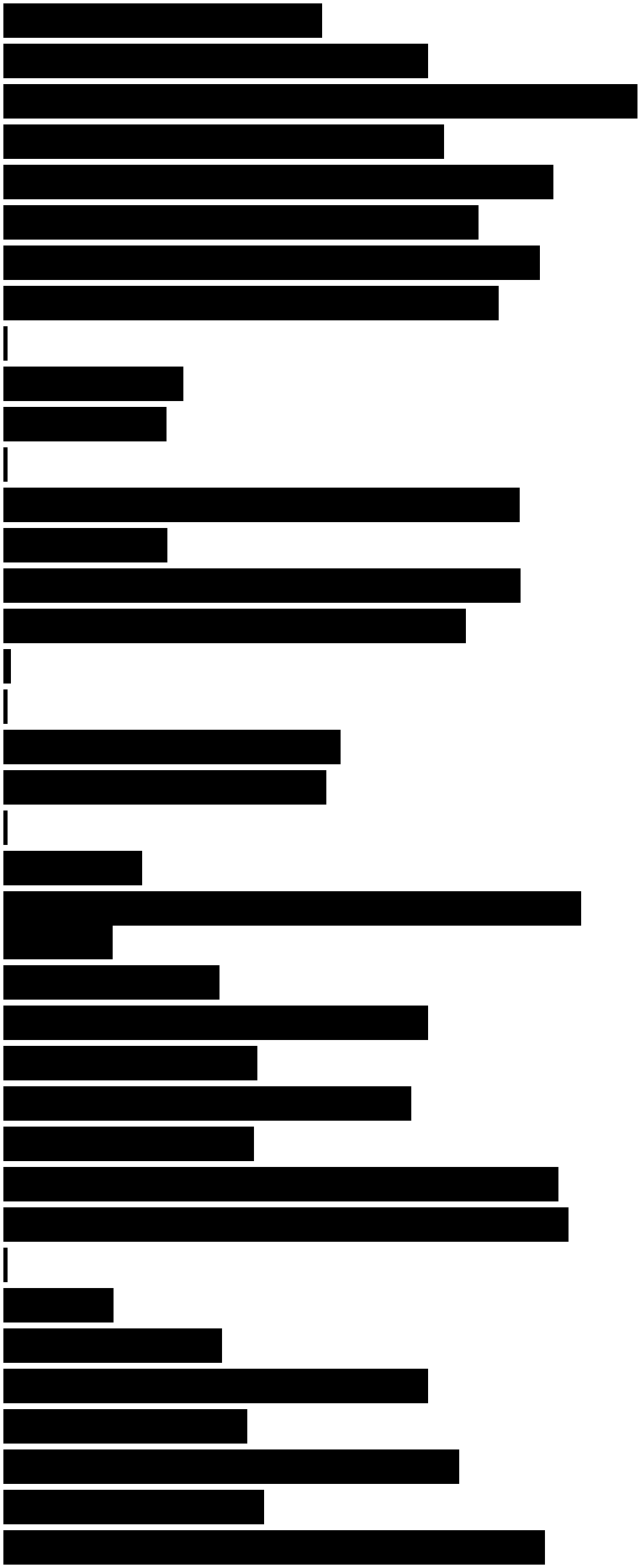

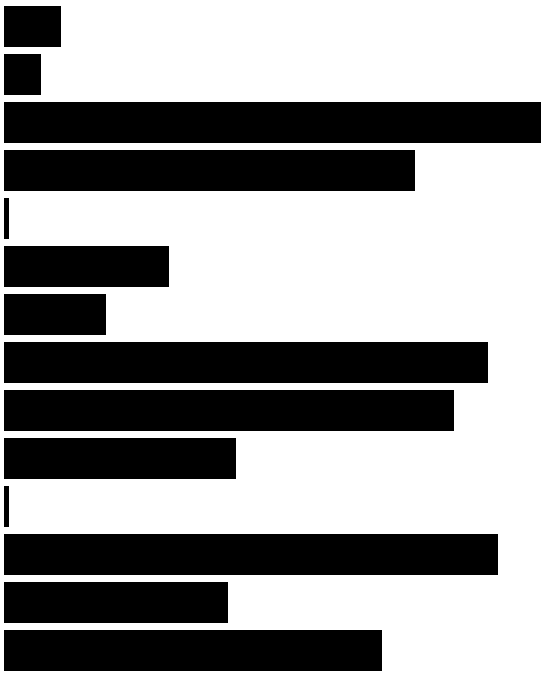

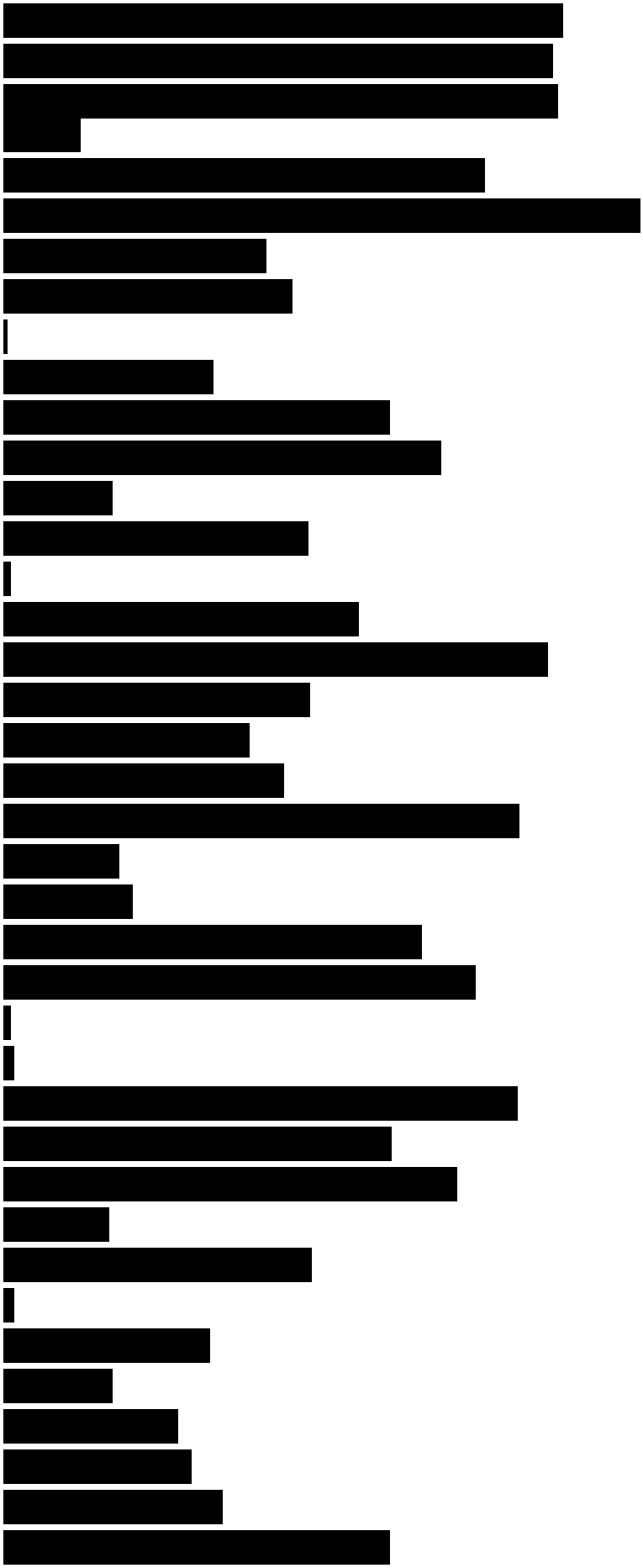

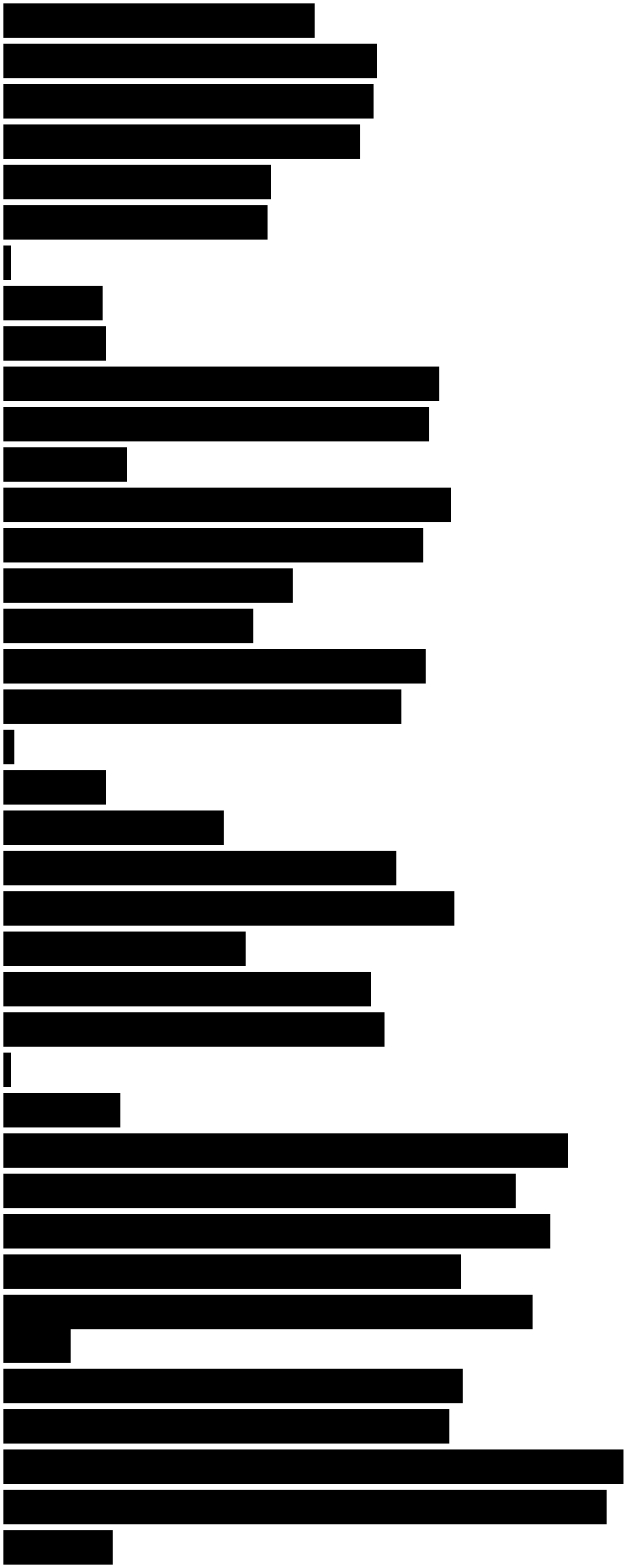

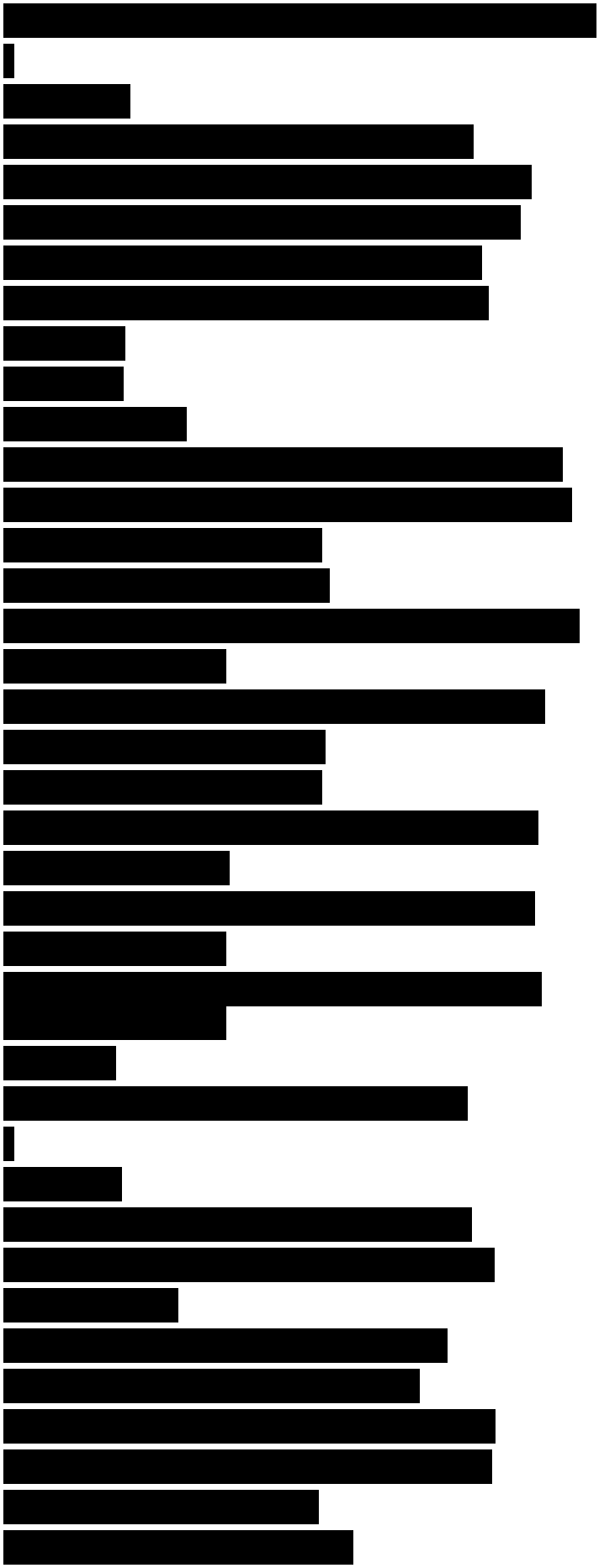

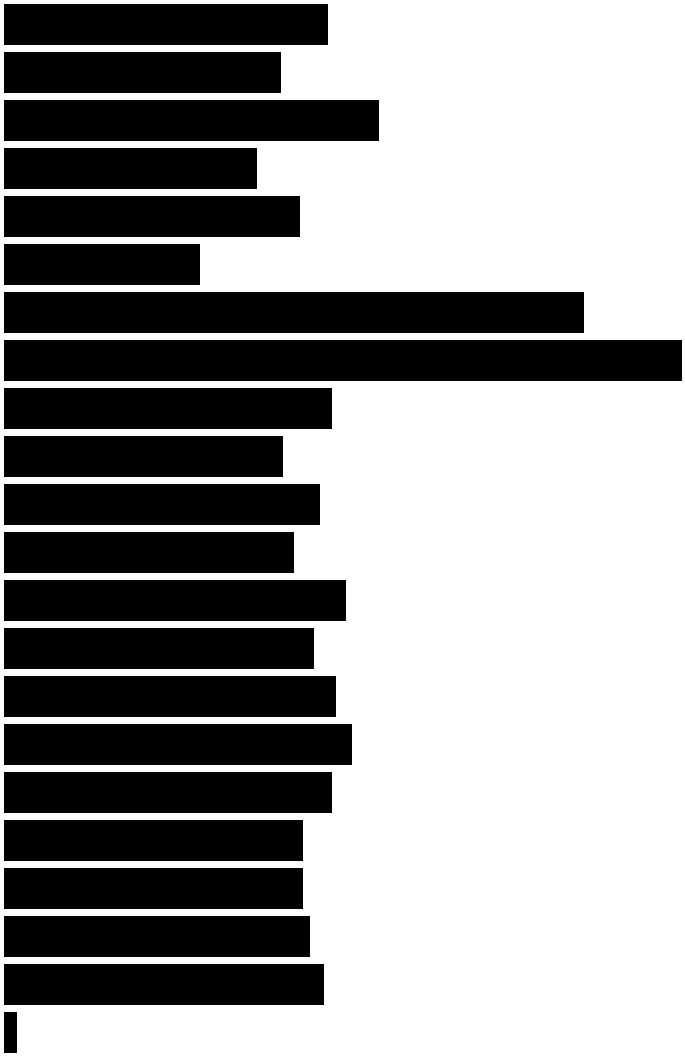

10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public

presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in red and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

10.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).