Appendix O: Cost-effectiveness analysis – Second line biologic therapy

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O.1 Introduction

There are many cost-effectiveness analyses in the published literature assessing the value of biologic therapies in a biologic naïve population; however, no cost-effectiveness analyses were identified that evaluated these treatments in a population with previous biologic exposure. There was some evidence from observational data presented in the clinical review (see Chapter 12) to suggest that biologic therapies might be slightly less effective in a population with previous exposure than in a biologic naïve population; however, the same clinical review also identified randomised controlled trial evidence to suggest that biologic therapies were still much more effective than placebo. On this basis, the GDG considered it inappropriate to assume that the economic evaluations for biologic naïve patients were wholly applicable to a previously exposed population; therefore, uncertainty in the cost-effectiveness of second line biologic therapy remained.

The GDG was also aware that there is variable interpretation of existing NICE guidance [1-4] regarding the use of biologic therapies in psoriasis, meaning that switching biologic therapies is quite common in some areas of the country and not in others. The GDG was also mindful that the group of patients likely to reach this point in the care pathway is quite small, but that the quality of life implications for these individuals is profound. Due to this lingering uncertainty and the importance of this area in clinical practice, the GDG considered the development of an original cost-effectiveness model to evaluate switching to a second biologic therapy to be a high priority. The decision modelling presented here was developed in close collaboration between the health economist, the NCGC technical team and GDG members.

O.2 Methods

O.2.1 Model overview

The analysis set out to evaluate the cost-effectiveness of switching to a second biologic therapy compared to best supportive care for patients with moderate to severe chronic plaque psoriasis who have previously received treatment with a biologic therapy. A cost-utility analysis was undertaken in line with the methods of the NICE reference case [5]. QALYs were calculated using utility weights from EQ-5D responses and UK public valuations. Costs were considered from a UK National Health Service and Personal Social Services perspective and expressed in 2011 UK sterling. Healthcare costs associated with starting and maintaining biologic therapy, as well as longer term costs of failing biologic therapy, were all included in the model.

The cost-effectiveness analysis must be relevant for decision-making over the longer term, as most people with psoriasis can be expected to require treatment for much of their lives. However, the evidence available for biological therapies is of short term duration and certain assumptions were made in order to extrapolate for many years beyond treatment initiation. A 10-year time horizon was considered sufficiently long enough to capture the relevant costs and benefits associated with both comparators.

Evidence of effectiveness for licensed biologic therapies, including adalimumab, etanercept, infliximab and ustekinumab was sparse for the subgroup of patients who have been previously treated with biologic therapy. In order to use all available data, the analysis assumed a class effect for biologic therapy and therefore pooled the results for any biologic therapy compared to placebo. This was performed as part of a meta-analysis using an ordered probit model, which enabled the estimation of probabilities for achieving different levels of PASI response, including PASI50, PASI75 and PASI90.

The performance of alternative strategies was estimated using incremental cost-effectiveness ratios (ICERs), defined as the added cost of a given strategy divided by its added benefit compared with the

next most expensive strategy. A threshold of £20,000 per QALY gained was used to assess cost-effectiveness although a threshold of up to £30,000 per QALY gained was explored in sensitivity analyses.

All analyses were conducted probabilistically, thus capturing the imprecision and uncertainty around input parameter point estimates (i.e. mean/median odds ratios, utility weights, etc). A probability distribution was defined for various model inputs and when the model is run, a value for each input was randomly selected from its specific probability distribution simultaneously and costs and QALYs were calculated using these random values. The model is run repeatedly – in this case 5,000 times – and results are summarised as mean costs and mean QALYs. Probability distributions in the analysis were based on error estimates from data sources, such as confidence intervals. In addition, a series of one-way and two-way deterministic sensitivity analyses were run in order to test the effect of certain structural or variable uncertainties.

O.2.1.1 Comparators

The aim of the analysis was to assess the cost-effectiveness of biologic therapy compared to best supportive care in the treatment of patients with moderate to severe chronic plaque psoriasis who have previously received treatment with a biologic therapy. Due to a scarcity of data for specific biologic therapies licensed for the treatment of psoriasis - adalimumab, etanercept, infliximab and ustekinumab - the analysis assumes a class effect for biologic agents. Therefore, the analysis does not aim to look at particular sequences of biologic agents, nor can it inform recommendations for any particular choice of biologic agents.

O.2.1.2 Population

The population consists of patients with moderate to severe chronic plaque psoriasis who have been previously treated with biologic therapy. The clinical data available to inform the economic analysis did not allow for subgroup analyses to be performed based on the reason for failure of previous biologic therapy. Therefore, the overall population modelled includes primary non-responders (i.e. patients who had an insufficient response to previous biologic), secondary non-responders (i.e. patients who initially responded to previous biologic therapy but lost that response over time) and patients who were intolerant to previous biologic therapy.

O.2.1.3 Time horizon, perspective, discount rates used

The analysis took a UK National Health Service and Personal Social Services costing perspective, with costs expressed in 2011 UK sterling. A 10-year time horizon was considered clinically relevant and sufficiently long enough to capture important costs and consequences of biologic treatment. Future costs and benefits were discounted at a rate of 3.5% per annum.

O.2.2 Approach to modelling

O.2.2.1 Model structure

A two-part model was constructed in TreeAge Pro 2009 to capture the different costs and effects associated with biologic therapy and best supportive care. The structure of the model was adapted from the model developed by Woolacott and colleagues[6] which has been used to inform related NICE guidance[1] and was validated by the GDG as a reasonable reflection of clinical practice.

For the biologic therapy arm, there was assumed to be a short 'trial' period, during which all hypothetical patients receive treatment and some level of benefit from treatment, and a 'treatment' period, during which only a subset of responders continue treatment and receive benefit.

'Trial' period:

- Hypothetical patients enter the model and receive a biologic therapy for an initial 'trial period.'
- During this 'trial period' they achieve a given level of PASI response (<PASI50, PASI50 to PASI75, PASI75 to PASI90, >PASI90) defined by the probabilities pPASI00, pPASI50, pPASI75, pPASI90 in Figure 1.

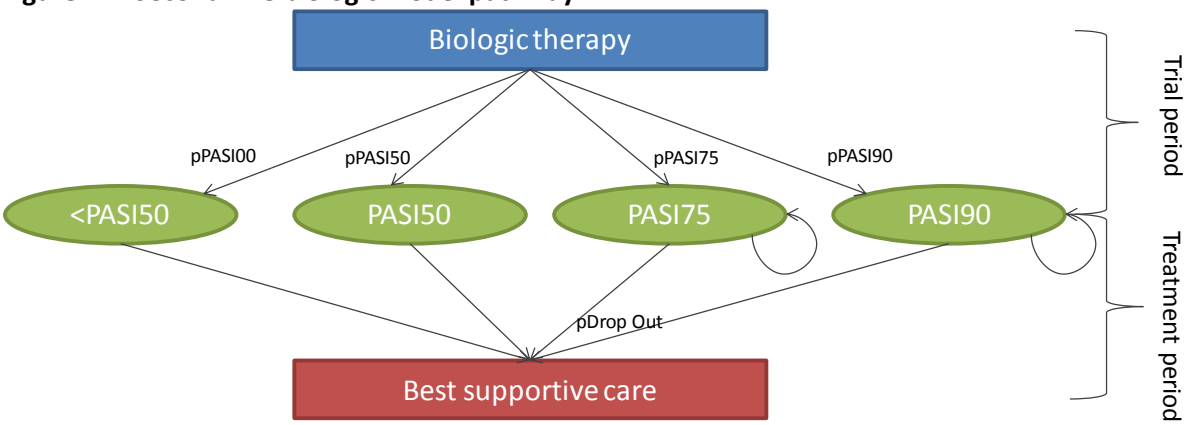
'Treatment' period:

- Patients who achieved a response >PASI75 during the trial period continue treatment and maintain that level of response until they drop out at some point in the future according to the probability pDrop Out in Figure 1.
- Patients who achieve a response of <PASI75 during the trial period discontinue treatment and move to best supportive care.

Key structural assumptions:

- Patients only receive benefit while they receive treatment, which is based on the assumption that treatments do not alter the progression of the disease
- Patients receiving treatment in the long term make no transitions between different levels of PASI response (i.e. they are assumed to maintain the same level of response observed at the end of the 'trial' period)

Figure 1: Second-line biologic model pathway



Patients on best supportive care may also achieve various levels of PASI response, which they are assumed to maintain until the end of the model. The model assumes no difference between treatments in terms of mortality.

O.2.2.2 Uncertainty

All analyses were conducted probabilistically, thus capturing the imprecision and uncertainty around input parameter point estimates (i.e. mean/median odds ratios, utility weights, etc). A probability distribution was defined for various model inputs and when the model is run, a value for each input was randomly selected from its specific probability distribution simultaneously and costs and QALYs were calculated using these random values. The model is run repeatedly – in this case 10,000 times – and results are summarised as mean costs and mean QALYs. Probability distributions in the analysis were based on error estimates from data sources, such as confidence intervals. In addition, a series of one-way and two-way sensitivity analyses were run in order to test the effect of certain structural or variable uncertainties.

O.2.3 Model inputs

O.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 1 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 1: Model specification

Input	Data	Source
Comparators	• Best supportive care • Biologic therapy	
Population	Individuals with moderate to severe plaque psoriasis who have been previously exposed to biologic therapy	
Perspective	UK NHS and & PSS	NICE reference case[7]
Time horizon	10 years	
Discounting	3.5% for costs; 3.5% for benefits	NICE reference case[7]

O.2.3.2 Baseline event rates

In the base case analysis, placebo response rates from the included randomised controlled trials were used to determine the effectiveness of patients receiving best supportive care (Table 3). The effect of this assumption was tested in a series of one-way sensitivity analyses in which the effectiveness of best supportive care was varied:

- Scenario 1: effectiveness assumed to be zero, i.e. no one receiving best supportive care achieved a PASI50 or higher
- Scenario 2: effectiveness based on observations from Woods 2008 wherein 65% of people admitted for inpatient treatment with baseline PASI10 to 20 achieved PASI50
- Scenario 3: effectiveness based on observations from Woods 2008 wherein 83% of people admitted for inpatient treatment with baseline >PASI20 achieved PASI50.

O.2.3.3 Relative treatment effects

The predicted response rates used in the model were derived from a pairwise meta-analysis of relevant subgroup data from three RCTs presented in the clinical evidence review (see Chapter 12). To allow a complete and coherent comparison to be made between biologic therapies and placebo, a fixed-effects ordered probit model was used to jointly model the different trial outcomes. The meta-analysis provided estimates of response for an average biologic therapy based on all observed data reported for any level of PASI response.

This method, reported in greater detail by Woolacott and colleagues[6], relies on two assumptions:

- That the treatment effects are constant across end-points on the probit scale
- That the treatment effects can be considered exchangeable between the trials

Table 2 presents the data from the RCTs which were included in the meta-analysis for biologic therapy compared to placebo.

Table 2: Response data extracted from the clinical trials and used in meta-analysis (numbers of patients)

Trial	Intervention	PASI response category				n=	Control	PASI response category				n=
		<50	50-75	75-90	90<			<50	50-75	75-90	90<	
PHOENIX1	Ustekinumab	41	43	53	75	212	Placebo	103	2	0	0	105
PHOENIX2	Ustekinumab	37	55	64	94	250	Placebo	116	4	3	1	124
Menter 2007	Infliximab	26		68		94	Placebo	27		0		27

Table 3 summarises the results of the meta-analysis in terms of absolute response rates and relative effects. In terms of mean response rates, biologic therapy is superior to placebo across all levels of PASI response. Based on these estimates, approximately 57% of patients receiving biologic therapy will achieve at least a PASI75 and continue treatment after the 'trial' period. Based on the estimates of response for placebo, regarded as representing 'best supportive care,' benefits are expected to be very small, with under 4% of patients achieving a PASI50 and less than 1% and 0.5% achieving a PASI75 and PASI90, respectively.

Table 3: Results of meta-analysis and summary of treatment effects used in model base case

	Probability of response			Risk ratio		
	Median	2.5% CI	97.5% CI	Median	2.5% CI	97.5% CI
Response = PASI50						
Best supportive care	3.8%	3.3%	4.4%	1.0	1.0	1.0
Biologic therapy	79.4%	70.4%	86.7%	20.7	17.7	24.0
Response = PASI75						
Best supportive care	0.8%	0.6%	1.1%	1.0	1.0	1.0
Biologic therapy	57.3%	46.1%	68.2%	71.1	50.4	102.4
Response = PASI90						
Best supportive care	0.1%	0.1%	0.2%	1.0	1.0	1.0
Biologic therapy	31.9%	22.6%	43.0%	287.7	173.0	485.2

Uncertainty in the response rates was captured by exporting the simulated posterior distribution from the Markov Chain Monte Carlo analysis in WinBUGS to the cost-effectiveness model, thus preserving any correlations.

It is important to note that this analysis is limited by the data available. Firstly, only data for infliximab and ustekinumab are available from randomised controlled trial evidence. It is unclear whether these values are likely to be an over or underestimate of likely response to etanercept and adalimumab in this subgroup of patients. Secondly, this analysis only draws conclusions regarding short term use, which is less than ideal for the treatment of a chronic, life-long condition.

O.2.3.4 Utilities

Achievement of different levels of PASI response and associated utility gain was used in the model to determine the impact of biological therapy on overall health. Estimates of utility gain were taken from a variety of sources, but for the base case values were taken from the cost-utility analysis conducted by Woolacott and colleagues[6], which were estimated from an analysis of data from etanercept trials and the HODaR Database (http://www.hodar.co.uk/). The authors estimated mean utility gain across 'all patients' regardless of baseline quality of life and for a subgroup of patients with the worst baseline quality of life (fourth quartile DLQI). The mean utility gains for 'all patients'

were used in the base case (see Table 4) and gains for those with the worst baseline DLQI were used in a sensitivity analysis. In a further three sensitivity analyses, utility gain estimates that were used in other models[3,4] informing NICE guidance were used. All estimates of utility gain are presented in Table 5.

Table 4: Estimated utility gains for different PASI response categories used in the base case

	Gains in utility: mean	
PASI Response category	**Base case (SE)**	**Distribution parameters (a)**
<50	0.05 (0.01)	Gamma: α=25, β=0.002
≥50 and <75	0.17 (0.04)	Gamma: α=8.471, β=0.014 (b)
≥75 and <90	0.19 (0.04)	Gamma: α=0.125, β=0.16 (c)
≥90	0.21 (0.05)	Gamma: α=0.098, β=0.205 (d)

(a) Utility gains were built into the model using gamma distributions around difference from next better health state to ensure the health state utilities added up logically (i.e. such that achieving PASI90 was always better than PASI70, which was always better than PASI50 and no response). Error estimates as above were used where available from the literature. and where not (as in the case of the values from the adalimumab and ustekinumab STAs), utility gains were entered deterministically.
(b) Distribution mean = 0.12, which was added to the utility gain for <PASI50 (0.05+0.12=0.17)
(c) Distribution mean = 0.02, which was added to the utility gain for ≥PASI50 and <PASI75 (0.17+0.02=0.19)
(d) Distribution mean = 0.02, which was added to the utility gain for ≥PASI75 and <PASI90 (0.19+0.02=0.21)

Table 5: Estimated utility gains for different PASI response categories used in sensitivity analyses

	Gains in utility: mean				
PASI Response category	**4th Quartile DLQI (SE)**	**Distribution parameters for 4th Quartile DLQI (a)**	**Adalimumab STA[3] (EQ-5D)**	**Ustekinumab STA[4] (DLQI)**	**Ustekinumab STA[4] (SF-36)**
<50	0.12 (0.03)	Gamma: α=16, β=0.0075	0.063	0.04	0.0016
≥50 and <75	0.29 (0.06)	Gamma: α=6.422, β=0.0264 (b)	0.178	0.17	0.0424
≥75 and <90	0.38 (0.08)	Gamma: α=0.81, β=0.111 (c)	0.178	0.22	0.0970
≥90	0.41 (0.09)	Gamma: α=0.062, β=0.483 (d)	0.308	0.25	0.1276

(a) Utility gains were built into the model using gamma distributions around difference from next better health state to ensure the health state utilities added up logically. Error estimates as above were used where available and where not (as in the case of the values from the adalimumab and ustekinumab STAs), utility gains were entered deterministically.
(b) Distribution mean = 0.17, which was added to the utility gain for <PASI50 (0.12+0.17=0.29)
(c) Distribution mean = 0.09, which was added to the utility gain for ≥PASI50 and <PASI75 (0.29+0.09=0.38)
(d) Distribution mean = 0.03, which was added to the utility gain for ≥PASI75 and <PASI90 (0.38+0.03=0.41)

O.2.3.5 Resource use and cost

Only direct health care costs were assessed, and these included the cost of drugs and their administration and monitoring and the cost of outpatient visits, day centre care visits and inpatient stays. The cost of tests undertaken to screen patients for eligibility of treatment was excluded from the analysis. Also excluded were the costs of treating adverse events, due to a lack of data of their impact on treatment pathways and resource use.

This section is broken into four parts. The first section focuses on resource use and costing information related to the drugs themselves. The second and third sections focus on parameters of resource use and unit costs included in the 'trial' period and 'treatment' period of biologic therapy, respectively. Finally, the fourth section presents the estimates of resource use and cost used to define best supportive care.

Note that the unit costs for inpatient stays, outpatient consultations, phototherapy and day care centre visits were each calculated as a weighted mean of several NHS reference cost components. Relative weights applied to each component were based on the activity level reported in the NHS reference cost schedule 2009-10. We assumed that the interquartile range for any given NHS reference cost fit a gamma distribution. Based on that assumption, we took the mean and manually adjusted the standard error estimate to calculate alpha and beta parameters for a gamma distribution that would come closest to reproducing the interquartile range reported in the NHS reference costs schedule. For the probabilistic analysis, each cost component was varied, multiplied by its relative weight and then summed with other cost components to equal the total unit cost for a given service.

Drug treatment

Drug dosages, administration schedules and unit costs were based on information from the BNF 62[8] and are presented in Table 6.

Table 6: Drugs: Dosages, administration schedules and unit costs

Drug	Dosage and schedule	Price per mg	Price per table/vial	Source
Ciclosporin (100 mg)	300 mg/day (a)	£0.0172	£1.72	BNF 62
Methotrexate (2.5 mg)	Titrated up to 15 mg/week (b)	£0.0467	£0.12	BNF 62
Adalimumab (40 mg)	80 mg loading dose followed by 40 mg every other week	£8.80	£352.14	BNF 62
Etanercept (50 mg)	50 mg/week	£3.58	£178.75	BNF 62
Infliximab (100 mg)	5 mg/kg at weeks 0, 2, 6 then every 8 weeks (c)	£4.20	£419.62	BNF 62
Ustekinumab (45 mg)	45 mg at weeks 0, 4 and then every 12 weeks	£47.71	£2147.00	BNF 62

(a) Based on 75 kg patient receiving 4 mg/kg/day
(b) Titrated up weekly from 2.5 mg
(c) Based on 80 kg patient receiving 5 mg/kg/infusion or 4 x 100 mg vials per infusion generally

'Trial' period

Previous NICE guidance has stipulated that biologic therapies should be trialled for a given number of weeks and discontinued if an adequate response has not been observed. The recommended trial period varies between drugs: 12 weeks for etanercept, 10 weeks for infliximab and 16 weeks for both adalimumab and ustekinumab. Because we were not modelling specific biologic therapies, but rather an average biologic, we took the mean of these different trial lengths: 13.5 weeks. Based on the dosing schedule in Table 4, a 13.5 week trial period does not affect the costs for drugs like infliximab and ustekinumab, however it might overestimate the costs for etanercept slightly and underestimate costs for adalimumab. Similarly, using a 13.5 week trial period may underestimate benefits for drugs such as adalimumab and ustekinumab as non-responding patients are forced to stop slightly earlier, but it will overestimate benefits for drugs such as infliximab and etanercept as it would mean that patients who should have stopped will continue to accrue benefits. Overall, the GDG expects the costs and benefits to even out reasonably using an average 13.5 week trial period.

In addition to the cost of the biologic agents themselves, the trial period includes costs of administration, monitoring and outpatient visits. Only infliximab was associated with additional administration costs, which amounted to a regular day/night admission for an infusion (JD02C: £316)[9]. Monitoring tests include full blood count, liver function test and urea and electrolytes (which includes serum creatinine testing). The frequencies and unit costs of each of these monitoring tests for each biologic agent are presented in Table 7. The unit costs of each of these monitoring tests were taken from Woolacott and colleagues and inflated to 2011, using the PSSRU inflation index[10].

The number of outpatient visits during the trial period for each biologic agent is also presented in Table 7.

Table 7: Quantity of monitoring tests and outpatient visits during 13.5 week trial period

Biologic	FBC (£2.83)	LFT (£0.71)	U&E (£1.31)	Outpatient visits (£82)
Adalimumab	2	2	2	2
Etanercept	2	2	2	2
Infliximab	3	3	3	1 (a)
Ustekinumab	2	2	2	2

(a) Patients are reviewed during infusion visits and then one additional outpatient appointment.
FBC, Full blood count; LFT, liver function test; U&E, Urea and Electrolytes, including serum creatinine

Based on the resource use and unit costs presented in Table 6 and Table 7, the total 13.5-week trial period cost for each biologic agent is presented in Table 8. The average across all biologics for the 'trial' period is £4,031.

Table 8: Total trial period cost of each biologic therapy and average across all biologic therapies

Drug	Total drug costs	Total administration costs	Total monitoring costs	Total outpatient costs	Total Cost
Adalimumab	£2,817		£9.70	£164	£2,991
Etanercept	£2,413		£9.70	£164	£2,587
Infliximab	£5,035	£947	£14.55	£82	£6,079
Ustekinumab	£4,294		£9.70	£164	£4,468
Average biologic agent					**£4,031**

'Treatment' period

Estimates of resource use and costs were quantified for annual cycles and include the same items (drugs, administration and monitoring) as those outlined in the previous section. In addition to the biologic agents, we have presented the annual cost of treatment with methotrexate and ciclosporin, two drugs included as part of best supportive care.

Table 9: Annual drug costs

Biologic	Dose	Notes/Assumption	Unit Cost	Total Cost
Methotrexate	15 mg per week		£0.05 per mg	£36
Ciclosporin	300 mg per day	Max 2 years	0.02 per mg	£1,880
Adalimumab	40 mg every two weeks		£352.14 per 40 mg	£9,156
Etanercept	50 mg once weekly		£178.75 per 50 mg	£9,295
Infliximab	5 mg/kg every 8 weeks	4 x 100 mg vials per infusion	£419.62 per 100 mg	£10,910
Ustekinumab	45 mg every 12 weeks		£2,147 per 45 mg	£9,304

Monitoring for patients continuing biologic therapy during the treatment period is assumed to be less frequent as are follow-up outpatient visitis, taking place only once every 3 months. Monitoring of patients undergoing treatment with methotrexate is assumed to include the additional costs of 3-monthly PIIINP testing and the infrequent, but occasional liver biopsy. The annual rate of 0.04 biopsies per year was taken from Chalmers and colleagues[11], an study that was included in the health

economic review for methotrexate monitoring (see chapter 11). Patients being treated with ciclosporin are also assumed to undergo glomerular filtration rate testing once per year. Annual frequencies and unit costs of these monitoring tests for each biologic agent and both conventional systemic therapies are presented in Table 10. Costs for glomerular filtration rate (GFR) testing and liver biopsy were taken from NHS reference costs. Liver biopsy was assumed to be performed as a day case procedure (code GB04Z) and GFR testing was based on a weighted average of the test performed as a diagnostic imaging outpatient procedure, direct access procedure or other (code RA37Z). The number of outpatient visits during the trial period for each biologic agent is also presented.

Table 10: Number of annual monitoring tests and outpatient visits

Biologic	FBC (£2.83)	LFT (£0.71)	U&E (£1.31)	PIIINP (£25.29)	GFR (£233)	Liver biopsy (£553)	Outpatient visit (£82)
Methotrexate	4	4	4	4		0.04 (a)	4
Ciclosporin	4	4	4		1		4
Adalimumab	4	4	4				4
Etanercept	4	4	4				4
Infliximab	4	4	4				4
Ustekinumab	4	4	4				4

(a) Frequency of liver biopsy with methotrexate with concurrent use of PIIINP test was based on estimates from Chalmers and colleagues[11]
(b) GFR, Glomerular Filtration Rate

Based on the resource use and unit costs presented in Table 9 and Table 10, the total annual treatment period cost for each biologic agent, ciclosporin and methotrexate is presented in Table 11. The average annual cost across all biologics for the 'treatment' period is £10,527.

Table 11: Total annual 'treatment' period costs

Biologic	Total drug costs (see Table 9)	Total administration costs (see Table 9)	Total monitoring cost (see Table 10)	Total outpatient costs (see Table 10)	Total Cost
Methotrexate	£36		£143	£328	£507
Ciclosporin	£1,880		£253	£328	£2,461
Adalimumab	£2,817		£19.40	£328	£9,503
Etanercept	£2,413		£19.40	£328	£9,643
Infliximab	£5,035	£2,052	£19.40	£328	£13,310
Ustekinumab	£4,294		£19.40	£328	£9,651
Average biologic agent					**£10,527**

Best supportive care

Based on discussions with the GDG, evidence from two retrospective cohort studies and assumptions made in previous NICE technology appraisals, the following definition for best supportive care was used in the NCGC model. For details about the evidence and discussions feeding into this definition, see Appendix P. The summary presented here is broken up into different resource categories and then summarised at the end in a single table (Table 12). Resource use and costing estimates for outpatient attendances, monitoring and laboratory testing for ciclosporin and methotrexate are presented in the previous sections.

Drug and other treatments

There is recognition that at the point at which patients become eligible for a first biologic therapy, they must have exhausted treatment options such as conventional systemic therapy and phototherapy, including PUVA. The GDG considered that although these therapies had either proved ineffective or given rise to certain toxicities, the patients for whom a second biologic was being considered were unlikely to go without treatment altogether. In the absence of a second biologic therapy, the likelihood is that they would be cycled through different modalities, accepting the associated risks. On this basis, the NCGC model has attempted to approach the treatments comprising 'best supportive care' in a pragmatic fashion, albeit with limitations.

Drugs included under 'best supportive care' (BSC) and the proportions of patients receiving each were defined by the GDG in the following way:

- 45% of patients will be managed with ciclosporin for a maximum of 2 years
- 45% of patients will be managed with methotrexate for the entire time horizon
- 10% will be managed with no active pharmacological treatment (some patients will opt for no treatment given the possible risks associated with conventional systemic therapies)

These proportions were varied in sensitivity and scenario analyses.

Phototherapy and day care attendances

We have assumed that 16% of patients will undergo one course of narrowband UVB each year (24 sessions). This is based on the estimated use of PUVA in the Driessen study[12] during the year prior to initiation of biologic therapy. Given the high probability of contraindication to PUVA in the hypothetical population of the NCGC model, a course of narrowband UVB was thought to be more realistic than further PUVA.

The GDG indicated that if the service is available, the population included in the NCGC model (failed biologic therapy) is very likely to utilise day care centre services for intensive, supervised topical or combination therapies. On this basis, the NCGC model has assumed that all patients receiving BSC will attend a day centre for specialist applied topicals or other specialist treatment 5 times per year.

Inpatient admissions and length of stay

For details on how resource use estimates for inpatient stays were derived, see Appendix P, section P5.2.5.

Patients receiving BSC were assumed to be stratified into two groups based on a recent Dutch cohort study[12]: 82% high-need and 18% very high-need. In the base case, it was assumed that high-need patients will require one hospital admission per year, which was assumed to correspond to a mean length of stay of 20.8 days (based on data from Woods and colleagues[13]). It was assumed that very high-need patients (18%) will require 2.55 hospital admissions per year, each also 20.8 days in length. The weighted average number of inpatient days per year is thus 26.6 days.

Given that these variables are quite uncertain, extensive sensitivity analyses were performed to explore how small and large changes in resource use might affect the cost-effectiveness of second line biologic therapy. In particular, the proportions of high- and very-high need patients and the number of annual admissions and mean length of stay per group were varied.

Summary of best supportive care

The working definition of best supportive care, in the context of patients with moderate to very severe plaque psoriasis who are being considered for further biologic therapy, is summarised in terms of resource use in Table 12. This is based on several different sources of information and

supplemented by GDG experience and opinion. This defined package of services is expected to cost an annual £10,731. Due to substantial uncertainties in these model parameters, they were subject to extensive sensitivity analyses, each of which was considered by the GDG as they looked to make guideline recommendations that would represent an effective and cost-effective use of NHS resources.

Table 12: Assumed resource use for best supportive care

	Total annual cost			
Component	**Proportion receiving**	**Resource use components**		**Total Cost**
Drugs				
Methotrexate	45% (a)			£228
Ciclosporin (b)	45% (a)			£1,107
No drug	10% (a)	5 OP visits		£41
Other treatment				
Day centre care	100% (a)	5 visits		£1,813
NBUVB	16% (c)	1 course	24 sessions	£327
Inpatient care (g)				
High need	82% (d)	1 admission (a)	20.8 days per admission (f)	£4,625
Very high need	18% (d)	2.55 admissions (e)		£2,589
TOTAL				**£10,730 (h)**

(a) Based on GDG opinion
(b) Maximum treatment 2 years; after 2 years then no drug
(c) Based on proportion receiving PUVA in year before starting biological therapy in Driessen and colleagues[12]
(d) Based on split in Driessen and colleagues[12] (under/over 30 days in hospital per annum)
(e) Calculated based on mean length of stay from Woods[13] (20.8) and mean in hospital days per annum in the very high need group in Driessen[12] (53.0).
(f) Based on mean length of stay for patients admitted with baseline PASI 10 to 20 in Woods[13]. 23.7 days used in sensitivity analysis.
(g) Weighted average length of stay equals 26.6 days per year per patient (20.8[0.82*1+0.18*2.55]=26.6) and weighted average cost equals £7,214 per patient.*
(h) Note: previous TAs[1-4] have estimated this cost to be approximately £5,327.71 (21 days in hospital + 2 outpatient visits per annum)

O.2.4 Computations

The model was constructed in TreeAge Pro 2009 and was evaluated by cohort simulation. All hypothetical patients start treatment with a biologic therapy and achieve a different level of PASI response, with >PASI75 classified as responding and <PASI75 classified as not responding. Only responders are assumed to continue treatment and can subsequently drop out and move on to best supportive care. Each annual cycle the cohort spends in a given health state is counted.

Total QALYs were calculated from the above information as follows. Each annual cycle, the time spent in each health state of the model was weighted by the utility for that state. The QALYs per cycle were then discounted to reflect time preference. QALYs during year one were not discounted. The total discounted QALYs was the sum of the discounted QALYs per cycle. The QALYs that were accrued during the initial 13.5 week trial period were added to the QALYs accrued in the first cycle.

$$Total \quad discounted \quad QALYs = \sum_{t=1}^{i} \frac{Q(t)}{(1+r)^{t-1}}$$

Where: t=cycle number; i=maximum cycle number; Q(t) = QALYs in cycle t; r = discount rate

Total costs were calculated from the above information as follows. Each cycle, the time spent in each state of the model was multiplied by the costs for that state. The costs per cycle were then discounted to reflect time preference. Costs during year one were not discounted. The total discounted costs were the sum of the discounted costs per cycle. The costs that were accrued during the initial 13.5 week trial period were added to the costs accrued in the first cycle.

$$Total\ \ discounted\ \ costs = \sum_{t=1}^{i} \frac{C(t)}{(1+r)^{t-1}}$$

Where: t=cycle number; i=maximum cycle number; C(t) = costs in cycle t; r = discount rate

The used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold, the result is considered to be cost effective. If both costs are lower and QALYs are higher, the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

When there are more than two comparators, as in this analysis, options were ranked in order of increasing cost and then options ruled out by dominance (i.e. those that were more costly and less effective than alternate strategies) or extended dominance (i.e. where a linear combination of other strategies could produce greater benefit at lower cost) were excluded before calculating ICERs.

ICERs were calculated based on mean costs and effects as estimated during the probabilistic implementation of the model. Results are presented on the cost-effectiveness plane where the total cost and total QALYs are plotted for both treatment options. Best supportive care is located at the origin, defined as the intersection between its total QALYs (on the x-axis) and total cost (on the y-axis). The slope of the line connecting best supportive care to biologic therapy is equal to the incremental cost-effectiveness ratio, the value of which is labelled.

The effect of uncertainty in the results is reflected by the reporting of 95% confidence intervals around mean total costs and effects. Secondly, uncertainty was illustrated by estimating the probability a given AED was the optimal treatment option. For strategy X, this was calculated as

$$Net\ \ Benefit(X) = (QALYs(X) \times D) - Costs(X)$$

Where: Costs/QALYs(X) = total discounted costs/QALYs for option X; D=threshold

The decision rule then applied is that the strategy with the greatest net benefit is the cost-effective option at that threshold. That strategy is expected to provide the highest number of QALYs at an acceptable cost. The probability a given AED is optimal is calculated as the proportion of simulations where that option had the greatest net benefit at the specified threshold.

O.2.5 Sensitivity analyses

A series of one-way sensitivity analyses and scenario analyses were performed to assess how changes in one or more parameters or assumptions might change the conclusions of the analysis. In the first series, we focused on inputs relating to the costs and effectiveness of biologic therapies. In the second set of sensitivity analyses, we explored how changes in the sources for health state utilities might impact the conclusions of the analysis. The third set of scenarios explored how changes in the effectiveness of best supportive care might alter the conclusions arising from the base case. Finally, an extensive set of scenario analyses was performed to explore how variation in the assumed resource use of best supportive care might impact the relative cost-effectiveness of the

strategies. The results of the sensitivity analysis were interpreted alongside the base case results such that the GDG was aware of the key drivers of cost-effectiveness and uncertainty.

O.2.6 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of many of the model calculations.

O.3 Results

O.3.1 Base case

Results of the base case suggest that compared to best supportive care, a second line biologic therapy is likely to be cost effective at a willingness to pay threshold of £20,000 per QALY gained. Results of the incremental analysis are presented in Table 13 and in Figure 2. Total costs disaggregated by type of resource use are presented in Table 14.

Table 13: Incremental analysis of base case results

Strategy	Total Costs	Incremental Cost	Total Benefit (QALYs)	Incremental Benefit (QALYs)	ICER (£/QALY)
BSC	£87,155		0.478		
Biologic	£90,661	£3,506	0.804	0.326	£10,755

Figure 2: Base case results on the cost-effectiveness plane

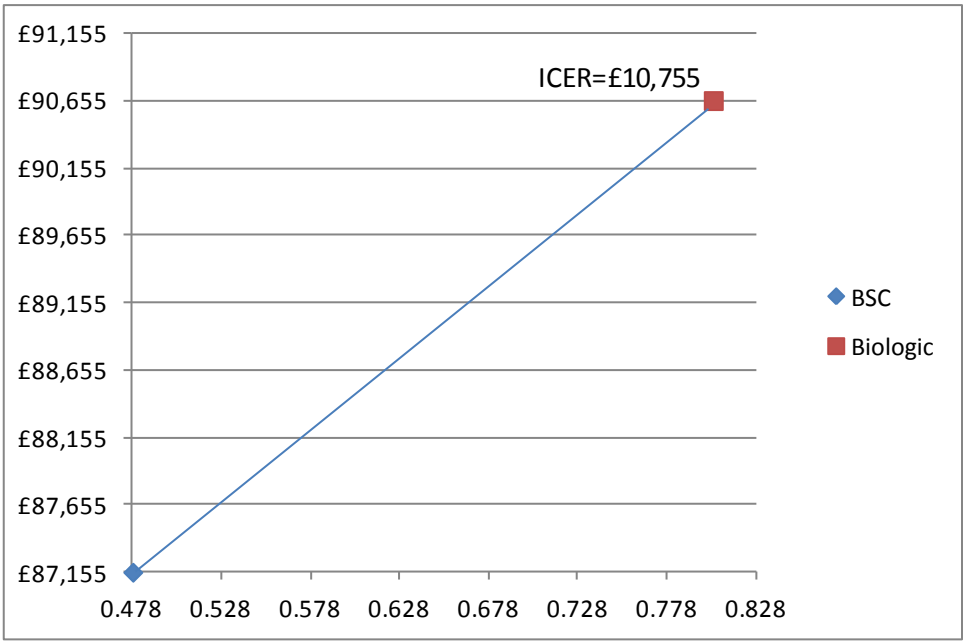


Table 14: Breakdown of costs

Sensitivity analysis	Biologic	BSC
Drug costs	£25,518	£1,603
Outpatient costs	£3,124	£3,192
Inpatient costs	£46,263	£62,916
Monitoring costs	£727	£756
Administration costs	£1,289	£0
NB-UVB	£2,104	£2,861
Day centre visits	£11,626	£15,811
TOTAL	**£90,650**	**£87,139**

Note: Totals reported here may differ slightly from those reported in Table 13, as costs for each category of resource use were estimated as part of a separate run of the probabilistic analysis and variation in the sampled values may give rise to slight differences.

Results indicate that switching to a second biologic following intolerance to or failure of a first biologic is likely to cost £3,506 more over 10 years than switching to best supportive care, but this cost is likely to be offset by a 0.326 gain in QALYs. The incremental cost-effectiveness ratio (ICER) of second biologic compared to best supportive care is £10,755 per QALY, a value well below the NICE willingness to pay threshold range of £20,000 to £30,000 per QALY gained.

Table 15: Total and incremental costs, benefits and net monetary benefits from PSA

	Biologic therapy (95% CI)	BSC (95% CI)	Incrementals (95% CI) Biologic vs BSC
Total cost (£)	90,661 (88,246 to 93,171)	87,155 (83,920 to 90,533)	3,506 (-617 to 1,687)
Total benefit (QALYs)	0.804 (0.517 to 1.291)	0.478 (0.323 to 0.665)	0.326 (-0.097 to 0.749)
NMB at £20k threshold (£)	-74,571 (-80,918 to -64,733)	-77,600 (-82,210 to -72,729)	3,029 (-6,350 to 12,408)
NMB at £30k threshold (£)	-66,526 (-75,475 to -51,888)	-72,823 (-78,584 to -66,321)	6,297 (-6,995 to 19,589)

O.3.2 Sensitivity analyses

A series of one-way sensitivity analyses were performed to explore how changes in key variables might affect the base case results.

Table 16: Results of sensitivity analyses around biologic inputs

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
Base Case	**£10,730**	**88%**	**98%**
Infliximab only	£34,212	7%	27%
Etanercept only	£782	100%	100%

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
Adalimumab only	£1,134	100%	100%
Ustekinumab only	£6,536	98%	100%
Infliximab and Ustekinumab only	£20,338	36%	75%
Weighted average biologics (15% Infliximab)	£7,497	97%	100%
Continue treatment if PASI50	£9,703	93%	99%
10% annual drop out	£7,760	97%	100%
30% annual drop out	£14,123	72%	93%
50% annual drop out	£21,881	31%	69%

Under base case assumptions, switching to a second biologic is likely to be cost-effective (£10,730 per QALY compared to best supportive care). Considerable uncertainty is revealed when assumptions about biologics are varied (Table 16).

- If highest cost biologic is assumed (Infliximab), a second biologic is less likely to be cost-effective given a £30k threshold (27% probability of being cost-effective).
- If lowest cost biologics are assumed, a second biologic is almost certainly cost-effective compared to best supportive care.
- If only infliximab and ustekinumab are included (i.e. etanercept and adalimumab are not options), then the ICER increases to £20,338 per QALY, but is still potentially cost-effective at a willingness to pay threshold of £30,000 per QALY.

Second line biologic becomes slightly more cost-effective if patients are allowed to continue with a PASI50 response and conclusions are not very sensitive to plausible estimates of annual drop out rate.

Table 17: Results of sensitivity analyses around utility inputs

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
Base Case	**£10,730**	**88%**	**98%**
No utility gain for BSC PASI00	£10,637	89%	98%
4th Quartile DLQI at baseline	£5,864	99%	100%
Adalimumab STA utilities	£8,041	100%	100%
Ustekinumab STA utilities	£8,655	100%	100%
Ustikinumab STA utilities (SF-36)	£25,048	14%	79%

Results of sensitivity analyses around utility inputs presented in Table 17 show that base case results are relatively insensitive to changes in the source of quality of life estimates.

- It appears that biologics become more cost-effective using utility values for patients with the worst DLQI at baseline, an unsurprising result given that these are the patients with the most to gain from successful treatment.
- The cost-effectiveness of second line biologic therapy diminishes when using utility estimates derived from SF-36, which were included in the ustekinumab single technology appraisal; however, even using these estimates a second biologic has a 79% probability of being cost-effective at a threshold of £30,000 per QALY.

Table 18: Results of sensitivity analyses around response rates for best supportive care

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
Base Case	**£10,730**	**88%**	**98%**
Placebo response from trials	£10,451	90%	99%
65% response rate (Woods 2008)	£22,411	24%	48%
83% response rate (Woods 2008)	£31,892	16%	24%

Results are very sensitive to changes in estimates of effect for best supportive care (Table 18).

- When best supportive care is assumed to offer no benefits at all (i.e. 0% of patients are assumed to achieve ≥PASI50), biologics are very slightly more cost-effective than in the base case.
- When response rates for inpatient admission observed in Woods 2008 are used, uncertainty in the cost-effectiveness of second line biologic therapy increases.
  - If inpatient care produces a PASI50 response rate of 65%, second line biologic is cost-effective in fewer than 50% of simulations at a £30k threshold
  - If inpatient care produces a PASI50 response rate of 83%, the probability of switching to a second line biologic therapy being cost-effective goes down to 24% (in other words, best supportive care has a 76% probability of being more cost-effective than second biologic).

Table 19: Results of sensitivity analyses around resource use inputs for best supportive care

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
Base Case	**£10,730**	**88%**	**98%**
No drugs in BSC	£9,307	93%	99%
Longer length of stay (23.7 days)	£5,137	100%	100%
30% very high need	£3,306	100%	100%
5% very high need	£18,694	45%	81%
0.25 hospitalisations for high need and 2.55 hospitalisations for very high need (match Driessen 2010)	£35,079	7%	25%
0.5 hospitalisations for high need and 2 hospitalisations for very high need	£30,944	10%	35%
1 hospitalisation for all	£21,926	30%	69%
0.312 hospitalisations for all (match Fonia 2010)	£49,575	2%	8%
No hospitalisations	£60,998	1%	5%
1 hospitalisation for all and no drugs	£20,369	37%	75%
1 hospitalisation and 5 outpatient visits per year	£35,259	7%	25%
1 hospitalisation and 5 outpatient visits per year and 4th Quartile DLQI	£19,391	43%	77%

Results are very sensitive to changes in estimates of resource use assumed for best supportive care (Table 19). The cost-effectiveness of switching to a second biologic improves if mean length of stay per admission increases and if a greater proportion of patients are classified as very high need (thus requiring more inpatient admissions per year).

The likelihood of switching to a second biologic being cost-effective decreases if

- The proportion of very high need patients decreases
- The number of hospitalisations decreases
- The other types of care in best supportive care are removed (i.e. no UVB, no day centre, no drugs)

It is worth highlighting two scenarios in particular:

- In Driessen 2010[12], the mean number of inpatient days for patients who had less than 30 days per annum was 5.1 and the mean number of inpatient days for patients who had more than 30 days per annum was 53.0. The weighted average length of stay was thus 13.722 inpatient days per annum. When this was recreated in the model, the ICER for biologic therapy compared to best supportive care when up to £35,079 and had a 25% probability of being cost-effective at £30k per QALY.
- In Fonia 2010[14], the mean number of inpatient days for all patients was 6.49. When this was recreated in the model, the ICER for biologic therapy compared to best supportive care when up to £49,575 and had an 8% probability of being cost-effective at £30k per QALY.

These studies estimated mean inpatient days in the year preceding initial treatment with biologic therapy and thus the values may underestimate the likely resource use in the minority of patients represented in this model, who are likely to be sicker since they have already failed one line of biologic treatment.

O.4 Discussion

O.4.1 Summary of results

In assessing the cost-effectiveness of biological therapy in patients with moderate to severe psoriasis who have previously been treated with biological therapy, no information was available from the published economic literature. It was therefore considered a priority to undertake original evaluation for the guideline in order to inform guideline recommendations. This analysis suggests that switching to a second line biological drug is potentially cost-effective compared to a strategy of best supportive care without biological therapy. Uncertainties in the analysis were explored through extensive sensitivity analysis which changed the conclusion in some cases, namely those in which best supportive care was assumed to produce some clinical and quality of life improvements or was assumed to be less resource intensive in terms of inpatient stays and other forms of hospital-based care (e.g. UVB, day centre treatments).

O.4.2 Limitations

Most parameters in the model are highly uncertain which makes the analysis quite exploratory and interpretation a challenge. The clinical evidence for biological treatments evaluated in this population is limited, although it clearly shows there to be a benefit compared to placebo. However, in reality, this population would never receive simply a placebo. In the absence of biological therapy, they would likely receive a package of care with multiple components which may or may not produce quality of life benefits. Defining this package of care was a significant challenge, and the analysis relied on a mixture of evidence from recent cost analyses and GDG opinion. Indeed, efficacy and resource use associated with best supportive care in the absence of biologic therapy were among the most significant drivers of uncertainty in the analysis.

In terms of the population, the clinical evidence is quite muddled with no distinctions between patients who were primary or secondary treatment failures, intolerant to treatment or simply switched as part of a clinical trial. There is also uncertainty as to whether these patients have more, less or equally severe psoriasis as patients who are naïve to biological therapy. The GDG considered it likely that this group would have more severe, treatment-resistant disease and would thus

represent a very resource-intensive group as well as one with a great deal to gain in terms of quality of life if treatment was successful.

As has been outlined in previous appraisals of biological therapy, there is relatively limited long-term experience with biological therapies, and thus estimates of drop out and sustained remission are based on assumptions. There was also limited data on adverse events, both in terms of their incidence as well as their impact on resource use and quality of life. These were excluded from the NCGC analysis, but the GDG did not think that this would change conclusions.

O.4.3 Interpretation of the evidence

There was no economic evidence from the published literature to inform the GDG on the cost-effectiveness of offering a second biological drug to patients with moderate to severe psoriasis who have not responded to, lost response to or been intolerant to a first biological drug. Original decision modelling undertaken for the guideline showed that switching to a second biological drug may be more cost-effective than moving to best supportive care without biological therapy, but there was substantial uncertainty surrounding this conclusion. Uncertainty was driven by unknowns regarding the definition and efficacy of best supportive care.

The GDG considered definitions of best supportive care from previous economic analyses in the UK and found that the defined resource use was likely to be a gross underestimate. Based on the NICE eligibility criteria for biological therapy, these patients will have failed to respond to or will have been intolerant to conventional systemic therapies (methotrexate and ciclosporin) thus limiting their further management options dramatically. In the absence of these relatively inexpensive treatment options, the GDG considered that the majority of these patients would rely on costly outpatient day care and very costly inpatient care to manage their disease. Based on recent resource utilisation studies from the UK and Netherlands and supported by their clinical experience, they outlined a much more resource intensive package of services likely to be used or required by people with moderate to severe psoriasis who did not have access to biological therapy.

The GDG considered the results of the extensive sensitivity analyses around the cost of best supportive care. They considered that when best supportive care was less resource intensive (i.e. fewer annual hospitalisations, shorter length of stay and/or less outpatient day care),switching to a second biological drug was less likely to represent better value for NHS resources. Results showed that only when patients were assumed to have the worst baseline quality of life (and hence have the most to gain from successful treatment) would the substantial additional cost of delivering biological therapy compared to a less resource intensive best supportive care be offset. Conversely, if best supportive care was assumed to be more resource intensive than in the base case, then biological therapy was very likely to be most cost-effective, regardless of baseline quality of life.

There was also uncertainty in the effectiveness of this newly defined best supportive care. Previous analyses have used the placebo response rates from the randomised controlled trials, which when used in the guideline model was virtually equivalent to assuming no response at all. This was varied upwards based on observational data from the UK which showed that response to inpatient treatment ranged between 65% and 83%. When inpatient treatment was assumed to be as effective as this, then the incremental cost-effectiveness ratio of switching to an alternative biological therapy increased to between £20,000 and £30,000 per QALY gained. Although quality of life gains are generally attached only to the clinical outcomes (i.e. PASI response), the GDG discussed whether gains might be affected by how the outcome was reached. They considered that although 3 weeks in hospital may induce an adequate level of response (PASI50), this could have a substantial negative impact on a patient's quality of life compared to a once or twice weekly injection or even an infusion every few months. Furthermore, in order to maintain that level of response, patients would likely have to carry on with regular outpatient day care appointments or use drug treatments that have failed in the past or have potentially serious adverse events (e.g. renal impairment or hepatotoxicity).

The GDG recognised that the model included a population of patients with variable reasons for undergoing treatment with a second biological drug. This includes patients who may have been primary or secondary non-responders, patients who may have been intolerant to an initial biological or other reasons unrelated to the initial treatment. There is also no information about what biological therapy or therapies to which they may have been exposed. It is also unclear as to whether these patients have more or less severe disease than in trials of patients naïve to biological therapy. The GDG considered whether any of these patient differences were likely to impact the cost-effectiveness of biological therapy over best supportive care, and they concluded that the benefit over placebo was likely to be significant enough in any of these groups to justify the additional cost of biological therapy. This was especially true if the patient had very severe disease, as this group would have the most to gain from successful treatment. They noted too that the population likely to reach this point in the care pathway is very small (fewer than 1000 patients). They decided that switching to a second biological drug should be considered in all patients following failure of a first biological drug and noted that the same criteria as outlined in previous NICE guidance should be used to determine eligibility.

O.4.4 Conclusion

New economic analysis from a current UK NHS and PSS perspective comparing biologic therapy to best supportive care found that further biologic therapy is likely to offer better value for NHS resources in the treatment of patients with moderate to severe plaque psoriasis who have previously been exposed to biologic therapy and either failed to respond, lost response or were intolerant to this initial biologic therapy. There is substantial uncertainty in this conclusion, which was explored through extensive sensitivity analyses around various parameters.

- Sensitivity analyses in which the cost of biologic therapy was assumed to be very high (e.g. the cost of infliximab) found that switching to an alternative biologic therapy was unlikely to be cost effective compared to best supportive care.
- Sensitivity analyses in which the cost of best supportive care was assumed to be lower than in the base case (due to fewer very high need patients, fewer hospitalisations, shorter length of stay or fewer visits to day care centre) or when it was more effective than in the base case found that switching to an alternative biologic therapy was unlikely to be cost effective compared to best supportive care.
- Sensitivity analysis in which patients were assumed to start treatment with the worst baseline quality of life, and therefore had the most to gain from successful treatment, found that further biologic therapy was likely to be more cost effective even when resource use for best supportive care was assumed to be low.

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