Section A. Clarification on search strategies

Response to A1

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

Response to A2

Please find the full cost search strategies below.
(HEED and NHS HEED were previously stated in error.)

Medline

#	Search History	Results
1	economics/	4282
2	exp "costs and cost analysis"/	68768
3	exp "Value of Life"/ec [Economics]	149
4	economics,dental/	93
5	exp economics, hospital/	6326
6	economics, medical/	508
7	economics, nursing/	377
8	economics, pharmaceutical/	1396
9	or/1-8	75685
10	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).tw.	147618
11	(expenditure$ not energy).tw.	6038
12	(value adj1 money).tw.	4
13	budget$.tw.	5886
14	or/10-13	153449
15	9 or 14	185014
16	letter.pt.	281760
17	editorial.pt.	122689
18	historical article.pt.	69668
19	or/16-18	468475
20	15 not 19	174468
21	Animals/	1503187
22	human/	4024739
23	21 not (21 and 22)	1008880
24	20 not 23	163966
25	(metabolic adj cost).ti,ab,sh.	248
26	((energy or oxygen) adj cost).ti,ab,sh.	850
27	24 not (25 or 26)	163144
28	etanercept.mp.	1307
29	enbrel.mp.	108
30	efalizumab.mp.	206
31	raptiva.mp.	24
32	infliximab.mp.	3027
33	remicade.mp.	115
34	or/28-33	3901
35	psoriasis/	5711
36	psoria$.mp.	8917
37	antipsoria$.mp.	209
38	anti psoria$.mp.	61
39	or/35-38	8940
40	27 and 34 and 39	34
41	limit 40 to (english language and yr="2004 - 2007")	22

Embase

#	Search History	Results
1	economics/ or exp health economics/	158703
2	cost/ or exp health care cost/	80876
3	exp fee/ or exp health insurance/ or exp pharmacoeconomics/ or health care organization/ or exp health care quality/	657652
4	economic aspect/ or budget.mp.	24985
5	economic aspect/ or budget/	22933
6	exp disease management/	599778
7	(econom$ or cost or costs or costly or costing or costed or price or prices or pricing or pharmacoeconom$).tw.	136497
8	(expenditure$ not energy).tw.	5560
9	(value adj5 money).tw.	310
10	budget$.tw.	4965
11	or/1-10	821642
12	(letter or editorial or historical note or note).pt.	524221
13	11 not 12	691614
14	exp animal/ or animal experiment/ or nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.	1582886
15	human/ or human experiment/	3291266
16	14 not (14 and 15)	1217990
17	13 not 16	664533
18	(metabolic adj cost).mp.	188
19	((energy or oxygen) adj cost).mp.	1344
20	17 not (18 or 19)	663487
21	exp Psoriasis/	10765
22	(psoria$ or anti psoria$ or antipsoria$).mp.	13341
23	21 or 22	13566
24	etanercept/	5311
25	etanercept.mp.	5352
26	enbrel.mp.	1325
27	efalizumab/	692
28	efalizumab.mp.	712
29	raptiva.mp.	286
30	infliximab/	7713
31	infliximab.mp.	7764
32	remicade.mp.	1718
33	or/24-32	9786
34	17 and 23 and 33	595
35	limit 34 to (english language and yr="2004 - 2007")	398

Medline In-Process

#	Search History	Results
1	cost$.mp. [mp=title, original title, abstract, name of substance word]	7167
2	cost$ analys$.mp. [mp=title, original title, abstract, name of substance word]	83
3	economic$.mp. [mp=title, original title, abstract, name of substance word]	2978
4	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).tw.	9431
5	(value adj1 money).tw.	1
6	budget$.tw.	424
7	or/1-6	10267
8	letter.pt.	9608
9	editorial.pt.	5171
10	historical article.pt.	1
11	or/8-10	14780
12	7 not 11	10130

13	etanercept.mp.	115
14	enbrel.mp.	4
15	efalizumab.mp.	21
16	raptiva.mp.	0
17	infliximab.mp.	206
18	remicade.mp.	7
19	or/13-18	279
20	(psoria$ or anti psoria$ or antipsoria$).mp. [mp=title, original title, abstract, name of substance word]	378
21	12 and 19 and 20	2

Cochrane
The search on Cochrane was the same as for the clinical section, without the limitation of economic wording. The reason for this was the fact that Cochrane presents the results by type of study i.e. RCTs, Economic Evaluations, HTA, Other reviews.

ID	Search	Hits
#1	MeSH descriptor Psoriasis explode all trees	1301
#2	etanercept	239
#3	enbrel	34
#4	efalizumab	40
#5	raptiva	6
#6	infliximab	269
#7	remicade	24
#8	(#2 OR #3 or #4 OR #5 OR #6 OR #7)	476
#9	(#1 AND #8), from 2004 to 2007	54

Response to A3

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

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

Section B. Clarification on clinical effectiveness data

Response to B1

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

Response to B2

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

as their results were heterogeneous and as their sample size differed, a random-effects analysis was undertaken.

Response to B3

Please see the attached appendix for a detailed breakdown of the literature search strategy and exclusions.

Response to B4

The indirect comparison and meta-analysis reported in Schering-Plough's STA submission, included data from the EXPRESS II and Tyring et al 2006 trials which had not been available at the time of the previous analysis reported in the technology assessment report, efalizumab and etanercept for the treatment of psoriasis (Woolacott et al 2005).

Section C. Clarification on indirect treatment comparison

Response to C1

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

Response to C2

WinBugs code was not in our original submission and is reproduced in Appendix A of thos document.

Section D. Clarification on cost-effectiveness data

Response to D1

Parameter	Description	Source	Uncertainty	Point Estimate		Uncertainty	
$c^{hospital}$	Yearly cost of hospitalisation for non-responding patient	Assumption based on survey data	Scenario analysis	£7,364.52		PSA £6,903.47	
c^{trial}	Cost of treatment with the infliximab for the 'trial' period	Various	Gamma or Beta distribution	£5,035.44		n/a	
$c^{treatment}$	Yearly cost of treatment with infliximab	Various	Gamma or Beta distribution	£10,910.12		n/a	
d^{trial}	Duration (in years) of the 'trial' period for infliximab	Assumption based on clinical trial designs	Scenario analysis	0.192308		n/a	
$d^{treatment,cost}$	Mean duration (in years) of the 'treatment' period for the calculation of costs	Assumption based on limited observational and trial data	Scenario analysis of patient attrition rate and cost discount rate	3.26		n/a	
$d^{treatment,effect}$	Mean duration (in years) of the 'treatment' period for the calculation of effects	Assumption based on limited observational data	Scenario analysis of patient attrition rate and effect discount rate	3.26		n/a	
u_{00} (all/4th quartile)	Utility for a patient not achieving a PASI 50 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution	0.05	0.12	0.01	0.03
u_{50} (all/4th quartile)	Utility for a patient achieving a PASI 50 response but not a PASI 75 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution	0.17	0.29	0.04	0.06
u_{75} (all/4th quartile)	Utility for a patient achieving a PASI 75 response but not a PASI 90 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution	0.19	0.38	0.04	0.08
u_{90} (all/4th quartile)	Utility for a patient achieving a PASI 90 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution	0.21	0.41	0.05	0.09
p^{pasi50}	Probability of a PASI 50 response	Bayesian hierarchical model of clinical trial data (see Section 6.2.1)	Simulated posterior distribution from MCMC analysis of trial data	Please see table below		Please see table below	
p^{pasi75}	Probability of a PASI 75 response	Bayesian hierarchical model of clinical trial data (see Section 6.2.1)	Simulated posterior distribution from MCMC analysis	Please see table below		Please see table below	
p^{pasi90}	Probability of a PASI 90 response	Bayesian hierarchical model of clinical trial data (see Section 6.2.1)	Simulated posterior distribution from MCMC analysis	Please see table below		Please see table below	

Response to D1 (continued)

	Probability of a Response			
	Mean	2.5% CI	97.5% CI	SD
Response = PASI 50				
Placebo/Supportive Care	0.143	0.1219	0.1669	0.01138
Etanercept 25 mg BIW	0.6258	0.5552	0.6958	0.03598
Etanercept 50 mg BIW	0.7525	0.6986	0.8048	0.02721
Efalizumab 1 mg/kg	0.556	0.498	0.6107	0.02851
Infliximab 5 mg/kg	0.9406	0.9172	0.9604	0.01105
Response = PASI 75				
Placebo/Supportive Care	0.04001	0.03189	0.05001	0.004527
Etanercept 25 mg BIW	0.3592	0.2928	0.4317	0.03565
Etanercept 50 mg BIW	0.5001	0.4348	0.5691	0.03426
Efalizumab 1 mg/kg	0.2939	0.2452	0.3435	0.02478
Infliximab 5 mg/kg	0.8102	0.7592	0.8567	0.02498
Response = PASI 90				
Placebo/Supportive Care	0.005815	0.004139	0.008012	0.0009806
Etanercept 25 mg BIW	0.1289	0.09218	0.1732	0.02073
Etanercept 50 mg BIW	0.2202	0.1729	0.2754	0.02611
Efalizumab 1 mg/kg	0.09438	0.07069	0.1213	0.01281
Infliximab 5 mg/kg	0.5427	0.4721	0.6164	0.03619

Response to D2

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

Response to D3

Patients commence active treatment and remain on it for a "trial" period during which treatment response is assessed. Patients who do not respond are then assumed to receive supportive care and responders continue treatment - the treatment period. The mean length of the treatment period is calculated using a 10 year Markov model with an annual cycle (Figure 6.2.6.1). Patients can "fail" for any reason during the "treatment" period and are assumed to switch to supportive care. This probability of failure is the annual drop out rate. The calculated value for the treatment period is then input into the cost-effectiveness analysis.

Response to D4

"the analysis adjusted the number of outpatient visits for infliximab by the number of infusion visits"-page 61

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

Response to D5

The base case of an 80kg patient cannot be used to demonstrate vial optimization and savings as a result of this, as exactly 4 vials are needed to treat these patients. In order to investigate the potential effects of vial optimization on the ICERs, patients weighing 65kg, 70kg and 90kg will be considered, using varying degrees of vial wastage.

65kg patient

Wastage	0%	50%	100%
Vials	3.25	3.625	4
ICERs	£10,262	£18,178	£26,095

70kg patient

Wastage	0%	50%	100%
Vials	3.5	3.75	4
ICERs	£15,540	£20,817	£26,095

90kg patient

Wastage	0%	50%	100%
Vials	4.5	4.75	5
ICERs	£36,650	£41,928	£47,205

Response to D6

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

Response to D7

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

The table below has utility values for ALL patients.

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

Response to D8

According to the reference case in the Guide for Methods of Technology Appraisal (April 2004), section 5.5.3, the need for consistency across appraisals, has resulted in the EQ-5D becoming the preferred source for utility estimates in the UK.

Health Status was assessed in the infliximab clinical trials using the SF-36 instrument and EQ-5D data was not available.

Utilities reported in the York Assessment Report for etanercept and efalizumab for the treatment of psoriasis (February 2005) were based on the EQ-5D and were considered most appropriate for use in the Schering-Plough model as they were in accordance with the reference case described by NICE in its methods guide.

Response to D9

A consultation exercise with clinical experts was conducted to review and validate key assumptions relating to the economic evaluation of infliximab for the treatment of plaque psoriasis.
The consultation exercise with clinical experts commenced with a detailed explanation and discussion of the decision problem for the STA of infliximab in psoriasis.
Following this introductory discussion, the key input parameters and assumptions in the Schering-Plough economic model were explained and presented for validation.
A detailed description of each assumption was presented, including the base case. This was followed by a roundtable discussion, which concluded with a summary and overall consensus on the parameter values to be assigned for each assumption.
All twelve clinical experts involved with the consultation exercise were registered consultant dermatologists, with a specific clinical interest (e.g. publications) in plaque psoriasis.

Response to D10

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

Response to D11

The underlying model structure is identical to that in the TAR (Woolacott et al 2005), as described in the submission and D3 above. The differences come in the analytical approach and formulas used in calculating costs and benefits. The aim of the TAR analysis was to evaluate, as a function of net-benefit, where within a sequence an individual treatment would be placed. This sequential approach was relevant to the scope of our submission and we evaluated a standard comparative cost-effectiveness analysis. Thus, the absolute values for costs and effects differ between the two approaches. As would be expected ours are more in line with treatment response rates. The ICERs as they are presented do differ, but this is largely due to differences in input values and primarily updated unit cost parameters and resource use in supportive care. When the same input values from the TAR analysis are used the ICERs are comparable.

Response to D12

The main differences in terms of assumptions and parameters between our submission and the technology assessment report are the following:

- the assumed number of outpatient appointments is higher in the Schering-Plough submission; this is based on clinical expert opinion and survey data (refer to sections 6.2.6 and 6.2.9.9);
- the reference costs differ compared to the assessment report; these have been updated using NHS reference costs for 2005-06;
- the response rates differ compared to those in the assessment report, as there is additional data included in the Bayesian hierarchical model (refer to section 5.6);
- efalizumab has been included in the sensitivity analysis as the treatment following failure to respond on infliximab and/or etanercept, as per NICE Guidance;

Appendix A: WinBUGS code for indirect comparison analysis

```
Random EFFECTS MODEL
model
{
# this just has to be large enough to ensure all phi[j]'s > 0
C <- 10000
#random effect baseline, equates to placebo/PASI50 endpoint
for (s in 1:nStudies)
{
mu[s]~dnorm(muMean,muTau)
}
#define mean treatment effects - beta[Tx]
#define random treatment effect variates - randBeta[ Tx]
for (t in 2:nTx)
{
beta[t] ~ dnorm(0,.001)
for (s in 1:nStudies)
{
randBeta[s,t]~dnorm(beta[t],txTau)
}
}
#treatment effect (and variance) is zero for placebo.
beta[1] <- 0
for (s in 1:nStudies)
{
randBeta[s,1]<-0
}
#Model data
for (j in 1:nObs)
{
#study baseline and treatment effect -random treatment effects model
base[j] <- mu[study[j]] + randBeta[study[j],Tx[j]]
#fixed treatment effects version
#base[j] <- mu[study[j]] + beta[Tx[j]]
#probability of <50 percent reduction in PASI
pOutcome[1,j] <- phi(base[j])
#probability of 50-75 percent reduction in PASI
pOutcome[2,j] <- phi(base[j]+c75) - phi(base[j])
#probability of 75-90 percent reduction in PASI
pOutcome[3,j] <- phi(base[j]+ c90) - phi(base[j]+c75)
#probability of >=90 percent reduction in PASI
pOutcome[4,j] <- 1-phi(base[j]+c90)
#probability of >=75 percent reduction in PASI
pOutcome[5,j] <- 1-phi(base[j]+c75)
#probability of >=50 percent reduction in PASI
pOutcome[6,j] <- 1-phi(base[j])
#probability of <75 (clearance) percent reduction in PASI
pOutcome[7,j] <- phi(base[j]+c75)
#probability of >=75 (clearance) percent reduction in PASI
pOutcome[8,j] <- 1-phi(base[j]+c75)
#probability of <75 percent reduction in PASI
pOutcome[9,j] <- phi(base[j]+c75)
#Likelihood function, probability of endpoint to the power of number of
observations
L[j]<- pow(pOutcome[outcome[j],j],n[j])
#use oness trick as described in winbugs manual
logL[j]<- log(L[j])
ones[j] <- 1
p[j] <- L[j] / C
ones[j] ~ dbern(p[j])
predictedP[j] <- pOutcome[outcome[j],j]
}
```

```
#predicted treatment effects in terms of absolute probabilities and Relative Risks
for (t in 1:nTx)
{
predictedTX50[t] <- 1-phi(muMean + beta[t])
rr50[t] <- predictedTX50[t] /predictedTX50[1]
predictedTX75[t] <- 1-phi(muMean + c75 + beta[t])
rr75[t] <- predictedTX75[t] /predictedTX75[1]
predictedTX90[t] <- 1-phi(muMean + c90 + beta[t])
rr90[t] <- predictedTX90[t] /predictedTX90[1]
}
#priors for ordered probit cut points
c75 ~ dunif(0,10)
c90inc ~ dunif(0,10)
c90 <- c75+c90inc
#prior for random baseline effect mean and precision
muMean ~ dnorm(0,.001)
muTau <- 1/(sd*sd)
sd ~ dunif(0,10)
#prior for random treatment effect precision
txTau <- 1/(txSd*txSd)
txSd ~ dunif(0,10)
}
list(mu = c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0), beta = c(NA,0,0,0,0,0,0,0), c75 = 0.5,
c90inc = 1)
list(nTx = 8, nObs = 118, nStudies = 18)
```