NCGC National Clinical Guideline Centre

Crohn's disease

Appendix H

Clinical Guideline <...>

Health economics report

10 October 2012

Commissioned by the National Institute for Health and Clinical Excellence

Royal College of Physicians
Setting higher medical standards

Royal College of Nursing

RCS
ADVANCING SURGICAL STANDARDS

RC GP Royal College of General Practitioners

NHS Evidence
accredited provider
NHS Evidence - provided by NICE
www.evidence.nhs.uk

Published by the National Clinical Guideline Centre at
The Royal College of Physicians, 11 St Andrews Place, Regents Park, London, NW1 4BT

First published 10 October, 2012

Contents

1 Cost-effectiveness analysis - induction of remission

1.1 Introduction

The comparators examined in the model were treatment sequences chosen by the GDG economic subgroup and agreed by the GDG. The economic subgroup comprised two consultant gastroenterologists, one IBD specialist nurse and one patient representative. The drug sequences were chosen by the economic subgroup, and efficacy taken from a network meta-analysis of induction of remission trials. It was decided that, in line with the recommendations made in TA 187[37] and GDG consensus view of clinical practice, biologics should be offered as the last therapy for each of the treatment strategies looked at. The specific treatment sequences were chosen based on the clinical practice of the economic subgroup members, and what they deemed to be the most likely treatment pathway for a patient experiencing an acute exacerbation of Crohn's disease. These are shown in Table 1.

1.2 Methods

1.2.1 Model overview

A cost-utility analysis was undertaken where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services perspective.

1.2.1.1 Comparators

The comparators examined in the model were treatment sequences chosen by the GDG economic subgroup and agreed by the GDG. The GDG elected to consider the cost-effectiveness of one-off induction treatment strategies in the induction of remission model, to reflect the nature of the treatment and the data that could be extracted from the clinical trials. The GDG were satisfied that, having established the most cost-effective induction sequence, longer term costs and effects could be captured in the maintenance model, where relapses from maintenance treatment are then assumed to be treated with the most cost-effective one-off induction sequence found from this analysis. The economic subgroup comprised two consultant gastroenterologists, one specialist IBD nurse and one patient representative. The GDG noted that, although 5-ASAs were considered as a class in the clinical review, the different preparations may have different costs and side-effect profiles, and therefore it was decided to separate them for the economic analysis. The drug sequences were those included in a network meta-analysis of induction of remission. It was decided that, in line with the recommendations made in TA 187[37] and GDG consensus view of clinical practice, biologics should be offered as the last therapy for each of the treatment strategies looked at. The specific treatment sequences were chosen based on the clinical practice of the economic subgroup members, and what they deemed to be the most likely treatment pathway for a patient experiencing an acute exacerbation of Crohn's disease. These are shown in Table 1.

Table 1- Treatment strategies in the model

Strategy	1st line	2nd line	3rd line	4th line
1	Sulfasalazine	Glucocorticosteroid	Azathioprine + a Glucocorticosteroid	Biologic
2	Sulfasalazine	Glucocorticosteroid	Methotrexate + a Glucocorticosteroid	Biologic

Strategy	1st line	2nd line	3rd line	4th line
3	Mesalazine	Glucocorticosteroid	Azathioprine +a Glucocorticosteroid	Biologic
4	Mesalazine	Glucocorticosteroid	Methotrexate + a Glucocorticosteroid	Biologic
5	Glucocorticosteroid	Azathioprine + a Glucocorticosteroid	Biologic	-
6	Glucocorticosteroid	Methotrexate + a Glucocorticosteroid	Biologic	-
7	Budesonide	Glucocorticosteroid	Azathioprine + a Glucocorticosteroid	Biologic
8	Budesonide	Glucocorticosteroid	Methotrexate + a Glucocorticosteroid	Biologic
9	Glucocorticosteroid	Biologic	-	-

1.2.1.2 Population

The population entering the model comprises people with an acute exacerbation of Crohn's disease, defined by a Crohn's Disease Activity Index (CDAI) score of > 150. Biologics are only recommended for people with severe Crohn's disease[37]; an assumption was made that people whose exacerbation failed to respond to two lines of treatment would be regarded as falling under the aegis of the TA, though it was noted that this may not always be the case. Strategy 9 in Table 1 is only relevant for people where the Crohn's disease has progressed to severe before initiation of biologic treatment, despite only failing one line of induction.

1.2.1.3 Time horizon

The time horizon considered in the base-case model was 30 weeks. This time horizon was chosen to reflect the longest drug treatment sequence based upon clinical practice. This also reflects the assumptions made in the conditional logistic regression conducted to derive efficacy inputs. In this analysis it was assumed, based on information from the trials and GDG opinion, that the trials were of sufficient duration such that remission or withdrawal would occur by a certain time, or not at all. For example, it was assumed that in a glucocorticosteroid trial lasting 16 weeks, the proportion of people entering remission would not be significantly higher than in a trial lasting eight weeks, since those people who are reported to be in remission at 16 weeks were likely to have entered remission by eight weeks. The effect of treatment durations that were closer to those used in the trials was explored in sensitivity analysis. Treatment durations for the base case and sensitivity analysis are shown in Table 2.

Table 2- Drug treatment durations

Drug	Treatment duration (weeks) in base case based upon clinical practice	Treatment duration (weeks) in sensitivity analysis based on average length of clinical trials
Glucocorticosteroid	8	11
Sulfasalazine	8	16
Mesalazine	8	14
Budesonide	8	10
Azathioprine + Glucocorticosteroid	8	20

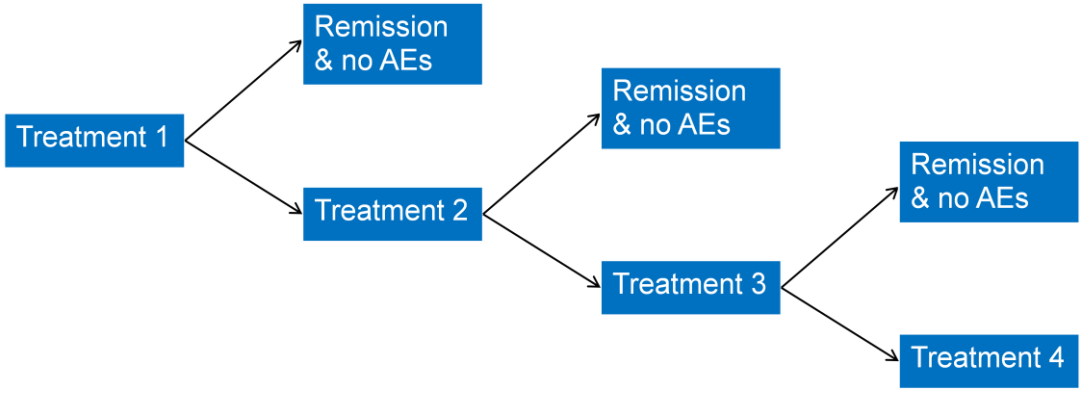
Drug	Treatment duration (weeks) in base case based upon clinical practice	Treatment duration (weeks) in sensitivity analysis based on average length of clinical trials
Methotrexate + Glucocorticosteroid	8	32
Biologic	6	6

1.2.2 Approach to modelling

1.2.2.1 Model structure

A decision tree was constructed, whereby the QALY gain was driven by the proportion of people in whom remission was successfully induced. Remission was defined as not withdrawing due to an adverse event and a CDAI score of < 150. People who withdrew due to an adverse event or did not respond to treatment moved on to the next line of treatment. Although the GDG noted it was unlikely that all treatments would have the same side-effect profile, they accepted that the reporting of specific adverse events in the RCTs was not sufficient to model specific treatment-related adverse events. On that basis, they agreed that withdrawals from treatment could be used as a proxy for adverse events, and that costs and disutilities pertaining to adverse events for each treatment would be captured by both the additional cost of further treatment, and by patients still having the utility weight associated with active disease. Sensitivity analyses were conducted which explored the effects of including drug-related adverse events for glucocorticosteroid monotherapy; observational data was used to conduct this analysis. To capture the benefits of inducing remission early, people in whom remission is induced on the first-line treatment gained more QALYs than those who respond on second-, third- or fourth- line treatment. The structure of the model is shown in Figure 1.

Figure 1- Model structure



Key assumptions:

- Treatment continues to the end of the treatment cycle regardless of whether people enter remission.
- Utility is assumed to improve in the middle of the treatment cycle for those entering remission.
- For time spent in active disease, people incur more contacts with the health service than they do in remission (see Table 11).
- Withdrawals are assumed to occur at the end of a treatment cycle.
- All people who do not enter remission by the end of the time horizon are assumed to undergo surgery.

1.2.3 Uncertainty

1.2.3.1 One-way sensitivity analysis

One-way sensitivity analyses were also conducted to test the robustness of model results to changes in key parameters. In one-way sensitivity analysis, one parameter is varied while all other parameters are kept constant and the effects of changing this parameter on the model results are explored. The one-way sensitivity analyses conducted are described in Table 20.

1.2.3.2 Probabilistic analysis

A Monte Carlo simulation[16] was conducted to explore the uncertainty in model results. In a Monte Carlo simulation, each parameter is assigned a distribution reflecting its uncertainty; random draws are then taken from this distribution and propagated through the model, to calculate costs and QALYs. This process is repeated 10,000 times and a model result which represents an average of the simulations is computed.

1.2.4 Model inputs

1.2.4.1 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 by the GDG. A summary of the model inputs used in the base-case analysis is provided in Table 3, Table 4, and Table 5 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 3: Cost inputs

Input	Data	Source
Drugs (see Table 12 to Table 18)		
Cost per course of glucocorticosteroid[(a)]	£362.17	BNF 63 [26]and NHS reference costs [14]
Cost per course of sulfasalazine[(a)]	£362.48	BNF 63 [26]and NHS reference costs [14]
Cost per course of mesalazine[(a)]	£416.32	BNF 63 [26]and NHS reference costs [14]
Cost per course of budesonide[(a)]	£492.01	BNF 63 [26]and NHS reference costs [14]
Cost per course of azathioprine + a glucocorticosteroid[(a)]	£429.34	BNF 63 [26]and NHS reference costs [14]
Cost per course of methotrexate + a glucocorticosteroid[(a)]	£355.67	BNF 63 [26]and NHS reference costs [14]
Cost per course of biologic[(a)]	£1,426.09	BNF 63 [26] and NHS reference costs [14]
Visits		
Yearly cost of Crohn's treatment while in remission	£232.00	GDG economic subgroup see maintenance of remission model
Consultant medical gastroenterology outpatient visit	£114.00	NHS reference costs[14]: Consultant led follow up

Input	Data	Source
		attendance non admitted face to face "Medical gastroenterology" (code 301M)
Non consultant medical gastroenterology outpatient visit	£95.00	NHS reference costs[14]: Non consultant led follow up attendance non admitted face to face "Medical gastroenterology" (code 301M)
Consultant surgical gastroenterology outpatient visit	£94.00	NHS reference costs[14]: Consultant led follow up attendance non admitted face to face "Surgical gastroenterology" (code 301S)
Non consultant surgical gastroenterology outpatient visit	£57.00	NHS reference costs[14]: Non consultant led follow up attendance non admitted face to face "Surgical gastroenterology" (code 301S)
Cost for average-length GP consultation	£41.00	PSSRU[11]
Phone call to IBD nurse	£5.70	Economic subgroup
Tests		
DEXA scan	£72.00	NHS reference costs [14]: Diagnostic imaging outpatient (code RA15Z)
Microbiology/virology tests for chickenpox	£8.00	NHS reference costs[14]: Direct access; Pathology services "Virology" (DAP831)
Full blood count	£3.00	NHS reference costs [14]: Direct access; Pathology services; "Haemotology: Excluding anti-coagulant services" (DAP823)
Renal and liver function tests	£1.00	NHS reference costs[14]: Direct access; Pathology services; "Biochemstry" (DAP841)
Chest X-ray	£17.00	NICE TB guideline[35]

Input	Data	Source
Surgery		
Pan-proctocolectomy with 'major complication or co-morbidity'[(b)]	£9,606.41	NHS reference costs[14]: Elective inpatient; "Complex Large Intestine Procedures with Major CC" (FZ08A)
Pan-proctocolectomy without 'major complication or co-morbidity'[(b)]	£6,411.23	NHS reference costs[14]: Elective inpatient; "Complex Large Intestine Procedures without Major CC" (FZ08B)
Colectomy with 'major complication or co-morbidity'[(b)]	£7,190.66	NHS reference costs[14]: Elective inpatient; "Proximal colon procedures with Major CC" (FZ09A)
Colectomy without 'major complication or co-morbidity'[(b)]	£5,259.60	NHS reference costs[14]: Elective inpatient; "Proximal colon procedures without Major CC" (FZ09B)
Right hemicolectomy with 'major complication or co-morbidity'[(b)]	£7,190.66	NHS reference costs[14]: Elective inpatient; "Proximal colon procedures with Major CC" (FZ09A)
Right hemicolectomy without 'major complication or co-morbidity'[(b)]	£5,259.60	NHS reference costs[14]: Elective inpatient; "Proximal colon procedures without Major CC" (FZ09B)
Small intestine resection with 'major complication or co-morbidity'[(b)]	£5,163.87	NHS reference costs[14]: Elective inpatient; "Major small intestine procedures with Major CC" (FZ07A)
Small intestine resection without 'major complication or co-morbidity'[(b)]	£3,792.33	NHS reference costs[14]: Elective inpatient; "Major small intestine procedures without Major CC" (FZ07B)
Strictureplasty with 'major complication or co-morbidity'[(b)]	£5,163.87	NHS reference costs[13]: Elective inpatient; "Major small intestine procedures with

Input	Data	Source
		Major CC" (FZ07A)
Strictureplasty without 'major complication or co-morbidity'[(b)]	£3,792.33	NHS reference costs[13]: Elective inpatient; "Major small intestine procedures without Major CC" (FZ07B)
Interferon gamma test for latent TB	£22.00	NICE TB guideline[35]
Weighted average cost of surgery (Table 19)	£5,351.24	NHS reference costs[14] [13]
Patient weight	77.9kg	National average body weight for UK[40]
10 yearly baseline myocardial infarction risk	24%	NICE hypertension guideline[33]
Odds ratio for myocardial infarction with intermittent high dose glucocorticosteroid therapy	3.0	Varaz-Lorenzo[61]
Cost of treating a myocardial infarction (initial and subsequent costs up to one year)	£5,329	NICE hypertension guideline[33]
Utility weight associated with myocardial infarction	0.76	NICE hypertension guideline[33]
England population excluding children	31,653,000	ONS[42]
Number of hip fractures per year	69,319	National hip fracture database[55]
Relative risk for hip fracture with intermittent high-dose glucocorticosteroid therapy	1.77	De Vries[12]
Cost of hip fracture	£13,367	NHS Reference Costs[14]
Utility weight associated with hip fracture	0.584	NICE hip fracture guideline[34]

(a) Including tests and consultations

(b) Used to calculate a weighted cost for surgery in the model (Table 19)

Table 4- Clinical inputs- probabilities of withdrawal and remission

Input	Probability of withdrawal due to adverse events	Probability of achieving remission conditional on no withdrawal
Glucocorticosteroid	13%	66%
Sulfasalazine	31%	44%
Mesalazine	7%	41%
Budesonide	5%	55%
Azathioprine + glucocorticosteroid	6%	66%
Methotrexate + glucocorticosteroid	11%	61%
Biologic	11%	62%

Source: Clinical review and resulting Network Meta-analysis (1.2.4.2)

Table 5- Utility weights in the model

Input	Data	Source

Disease remission	0.89	Stark et al[54]
Active disease	0.61	Stark et al[54]

1.2.4.2 Treatment effects (remission and withdrawal)

The results of conventional meta-analyses of direct evidence alone make it difficult to determine which intervention is the most effective treatment. The challenge of interpretation has arisen for two reasons:

- Some pairs of alternative strategies have not been directly compared in a randomised controlled trial
- There are frequently multiple overlapping comparisons that could potentially give inconsistent estimates of effect.

This is particularly problematic for probabilistic analysis. To overcome these problems, a Bayesian network meta-analysis (NMA) was conducted in WinBUGS, using code and assistance provided by the NICE technical support unit.

Conventional meta-analysis assumes that for a fixed-effect analysis, the relative effect of one treatment compared to another is the same across an entire set of trials. In a random-effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same relative effect across all trials of intervention A compared to intervention B as it does across trials of intervention A versus intervention C, and so on. Thus, in a random-effects network meta-analysis, the assumption is that intervention A has the same effect distribution across all trials of A versus B, A versus C and so on.

The aim of the NMA was to calculate treatment-specific probabilities for withdrawal and remission conditional on non withdrawal. It is assumed that people who withdraw cannot go into remission, and similarly people counted as 'a remission' have not withdrawn due to adverse events, in other words, the two events are mutually exclusive. Treatment effects for the model had to be accounted for such that the number of withdrawals and remissions could not exceed the number of people in the trial. This negative correlation in outcomes is taken account of by carrying out a conditional logistic regression NMA.

For the network meta-analysis, treatment effects were calculated so as to reflect the clinical review as closely as possible in terms of pooling of studies. In order to obtain treatment effects for remission conditional on non withdrawal, the number of withdrawals was removed from the denominator when entering data for remission into WinBUGS. Baseline log odds of withdrawal and remission conditional on non-withdrawal were calculated using a logistic regression conducted on the placebo arms in the trials and then adjusted by the treatment specific log odds ratios calculated by the NMA using the following logic:

Let $\mathbf{BO_w}$, $\mathbf{BO}_{r|w^c}$, $\boldsymbol{\theta}_w$, $\boldsymbol{\theta}_{r|w^c}$ and $\mathbf{OR_w}$,$\mathbf{OR}_{r|w^c}$ denote the baseline odds (from the placebo arms), treatment-specific odds and treatment-specific log odds ratio for withdrawal and remission given no withdrawal respectively. Then:

$$\boldsymbol{\theta}_w = \boldsymbol{Ln}(\mathbf{OR_w}) + \boldsymbol{Ln}(\mathbf{BO_w})$$

$$\boldsymbol{\theta}_{r|w^c} = \boldsymbol{Ln}\left(\mathbf{OR}_{r|w^c}\right) + \boldsymbol{Ln}(\mathbf{BO}_{r|w^c})$$

And:

$$p_w = \frac{e^{(\theta_w)}}{1 + e^{(\theta_w)}}$$

$$p_{r|w^c} = \frac{e^{(\theta_{r|w^c})}}{1 + e^{(\theta_{r|w^c})}}$$

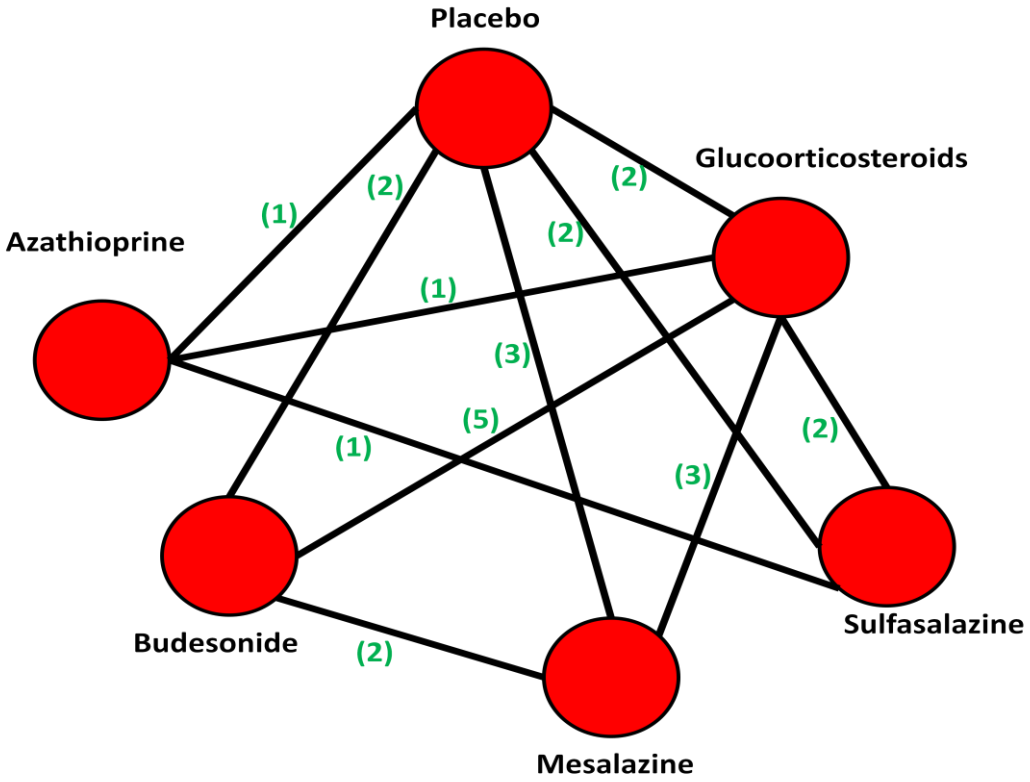
This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale. It also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

To reflect the populations explored in the clinical review, two separate analyses were conducted; one for people on first-line monotherapy treatment, and one for people on second-line treatment in combination with a glucocorticosteroid, having failed first-line glucocorticosteroid monotherapy.

1.2.4.3 First-line NMA

The schematic of trials compared in the first line NMA is shown in Figure 2.

Figure 2-Network of trials compared in the first-line NMA



In the trial network in Figure 2, glucocorticosteroid treatment featured in the most trials (10) followed by budesonide (9), mesalazine (8), placebo (7), sulfasalazine (2) and azathioprine monotherapy (1). For ease of interpretation, placebo was chosen as the baseline treatment for comparisons in the NMA. The data used in the first-line induction NMA can be found in Table 6. Please note that although azathioprine monotherapy was included in the NMA for completeness, it was not compared in the cost-effectiveness analysis. First-line azathioprine monotherapy was not

included because of the lack of evidence and because it has a slower response than the other treatments considered. (3 – 4 months i.e. longer than the 2 month time horizon considered)

Table 6- Data for the first-line NMA

Study Name	Withdrawals				Remissions				Total number of people				Treatments compared			
	arm 1	arm 2	arm 3	arm 4	arm 1	arm 2	arm 3	arm 4	arm 1	arm 2	arm 3	arm 4	arm 1	arm 2	arm 3	arm 4
Mahida[28]	1	3	-	-	7	8	-	-	20	20	-	-	PLA	MES	-	-
Malchow[30]	1	1	1	-	22	39	27	-	58	47	54	-	PLA	CS	SUL	-
Rasmussen[48]	2	1	-	-	9	13	-	-	37	30	-	-	PLA	MES	-	-
Singleton[51]	14	43	-	-	14	68	-	-	80	230	-	-	PLA	MES	-	-
NCCDS[52]	0	4	5	4	20	40	28	21	77	85	74	59	PLA	CS	SUL	AZA
Greenberg [22]	3	3	-	-	13	31	-	-	66	61	-	-	PLA	BUD	-	-
Tremaine[58]	3	14	-	-	13	78	-	-	41	159	-	-	PLA	BUD	-	-
Bar-Meir[5]	4	4	-	-	56	51	-	-	101	100	-	-	CS	BUD	-	-
Escher[17]	7	1	-	-	17	12	-	-	26	22	-	-	CS	BUD	-	-
Gross[24]	0	1	-	-	24	19	-	-	33	34	-	-	CS	BUD	-	-
Rutgeerts [49]	2	0	-	-	56	45	-	-	88	88	-	-	CS	BUD	-	-
Tursi[60]	0	0	-	-	8	10	-	-	15	15	-	-	CS	BUD	-	-
Tromm[59]	8	4	-	-	95	107	-	-	153	154	-	-	MES	BUD	-	-
Thomsen[56]	8	3	-	-	37	63	-	-	89	93	-	-	MES	BUD	-	-
Scholmerich[50]	2	2	-	-	-	-	-	-	32	30	NA	NA	CS	MES	-	-
Prantera 1999[44]	5	1	-	-	-	-	-	-	31	63	NA	NA	CS	MES	-	-
Martin 1990[31]	2	2	-	-	-	-	-	-	28	22	NA	NA	CS	MES	-	-

A logistic regression was run on the placebo arms of the trials shown in Table 6; this produced a baseline odds, BO which was used in the NMA to derive treatment-specific probabilities as described above. The baseline odds for withdrawal and remission had lognormal distributions parameterised as:

$$ln(BO_{Withdrawal}) \sim N(-3.3, 1.15)$$

$$ln(BO_{Remission}) \sim N(-0.95, 2.27)$$

The model was run for 50,000 iterations with a burn in period of 50,000. Vague uninformative priors were combined with data-driven likelihood functions to produce posterior probability estimates. The final treatment-specific probability estimates and their associated confidence intervals can be seen in Table 7.

Table 7- Probabilities from 1st line NMA

Treatment	Withdrawals				Remission given no withdrawal			
	mean	sd	median	CrI	mean	sd	median	CrI

Glucocorticosteroids	13.2%	0.10	10.3%	(0.9% , 14.3%)	66.1%	0.07	66.3%	(52.5% , 78.6%)
Sulfasalazine	34.6%	0.21	31.3%	(5.2% , 80.2%)	43.8%	0.09	43.6%	(27.5% , 61.0%)
Mesalazine	6.9%	0.06	5.2%	(0.6% , 16.2%)	40.7%	0.07	40.4%	(27.2% , 55.2%)
Budesonide	4.7%	0.04	3.4%	(1.1% , 22.5%)	55.2%	0.07	55.2%	(41.0% , 69.2%)
Azathioprine	20.4%	0.17	15.4%	(0.6%% , 16.2%)	46.6%	0.11	46.4%	(26.2% , 68.2%)

It can be seen from Table 7, that among first-line treatments, sulfasalazine was associated with the highest probability of withdrawal- 35%- but with the 95% confidence interval ranging from 5% to 80%. Glucocorticosteroid treatment was associated with the highest probability of remission conditional on non-withdrawal- 66% with 95% confidence interval ranging from 53% to 79%. These estimates were used to parameterise treatment effects in the model; it should be noted that there is a large amount of imprecision in these estimates, particularly for withdrawal. This is often the case when calculating treatment effects for withdrawal due to small event numbers.

Model fit was assessed by calculating the total residual deviance and comparing with the number of unconstrained data points. In the withdrawals NMA, the total residual deviance was 38.6 which, when compared to 43 unconstrained data points, shows that the model fitted the data reasonably well. In the remission conditional on no-withdrawal NMA, the total residual deviance was 35.94 which again, when compared to 31 unconstrained data points, showed that the model fitted the data reasonably well. DIC statistics of 154.9 and 200.1 were calculated for the withdrawal and remission conditional on no-withdrawal NMAs respectively.

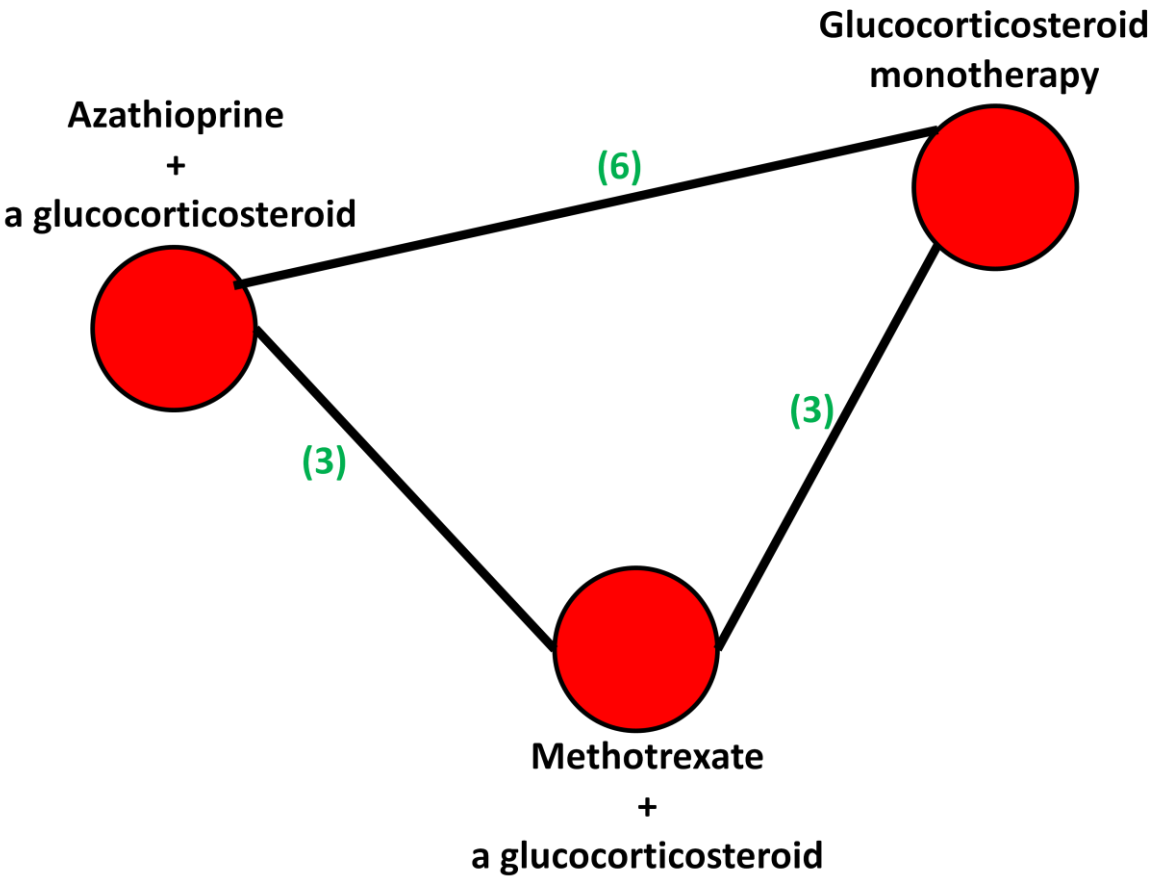
Posterior estimates of heterogeneity- between trial variance- were calculated and values of 0.29 and 0.22 were found for the withdrawal and remission trials. This shows there was a large amount of variation in treatment effects calculated from different trials.

Inconsistency in the network was assessed by fitting an 'inconsistency model'[15]

1.2.4.4 Second-line NMA

The schematic of trials compared in the second line NMA is shown in Figure 3.

Figure 3-Network of trials compared in the second-line NMA



In the trial network in Figure 3, glucocorticosteroid monotherapy and azathioprine + a glucocorticosteroid featured in the most trials (eight); methotrexate + a glucocorticosteroid featured in five trials. For ease of interpretation, glucocorticosteroid treatment- which can be thought of here as the placebo comparison- was chosen as the baseline treatment for the NMA. The data used in the second-line induction NMA can be found in Table 8.

Table 8- Data for the first-line NMA

Study	Withdrawals			Remissions			Total number of people			Treatments compared		
	arm 1	arm 2	arm 3	arm 1	arm 2	arm 3	arm 1	arm 2	arm 3	arm 1	arm 2	arm 3
Mate-Jimenez[32]	1	2	-	15	12	-	16	15	-	AZA + CS	MTX + CS	-
Ardizonne[3]	3	3	-	9	12	-	27	27	-	AZA + CS	MTX + CS	-
Oren[43]	0	1	1	12	13	10	26	32	26	CS	AZA + CS	MTX + CS
Arora[4]	0	3	-	3	7	-	18	15	-	CS	MTX + CS	-
Feagan[19]	1	16	-	9	37	-	47	94	-	CS	MTX + CS	-

Candy [8]	2	0	-	20	25	-	30	33	-	CS	AZA + CS	-
Ewe[18]	0	1	-	8	16	-	21	21	-	CS	AZA + CS	-
Klein[27]	0	2	-	6	6	-	13	13	-	CS	AZA + CS	-
Willoughby[63]	0	0	-	1	6	-	6	6	-	CS	AZA + CS	-
Present[46]	3	10	-	5	26	-	56	68	-	CS	AZA + CS	-

It should be noted that since Present was a crossover trial, the denominators reported for safety and efficacy are different; this is reflected in the clinical review. To account for this, the numerator for remission given no withdrawal was not adjusted by removing withdrawals, since it is not possible to determine exactly which of the people eligible to be assessed for the remission outcome withdrew. This is a conservative approach since it means the number of people being assessed for the remission outcome is bigger and thus the overall probability of achieving remission becomes smaller. Denominators of 36 were used for both arms of the Present study for the remission outcome.

A logistic regression was run on the glucocorticosteroid monotherapy arm of the trials shown in Table 8; this produced a baseline odds, BO which was used in the NMA to derive treatment-specific probabilities as described above. The baseline odds for withdrawal and remission had lognormal distributions parameterised as:

$$\boldsymbol{ln(BO_{Withdrawal})} \sim \boldsymbol{N(-4.49, 0.89)}$$

$$\boldsymbol{ln(BO_{Remission})} \sim \boldsymbol{N(-0.74, 1.46)}$$

The model was run for 50,000 iterations with a burn in period of 50,000. Vague uninformative priors were combined with data-driven likelihood functions to produce posterior probability estimates. The final treatment-specific probability estimates and their associated confidence intervals can be seen in Table 9.

Table 9- Probabilities from first-line NMA

	Withdrawals				Remission given no withdrawal			
	mean	sd	median	CrI	mean	sd	median	CrI
Azathioprine + a glucocorticosteroid	6.3%	0.12	1.7%	(0.0% , 46.4%)	66.0%	0.15	67.3%	(33.3% , 91.5%)
Methotrexate + a glucocorticosteroid	11.1%	0.18	3.6%	(0.1% , 69.7%)	61.4%	0.18	63.1%	(23.0% , 90.8%)

It can be seen from Table 9 that out of the two second-line treatments, methotrexate + a glucocorticosteroid was associated with the highest probability of withdrawal- 11%- with 95% confidence interval ranging from 0% to 70%. Azathioprine + a glucocorticosteroid was associated with a higher probability of remission conditional on no withdrawal- 66% with 95% confidence interval ranging from 33% to 92%. These estimates were used to parameterise treatment effects in the model; it should be noted that there is a large amount of imprecision in these estimates, particularly for withdrawal. This is often the case when calculating treatment effects for withdrawal due to small event numbers, but the remission conditional on no withdrawal outcome is also associated with large imprecision.

Model fit was assessed by calculating the total residual deviance and comparing this with the number of unconstrained data points. In the withdrawals NMA, the total residual deviance was 20.94 which, when compared to 21 unconstrained data points, shows that the model fitted the data well. In the remission conditional on no withdrawal NMA, the total residual deviance was 23.71 which, when compared to 21 unconstrained data points, shows that the model fitted the data reasonably well. DIC statistics of 70.4 and 105.5 were calculated for the withdrawal and remission conditional on no-withdrawal NMAs respectively.

Posterior estimates of heterogeneity- between trial variance- were calculated and values of 0.67 and 1.22 were found for the withdrawal and remission trials. This shows there was a very large amount of variation in treatment effects calculated from different trials.

Posterior estimates of heterogeneity were calculated for the 'inconsistency model' and values of 0.61 and 1.53 were found for the withdrawal and remission trials. This shows that the incorporation of the consistency equations did not force the between trial variance to increase in the remission conditional on no-withdrawal and therefore it is unlikely that there is inconsistency within the network. There was, however, an increase in heterogeneity in the withdrawal NMA (0.61 vs 0.67), which prompted further investigation of inconsistency within the network. Since there were only three treatments in the network the Bucher method[7] can be used to detect whether the amount of inconsistency in the network is statistically significant or a chance finding. A p-value of 0.46 was calculated to test the null hypothesis that there was no inconsistency in the network; this shows that there is insufficient evidence to reject the null and therefore it cannot be said that there is inconsistency.

Figure 4- Patient pathway and probabilities (one treatment cycle)

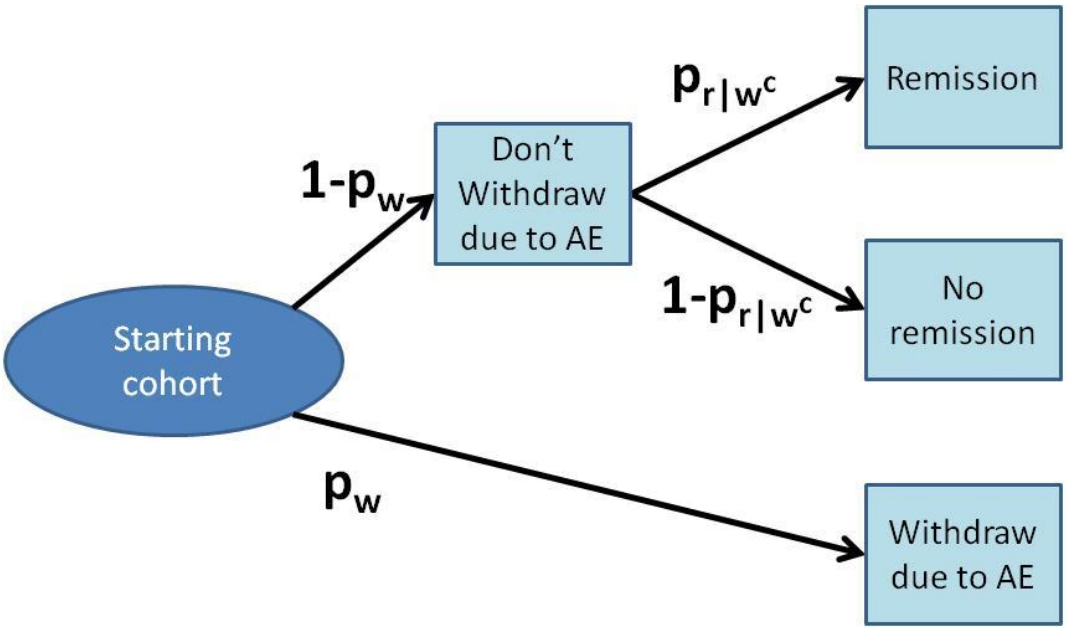


Figure 4 shows how the model probabilities interact for one treatment cycle in the patient pathway. Figure 4 shows that from the number of people entering the model, $\boldsymbol{n}$, the number of people entering remission $\boldsymbol{n_{rem}}$ after one treatment cycle and the number of people failing to enter remission $\boldsymbol{n_{no\,rem}}$ for a given drug can be calculated using the equations:

$$\boldsymbol{n_{rem} = n \times (1 - p_w) \times p_{r|w^c}}$$

$$\boldsymbol{n_{no\,rem} = n \times p_w + n \times (1 - p_w) \times (1 - p_{r|w^c})}$$

1.2.4.5 Utilities

For economic evaluation, a specific measure of Health Related Quality of Life (HRQoL) known as utility is required to calculate QALYs. Utilities indicate the preference for health states on a scale from 0 (death) to 1 (perfect health). The NICE reference case[36] specifies that the preferred way for this to be assessed is by the EQ-5D instrument.

A systematic search identified four studies[9,21,23,54] with appropriate data to use as utility weights for the model. A description of these studies is shown in Table 10

Table 10-Selecting utility weights for the model

Name	Population and brief methods	Limitations	Values
Impairment of Health-related Quality of Life in Patients with Inflammatory Bowel Disease: A Spanish Multicenter Study[9]	1156 patients (528 UC, 628 Crohn's) were stratified by disease severity according to Harvey Bradshaw Index, where patients with a score of < 2 was considered to be in disease remission and patients with a score ≥ 2 was considered to be in clinical relapse. The EQ-5D questionnaire was administered	Utility weights were not calculated by the authors, but were calculated in a separate economic evaluation[47]; the technical team were unable to replicate these authors' calculations. The highest dimension of the EQ-5D questionnaire was not used.	Remission = 0.83 Active disease = 0.55
Relationship between disease severity, quality of life and health-care resource use in a cross section of Australian patients with Crohn's disease[21]	143 Patients > 18 with CD (110 without fistulising disease). Patients' CDAI and AQoL assessed.	AQoL score was used to calculate utility weights, EQ-5D is preferable.	CDAI < 150 = 0.766 CDAI 150-219 = 0.68 CDAI ≥ 220 = 0.45
An Evaluation of Utility measurement in Crohn's Disease[23]	180 patients with Crohn's disease. Patients were stratified into chronically active- therapy responsive, chronically active- therapy resistant, acute disease exacerbation, remission and asked to complete the IBDQ and determine utility of their disease by way of standard gamble, time trade off and visual analogue scale	A validated questionnaire was not used. Values are not from the general public.	Active therapy resistant (TTO, SG, VAS) = (0.88, 0.74, 0.61) Active therapy responsive (TTO, SG, VAS) = (0.98, 0.86, 0.62) Acute disease exacerbation (TTO, SG, VAS) = (0.89, 0.77, 0.60) Remission (TTO, SG, VAS) = (0.96, 0.88, 0.84)
Validity, Reliability and Responsiveness of the EQ-5D in Inflammatory Bowel Disease in Germany[54]	270 Crohn's disease patients in the UK and Germany completed the EQ-5D questionnaire; results of the questionnaire are stratified by disease activity, determined by CDAI score. EQ-5D was calculated using both the German and UK tariff.	None	Remission (EQ-5D TTO, EQ-5D VAS) = (0.89, 0.85) Active disease (EQ-5D TTO, EQ-5D VAS) = (0.61, 0.63) UK tariff reported here.

Utility weights derived by Stark et al[54] were used due to the comparative lack of limitations and the directness of the population. In particular, the Stark data was favoured due to:

- Use of EQ-5D to elicit utility weights directly from patients

- UK EQ-5D tariff used
- Use of CDAI thresholds that mirrored those used in most of the papers in the clinical review.

1.2.4.6 Resource use and cost

The GDG thought it likely that, as well as the treatment-specific tests and consultations, people with an exacerbation of Crohn's disease would have regular consultations and tests regardless of the drug. These consultations and tests are summarised in Table 11 and the weighted average cost calculated is shown in Table 3.

Table 11- Consultations and tests for people not in remission (regardless of induction treatment)

Type of consultation	Frequency
Consultant gastroenterologist	30 visits per 100 people every 2 weeks
Nurse specialist	30 visits per 100 people every 2 weeks
Specialist registrar	30 visits per 100 people every 2 weeks
Phone call to IBD nurse	60 per 100 people every 2 weeks
GP	10 visits per 100 people every 2 weeks

Weighted average costs of drug preparations were used in the model; weights were calculated using prescription-cost-analysis data[39] in order to calculate drug costs which reflect how they are prescribed in clinical practice.

Table 12- Prednisolone costs in the model including tests

Cost item	Value	Frequency	Prescriptions (1,000s)	Weight	Source
Prednisolone 5 mg	£1.21	40 mg initially then taper by 5 mg weekly	696	65%	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
Prednisolone 5 mg E/C	£9.68	40 mg initially then taper by 5 mg weekly	374	35%	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
DEXA scan	£72.00	15% of people at baseline	-	-	NHS reference costs[14] (code RA15Z) and GDG economic subgroup

Based on the costs, weights and dosing schedule described in Table 12, a cost of £38.10 was calculated for an eight week course of prednisolone drug treatment in the base case. The total cost including tests and consultations was £362.17 (Table 3).

Table 13- Budesonide costs in the model including tests

Cost item	Value	Prescriptions (1,000s)	Weight	Frequency	Source
100 pack Entocort 3 mg	£99	4.97	63%	9 mg per day initially then reduce to 3 mg after 6 weeks	BNF 6 [25]and GDG economic subgroup

Cost item	Value	Prescriptions (1,000s)	Weight	Frequency	Source
100 pack Budenofalk 3 mg	£75.05	2.95	37%	9 mg per day initially then reduce to 3 mg after 6 weeks	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
DEXA scan	£72.00	-	-	15% of people at baseline	NHS reference costs NHS reference costs[14] (code RA15Z) and GDG economic subgroup

Based on the costs, weights and dosing schedule described in Table 13, a cost of £167.94 was calculated for an eight week course of budesonide drug treatment in the base case. The total cost including tests and consultations was £492.01 (Table 3).

Table 14- Mesalazine costs in the model including tests

Cost item	Value	Prescriptions (1,000s)	Weight	Frequency	Source
90 pack Asacol MR 400 mg	£29.41	351	56%	2.4 mg daily	BNF 63[26],GDG economic subgroup and prescription cost analysis data[39]
100 pack Pentasa 500 mg	£24.21	272	43%	2.5 mg daily	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
100 pack Salofalk E/C 250 mg	£16.19	5.73	1%	2.5 mg daily	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
Liver function test	£1.00	-	-	2 per course	NHS reference costs [14] (code DAP841) and GDG economic subgroup
Renal function test	£1.00	-	-	2 per course	BNF 61, NHS reference costs (code DAP841) and GDG economic subgroup

Based on the costs, weights and dosing schedule described in Table 14, a cost of £98.01 was calculated for an eight week course of mesalazine in the base case. The total cost including tests and consultations was £416.32 (Table 3).

Table 15- Sulfasalazine costs in the model including tests

Cost item	Value	Prescriptions (1,000s)	Weight	Frequency	Source
112 pack Sulfasalazine 500 mg	£6.74	116	16%	4 g daily	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
112 pack Sulfasalazine Tab E/C 500 mg	£14.46	365	49%	4 g daily	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
112 pack Salazopyrin 500 mg	£6.97	45	6%	4 g daily	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
112 pack Salazopyrin-En 500 mg	£8.43	215	29%	4 g daily	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
Liver function test	£1.00	-	-	2 per course	BNF 63[26], NHS reference costs NHS reference costs[14] (code DAP841) and GDG economic subgroup
Renal function test	£1.00	-	-	2 per course	BNF 63[26], NHS reference costs NHS reference costs[14] (code DAP841) and GDG economic subgroup

Based on the costs, weights and dosing schedule described in Table 15, a cost of £44.16 was calculated for an eight-week course of sulfasalazine in the base case. The total cost including tests and consultations was £362.48 (Table 3).

Table 16- Methotrexate costs in the model including tests

Cost item	Value	Frequency	Source
65 pack methotrexate 2.5 mg	£24.21	17.5 mg weekly	BNF 63[26]and GDG economic subgroup
Liver function test	£1.00	Weekly for the first month then once per month thereafter	BNF 61, NHS reference costs NHS reference costs[14] (code DAP841) and GDG economic subgroup
Full blood count	£3.00	Weekly for the first month then once per month thereafter	BNF 63[26]and GDG economic subgroup
Folic acid	£0.24	Six days out of seven during	BNF 63[26]and GDG economic

Cost item	Value	Frequency	Source
		treatment	subgroup
Virology tests for Hep B, Hep C and Chickenpox	£8.06 each	All people at baseline	NHS reference costs[14] and GDG economic subgroup

Based on the cost and dosing schedule described in Table 16, a cost of £6.54 was calculated for an eight week course of methotrexate + a glucocorticosteroid drug treatment in the base case. The total cost including tests and consultations was £355.67 (Table 3).

Table 17- Azathioprine costs in the model including tests

Cost item	Value	Prescriptions (1,000s)	Weight	Frequency	Source
28 pack Azathioprine 25 mg	£6.67	154.043	21%	2.5 mg/kg daily	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
56 pack Azathioprine 50 mg	£5.56	559.16	75%	2.5 mg/kg daily	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
25 pack Mercaptopurine 50 mg	£22.54	36.859	5%	1.5 mg/kg daily	BNF 63[26], GDG economic subgroup and prescription cost analysis data[39]
Liver function test	£1.00	-	-	Weekly for the first month then once per month thereafter	NHS reference costs[14] (code DAP841) and GDG economic subgroup
Full blood count	£3.00	-	-	Weekly for the first month then once per month thereafter	NHS reference costs[14] (code DAP823) and GDG economic subgroup
Virology tests for Hep B, Hep C and Chickenpox	£8.06 each	-	-	All people at baseline	NHS reference costs[14] (code DAP831) and GDG economic subgroup

Based on the cost and dosing schedule described in Table 17, a cost of £42.11 was calculated for an eight-week course of azathioprine + a glucocorticosteroid treatment in the base case. The total cost including tests and consultations was £429.34 (Table 3).

Table 18- Biologic costs in the model including tests

Cost item	Value	Frequency	Source
Pre-filled syringe 40 mg	£355.12	Three doses, administered in outpatient setting	BNF 63[26]and GDG economic subgroup
Test for latent TB (interferon gamma test)	£10.00	Once per patient at baseline	NICE TB guideline[35] and GDG economic subgroup
Chest X-ray	£16.00	Once per patient at baseline	NICE TB guideline[38] and GDG economic subgroup
Virology tests for Hep B, Hep C and Chickenpox	£8.06 each	All people at baseline, assuming they haven't previously been tested during immunomodulator therapy	NHS reference costs[14] (code DAP831) and GDG economic subgroup

Based on the cost and dosing schedule described in Table 18, a cost of £1,056.36 was calculated for biologic drug treatment in the base case. The total cost including tests and consultations was £1,426.09 (Table 3).

1.2.4.7 Cost of surgery

The cost of surgery was calculated in close collaboration with the surgeon on the GDG as described below and in Table 19.

1. The five most common operations in Crohn's disease- pan proctocolectomy, colectomy, right hemicolectomy, small intestine resection and strictureplasty- were chosen and matched to their closest fitting OPCS and HRG codes.
2. Weights were calculated using HES data[41], selected OPCS codes and assuming that 10% of all operations would be associated with a 'major complication or comorbidity'
3. An average cost per operation was calculated by multiplying these weights by the costs attached to selected HRG codes, and adding in a pre-operative and post-operative consultation for each operation.

Table 19- Surgery costs in model

Operation	OPCS code	HRG	HES[41] activity number (adjusted for 10% CC rate)	Weight	Cost
Pan proctocolectomy + CC	HO 4.1	FZ08A	47	1.28%	£9,537.09
- CC		FZ08B	423	11.49%	£6,518.89
Colectomy + CC	HO5.1	FZ09A	23	0.64%	£7,311.29
-CC		FZ09B	211	5.72%	£5,378.79
Right hemicolectomy + CC	HO6.2	FZ09A	75	2.04%	£7,311.29
-CC		FZ09B	675	18.34%	£5,378.79
Small intestine resection + CC	G69.3	FZ07A	210	5.70%	£5,190.81
-CC		FZ07B	1890	51.34%	£3,820.43
Strictureplasty + CC	G78.2	FZ07A	13	0.35%	£5,190.81
- CC		FZ07B	114	3.11%	£3,820.43

So, assuming pre-operative and post-operative costs for a consultation of £94 and £57 (Table 3), and a re-operation rate of 10%, the overall cost of surgery assumed in the model was assumed to be £5,351.24.

1.2.5 Computations

The mean cost and effectiveness of the competing strategies were calculated using Microsoft Office Excel 2007.

1.2.5.1 Calculating QALYs

To calculate QALYs for a given treatment sequence, both the probability of inducing remission for each individual treatment, and the time spent in remission over the course of the model for a given treatment strategy are considered. To do this, the treatment strategy is partitioned into individual treatments and the number of weeks of remission and active disease that occur as a direct result of each treatment are calculated. These are then aggregated over the duration of the strategy and QALYs for a given strategy are calculated by multiplying the number of weeks of remission and active disease by the appropriate utility weights.

Figure 5- Calculating weeks of remission and active disease for a given treatment strategy

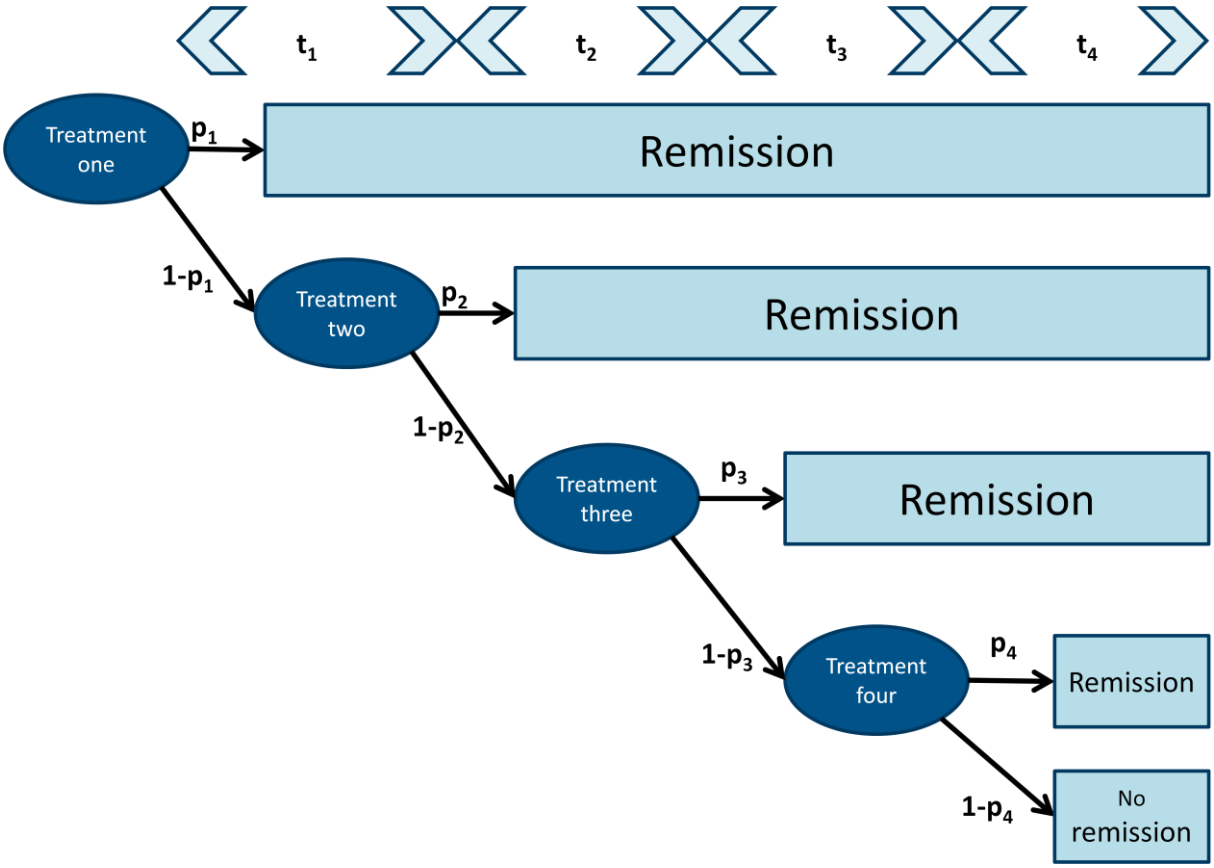


Figure 5 is a visual representation of how weeks of remission and active disease are calculated in the model. Note that, in the absence of data, it was assumed that for all people in whom remission is successfully induced, remission occured half-way through treatment, and people do not relapse.

It can be seen from the diagram that QALYs are calculated as follows:

Let $\boldsymbol{p_1}, \boldsymbol{p_2}, \boldsymbol{p_3}$ and $\boldsymbol{p_4}$ be the probabilities of successfully inducing remission with treatments 1, 2, 3 and 4 respectively.

Let $\boldsymbol{t_1}, \boldsymbol{t_2}, \boldsymbol{t_3}$ and $\boldsymbol{t_4}$ be the durations of treatment in weeks associated with treatments 1, 2, 3 and 4 respectively.

Let $\boldsymbol{W_{R1}}, \boldsymbol{W_{R2}}, \boldsymbol{W_{R3}}$ and $\boldsymbol{W_{R4}}$ denote the expected number of weeks of remission associated with treatments 1, 2, 3 and 4 respectively.

Let $\boldsymbol{U_R}$ and $\boldsymbol{U_A}$ be the utility weights associated with remission and active disease respectively.

Let **H** denote the time horizon in the model, which will be equal to the length of the longest treatment strategy and is 30 weeks in the base case.

Treatment one:

$$W_{R1} = p_1 \times \left(H - \frac{1}{2}t_1\right)$$

Treatment two:

$$W_{R2} = (1 - p_1) \times p_2 \times \left(H - t_1 - \frac{1}{2}t_2\right)$$

Treatment three:

$$W_{R3} = (1 - p_1) \times (1 - p_2) \times p_3 \times \left(H - t_1 - t_2 - \frac{1}{2}t_3\right)$$

Treatment four:

$$W_{R4} = (1 - p_1) \times (1 - p_2) \times (1 - p_3) \times p_4 \times \left(H - t_1 - t_2 - t_3 - \frac{1}{2}t_4\right)$$

Note that the term $p_4 \times (H - t_1 - t_2 - t_3 - t_4)$ is added to the equation for cases when the overall length of the treatment strategy is less than the time horizon. In the event that the duration of the treatment strategy is equal to the time horizon this term is equal to zero, since $H = t_1 + t_2 + t_3 + t_4$.

Then the total number of weeks of remission, $\boldsymbol{W_R}$ and number of weeks of active disease $\boldsymbol{W_A}$ are given by:

$$W_R = W_{R1} + W_{R2} + W_{R3} + W_{R4}$$

$$W_A = \boldsymbol{H} - W_R$$

And the total treatment specific QALYs, Q, are calculated as:

$$Q = \frac{1}{52} \times (W_R \times U_R + W_A \times U_A)$$

1.2.5.2 Probabilistic analysis in the model

In the probabilistic analysis, distributions were assigned to treatment effects, utilities and, where possible, costs in order to account for the uncertainty in model inputs and capture the effect of this uncertainty on model outputs.

Treatment effects:

To capture the uncertainty in treatment effects, a sample of 1000 random sets of treatment effects was taken from the NMA using the CODA function in WinBUGS. This has the advantage of preserving the correlation between variables, which would not be accounted for if they were sampled from their individual distributions. For the probabilistic cost-effectiveness analysis, for each simulation a random set of treatment effects was chosen from the sample using random number generation.

Reference costs:

To assign a distribution to reference costs, it was assumed that they followed a lognormal distribution and used the inter-quartile range to calculate an approximate standard error on the log scale.

Let $\boldsymbol{X}$ be the cost for which a distribution is required, i.e. $\ln(\boldsymbol{X}) \sim \boldsymbol{Normal}(\boldsymbol{\mu}, \boldsymbol{\sigma^2})$

Let M be the mean associated with the cost.

Let $\boldsymbol{IQR}$ be the inter-quartile range associated with the cost.

Note that for normally distributed data:

$$IQR \approx 1.35\sigma$$

and the standard error, $\boldsymbol{s}$, is related to the standard deviation by:

$$s = \frac{\sigma}{\sqrt{n}}$$

Then the standard error on the log scale can be calculated as:

$$\sigma = \frac{\ln(IQR)}{1.35 \times \sqrt{n}}$$

And random draws can be taken from the distribution:

$$\ln(X) \sim Normal\left(ln\left(\mu - \frac{\sigma^2}{2}\right), \left(\frac{\ln(IQR)}{1.35 \times \sqrt{n}}\right)^2\right)$$

Utilities:

Utilities were sampled probabilistically by assigning lognormal distributions to utility decrements as described in (ref Briggs). Normal distribution parameters were converted to lognormal parameters by method of moments, as defined below:

Let $E[X]$ and $Var[X]$ be the mean and variance respectively, of the utility decrement U

Then the parameters of the lognormal distribution, μ and σ^2 are found by:

$$\mu = \ln(E[X]) - \frac{\ln\left(1 + \frac{Var[X]}{E[X]^2}\right)}{2}$$

$$\sigma^2 = \ln\left(1 + \frac{Var[X]}{E[X]^2}\right)$$

1.2.5.3 Calculating cost effectiveness

It is possible, for a particular cost-effectiveness threshold, to express cost-effectiveness results in term of net benefit (NB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs. The decision rule then applied is that the comparator with the highest NB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation NB is used to identify the optimal strategy in the probabilistic-analysis simulations.

Let $\mathrm{C_t}$ and $\mathrm{Q_t}$ denote the mean costs and mean QALYs respectively, associated with a given treatment. Then mean net benefit $\mathrm{NB_t}$ is calculated as:

$$\mathrm{NB_t} = \mathrm{C_t} - (20{,}000 \times \mathrm{Q_t})$$

where £20,000 per QALY represents the cost-effectiveness threshold in the NICE reference case.

The net benefit for each of the 1000 simulations in the probabilistic analysis is calculated. This allows the probability that a given treatment would be optimal, based on the number of times it has the highest net benefit, can be estimated.

However, the strategy that is optimal overall is the one that has the highest net benefit calculated using the mean costs and QALYs, where means were the average of the 1,000 simulated estimates.

1.2.6 Sensitivity analyses

The results of the model were tested by changing those parameters which are most uncertain, as described in Table 20.

Table 20- One-way sensitivity analyses in the model

Sensitivity analysis	Description	Value in base case	Value or range in sensitivity analysis
1- Utility weights	VAS score from Stark et al used instead of Time Trade Off TTO	Disease remission = 0.89 Active disease = 0.61	Disease remission =0.848 Active disease = 0.634
2- Budesonide adjustment factor	Based upon RCT evidence, the efficacy effect of glucocorticosteroid treatment following treatment failure with budesonide was unclear. The GDG reasoned that glucocorticosteroid treatment would be less effective following budesonide failure, and decided it would be appropriate to multiply the efficacy of glucocorticosteroid treatment after budesonide by an adjustment factor between 0 and 1.	75%	50%-100%
3- Consultations	Since the consultations described in Table 11 were chosen by the GDG, it was decided to vary these in the sensitivity analysis in order to test the effects of high and low resource use on the results of the model.	**Consultant gastroenterologist:** 30 visits per 100 people every 2 weeks **Nurse specialist:** 30 visits per 100 people every 2 weeks **Specialist registrar:** 30 visits per 100 people every 2 weeks	**Consultant gastroenterologist:** 0-100 visits per 100 people every 2 weeks **Nurse specialist:** 0-100 visits per 100 people every 2 weeks **Specialist registrar:** 0-100 visits per 100 people every 2 weeks
4- Efficacy of biologics	The efficacy of biologic treatment was extracted from the same trial[10] as the model in TA187[37]. There is some uncertainty as to the most accurate figures to use, due to the trial design of the original studies. A sensitivity analysis exploring the more conservative efficacy estimate was undertaken.	Biologic: $\frac{96}{172} = 56\%$	Biologic: $\frac{96}{260} = 33\%$
5- TPMT cost	The GDG decided to explore	£0	£26. Source: personal

Sensitivity analysis	Description	Value in base case	Value or range in sensitivity analysis
	the effects of adding the cost of TPMT testing onto the cost of azathioprine.		communication with TPMT laboratory at Guys and St Thomas's hospital
6- Trial durations	As well as trial durations chosen by the GDG trial durations that better reflected those used in the actual trials were explored. These were calculated by taking the mean duration of all the trials for which a given treatment was used as a comparator. See Table 2	See Table 2	See Table 2

1.2.7 Model validation

The model was developed in consultation with the health economic sub group and all decisions were signed off by the GDG. The 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 health economist from the NCGC; this included systematic checking of the model formulae and calculations. The model parameters and results were also assessed against the content of this appendix.

1.2.8 Interpreting results

The strategy with the highest mean net benefit is the one that should be recommended[20], though the uncertainty around costs and QALYs should also be taken into consideration. Due to lack of data, the disutility of treatment-specific adverse events could not be captured; caution should therefore be exercised in recommending strategies containing treatments with high withdrawal rates. However, a sensitivity analysis around the side-effects associated with glucocorticosteroids indicated that the optimal strategy is not affected by the inclusion of side-effects.. Furthermore, in line with TA 187, strategy 9 within this model, which explores the cost effectiveness of glucocorticosteroid treatment followed by a biologic, should be considered only in people whose Crohn's disease has progressed to severe before initiation of biologic treatment. All other treatment strategies within this model relate to moderate disease.

1.3 Results

1.3.1 Base case

In the base case, model inputs were set as shown in Table 3 and the model was run probabilistically. The results were as follows:

Table 21- Mean costs in the base case

Strategy number	Strategy	Drugs	Tests	Consultations	Surgery	Total
5	CS , AZA+CS , BIO	£218	£34	£446	£402	£1,099
7	BUD , CS , AZA+CS , BIO	£301	£31	£574	£258	£1,164
3	MES , CS , AZA+CS , BIO	£235	£26	£614	£253	£1,128
6	CS , MTX+CS , BIO	£282	£44	£586	£487	£1,398
8	BUD , CS , MTX+CS , BIO	£343	£37	£664	£313	£1,358
1	SUL , CS , AZA+CS , BIO	£202	£29	£642	£292	£1,164
4	MES , CS , MTX+CS , BIO	£275	£33	£703	£307	£1,318
2	SUL , CS , MTX+CS , BIO	£249	£37	£744	£354	£1,383
9	CS , BIO	£488	£72	£501	£1,007	£2,068

Table 21 shows that, in the base case, strategy 5, where people start with first line glucocorticosteroid monotherapy, followed by second line azathioprine in combination with a glucocorticosteroid following treatment failure then move on to a third-line biologic following a second treatment failure was the cheapest treatment option at £1,100.

Table 22- Clinical outcomes in the base case (mean)

Strategy number	Strategy	Weeks of remission	Weeks of non remission	QALYs
5	CS , AZA+CS , BIO	20.6	9.4	0.463
3	BUD , CS , AZA+CS , BIO	19.1	10.9	0.455
7	MES , CS , AZA+CS , BIO	18.0	12.0	0.450
1	CS , MTX+CS , BIO	20.2	9.8	0.461
6	BUD , CS , MTX+CS , BIO	18.9	11.1	0.454
4	SUL , CS , AZA+CS , BIO	16.8	13.2	0.443
8	MES , CS , MTX+CS , BIO	17.8	12.2	0.448
2	SUL , CS , MTX+CS , BIO	16.6	13.4	0.442
9	CS , BIO	19.4	10.6	0.457

Table 22 shows that in the base case, strategy 5 was the most effective option yielding 21 weeks of remission and 0.463 QALYs.

Table 23- Cost effectiveness in the base case (mean)

Strategy number	Strategy	Cost	QALYs	Net monetary benefit*	Rank (95% confidence interval)*	Probability of being most cost-effective strategy
5	CS , AZA+CS , BIO	£1,099	0.463	£8,169	1 (1,6)	72.7%
3	BUD , CS , AZA+CS , BIO	£1,164	0.455	£7,945	2 (1,6)	9.1%
7	MES , CS , AZA+CS , BIO	£1,128	0.450	£7,862	3 (2,7)	2.5%
1	CS , MTX+CS , BIO	£1,398	0.461	£7,823	4 (1,8)	11.1%
6	BUD , CS , MTX+CS , BIO	£1,358	0.454	£7,731	5 (2,8)	1.2%
4	SUL , CS , AZA+CS , BIO	£1,164	0.443	£7,696	6 (1,8)	2.7%
8	MES , CS , MTX+CS , BIO	£1,318	0.448	£7,652	7 (3,8)	0.2%
2	SUL , CS , MTX+CS , BIO	£1,383	0.442	£7,454	8 (3,9)	0.4%
9	CS , BIO	£2,068	0.457	£7,079	9 (5,9)	0.1%

* Using a willingness-to-pay threshold of £20,000 per QALY.

Table 23 shows that strategy 5 was the cheapest, and most effective strategy in the model; it was therefore the dominant treatment strategy. There was a great deal of uncertainty in the analysis, which arises mainly from the imprecision in estimating treatment effects. Though strategy 5 was dominant in terms of mean net monetary benefit, the 95% confidence interval of its rank in terms of net monetary benefit ranged from 1 to 6 and its probability of being the most cost-effective strategy was around 73%.

Figure 6 shows the cost-effectiveness plane, depicting the mean costs and QALYs associated with each treatment strategy.

Since the costs and disutility associated with treating adverse events in the model could not be explicitly quantified for all treatments, a threshold analysis was conducted on the cost of treating adverse events. This involved varying the cost of treating an adverse event until strategy 5 was no longer the most cost-effective strategy and noting the value at which this change occurred. This change occurred when the cost of treating adverse events was set to £6,000, whereupon strategy 7 became most cost-effective.

A sensitivity analysis was conducted, where the costs and disutilities of myocardial infarction and hip fracture were added in for patients receiving glucocorticosteroid therapy in the most cost-effective strategy (a glucocorticosteroid, a glucocorticosteroid + azathioprine, a biologic). The fact that these adverse events were only modelled for the most cost-effective strategy represents a conservative approach since glucocorticosteroid therapy is included in every other strategy and therefore including adverse events in other strategies would only weaken their cost-effectiveness relative to the most cost-effective strategy.

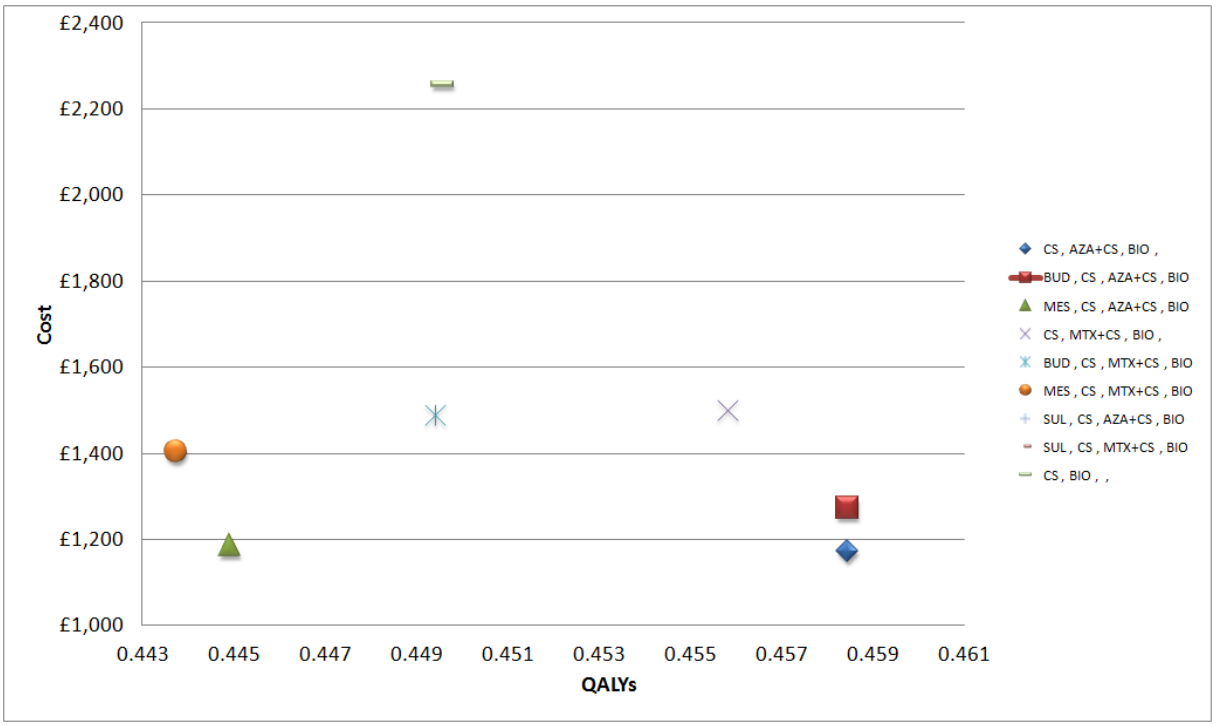
The approach taken was as follows:

- Baseline 8-weekly risks were calculated for myocardial infarction and hip fracture:

  - Myocardial infarction: 10-year baseline risk $\theta_{10\ yr}$ was turned into a 8-weekly risk using the equation[6]: $\theta_{8\ wk} = 1 - e^{\frac{8}{52\times10}\ln(1-\theta_{10\ yr})}$
  - Hip fracture: 8-weekly baseline risk $\sigma_{8\ wk}$ was calculated by dividing the number of hip fractures that occur yearly in the UK N_{HF} by the total adult population in England P (Table 3) to get the yearly risk $\sigma_{1\ yr}$ and then applying the formula $\sigma_{8\ wk} = 1 - e^{\frac{8}{52}\ln(1-\sigma_{1\ yr})}$
- The relative effects associated with intermittent high-dose glucocorticosteroid therapy (Table 3) were then applied to the baseline risks to obtain drug-specific risks:
  - Myocardial infarction: The log odds associated with baseline risk of MI ($\sigma_{8\ wk}$) and treatment specific log odds ratios (Table 3) were calculated and methods described in 1.2.4.2 were applied to obtain a glucorticosteroid-related myocardial infarction risk of 0.0043.
  - Hip fracture: The baseline risk of hip fracture $\sigma_{8\ wk}$ was adjusted by the treatment-specific relative risk for hip fracture (Table 3) to obtain a glucocorticosteroid-related hip fracture risk of 0.0006
- Utility weights associated with myocardial infarction and hip fracture can be found in Table 3. Utility weights used for these adverse events in the model were calculated as a decrement from both perfect health and active Crohn's disease. This makes the assumption that the reduction in quality of life is additive and that all patients who experience a glucocorticosteroid-related adverse event still have active disease. Utility weights were calculated this way since calculating only the decrement from perfect health is unlikely to fully capture utility loss in the presence of co-morbidities- in this case active Crohn's disease. Note that $ModelUtil_{MI}$ and $ModelUtil_{HF}$ denote the calculated utility weights for myocardial infarction and hip fracture used in the model; and $Util_{MI}$, $Util_{HF}$ and $Util_{AC}$ denote the utility weights associated with myocardial infarction, hip fracture and active Crohn's disease identified in the literature(Table 3). The utility weights were thus derived as follows:
  - Myocardial infarction: $ModelUtil_{MI} = Util_{AC} - (1 - Util_{MI}) = 0.61 - (1 - 0.76) = 0.37$
  - Hip fracture: $\mathrm{ModelUtil_{HF}} = \mathrm{Util_{AC}} - (1 - \mathrm{Util_{HF}}) = 0.61 - (1 - 0.58) = 0.19$

The adverse-event specific risks, costs (Table 3), and utility weights were then applied to ***everyone*** in the most cost-effective strategy in the model receiving glucocorticosteroid monotherapy or azathioprine + a glucorticosteroid combination therapy and the model was run. The cost effectiveness ranking did not change.

Figure 6- Cost-effectiveness plane (mean costs and QALYs from probabilistic analysis)



1.3.2 Sensitivity analyses

1.3.2.1 One-way sensitivity analysis

One-way sensitivity analyses were also conducted in order to test the robustness of model results to changes in key parameters. In all deterministic sensitivity analyses, the same strategy namely glucocorticosteroid treatment, glucocorticosteroid + azathioprine then a biologic was the most cost-effective strategy.

Table 24: One-way sensitivity analysis – mean net monetary benefit*

Strategy	Base case	SA1	SA2-50%	SA2-100%	SA3-low	SA3-high	SA4	SA5	SA 6
1	7346	7259	7370	7383	7946	6092	7264	7391	17414
2	7045	6969	7082	7083	7752	5500	6919	7084	16405
3	7711	7562	7729	7740	8246	6575	7644	7747	18221
4	7471	7330	7499	7501	8090	6101	7368	7502	17414
5	**7996**	**7795**	**8024**	**8045**	**8379**	**7280**	**7874**	**8056**	**18931**
6	7613	7429	7658	7665	8124	6541	7429	7665	17668
7	7738	7563	7577	7942	8234	6690	7672	7774	18792
8	7496	7330	7297	7753	8078	6215	7395	7527	17975
9	6735	6555	6743	6731	7134	5827	6185	6734	17422

* Using a willingness-to-pay threshold of £20,000 per QALY. Bold font denotes the most cost-effective strategy

1.4 Discussion

1.4.1 Summary of results

The cost-effectiveness analysis shows that, based on a conditional logistic regression network meta-analysis conducted using RCT data, acquisition costs, PSSRU costs and NHS reference costs, glucocorticosteroid treatment followed by azathioprine + a glucocorticosteroid then a biologic is the most cost-effective treatment strategy to induce remission of an acute exacerbation of Crohn's disease. These results were robust to both one-way and probabilistic- sensitivity analyses.

1.4.2 Limitations and interpretation

This model is based on findings from RCTs and therefore any issues concerning interpretation of the clinical review also apply to interpretation of the economic analysis. The limitations of the model include:

- The utility loss and treatment cost associated with adverse events have not been explicitly incorporated. Adverse events are only incorporated in as much as people withdrawing due to adverse events have to start an additional treatment cycle and therefore their time to remission is delayed by at least eight more weeks. This is likely to mean the cost effectiveness of all the treatment strategies has been over-estimated in the economic analysis, though since each treatment is likely to have a different side-effect profile, it is unlikely that ICERs have been underestimated by the same magnitude for all treatment strategies. For treatment strategies with more severe side-effects, the over estimation of the ICER is likely to be higher than in treatment strategies with less severe side-effect profiles.' However, the sensitivity analysis conducted on side effects associated with glucocorticosteroid monotherapy provides some extra assurance.
- Relapses are not accounted for; this is explored in the maintenance of remission model.
- Simplifying assumptions
    - For people in whom remission is induced, utility returns to normal, half way through the treatment cycle.
    - Withdrawals are assumed to occur at the end of a treatment cycle.
- No clinical review was conducted on the efficacy of biologic treatments as this was outside of the Crohn's disease guideline remit therefore efficacy data has been derived from the two study used in the TA [37].

1.4.3 Generalisability to other populations and settings

It should be noted that all of the findings relate to an adult population and the conclusions may not apply to paediatric treatment. A separate model for children could not be constructed due to the paucity of both clinical and quality of life studies conducted in this area. Furthermore, the population clinical data used in the model relates to a moderate to severe active Crohn's disease population and thus these conclusions should not be applied to a population consisting entirely of people with severe active disease.

1.4.4 Comparisons with published studies

No relevant or applicable published health economics studies were identified in the area of medical induction of remission.

1.4.5 Conclusion and evidence statement

The analysis suggests that glucocorticosteroid treatment, followed by azathioprine + a glucocorticosteroid then a biologic is the most cost-effective treatment strategy for a moderate to severe acute exacerbation of Crohn's disease.

1.4.6 Implications for future research

Potential areas for future Crohn's disease research that have been identified by this analysis and include:

- Medical induction of remission trials - despite pooling the results of all the studies in a network meta-analysis, there was still a large amount of imprecision in the estimates of effect size. Conducting more clinical trials in the area of medical induction of remission would reduce this uncertainty.
- Paediatric clinical trials and quality of life studies.
- Enteral nutrition studies reporting withdrawal from treatment as a clinical outcome.

2 Cost-effectiveness analysis –maintenance of remission

2.1 Introduction

This economic analysis explores the cost effectiveness of different treatments for medical maintenance of remission in active Crohn's disease. The topic of medical maintenance of remission was chosen by the GDG as one of their top priorities for original economic analysis, since medical maintenance therapy is likely to be a consideration for most people with Crohn's disease at some point. No fully applicable published economic studies were identified in this area.

2.2 Methods

2.2.1 Model overview

A cost-utility analysis was undertaken where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services perspective (PSS).

2.2.1.1 Comparators

The comparators examined in the model were the same as in the clinical review and approved by the GDG economic subgroup. The economic subgroup comprised two consultant gastroenterologists, one specialist IBD nurse and one patient representative. Methotrexate could not be included since withdrawals from treatment - a key driver of treatment effects in the model- were not reported in the only methotrexate study found in the clinical review. The comparators explored in the model were:

- No treatment
- Azathioprine
- Mesalazine
- Olsalazine
- Budesonide
- Glucocorticosteroids

It should be noted that although they were combined in the clinical review, mesalazine and olsalazine were separated in the economic analysis due to potential differences in costs and side-effect profiles.

2.2.1.2 Population

The population entering the model comprises people in medically-induced remission of Crohn's disease. In most cases, remission was defined by a Crohn's Disease Activity Index (CDAI) score of ≤ 150, though due to paucity of evidence, trials using other definitions, for example physician's objective assessment was used.

2.2.1.3 Time horizon

The time horizon considered in the base case model was two years; this time horizon was chosen to reflect the duration of the longest trial explored in the clinical review for maintenance of remission. A longer time horizon of 10 years was explored in sensitivity analysis. A lifetime time horizon was not explored, since the incremental QALYs vs no treatment at two and ten years were not substantially

different, and therefore using a longer time horizon was unlikely to have a significant impact on model results.

2.2.2 Approach to modelling

2.2.2.1 Model structure

A Markov model was constructed, wherein the QALY gain is driven by the amount of time people spend in remission and active disease. A cycle length of two months was chosen to reflect the duration of induction treatments for people in relapse.

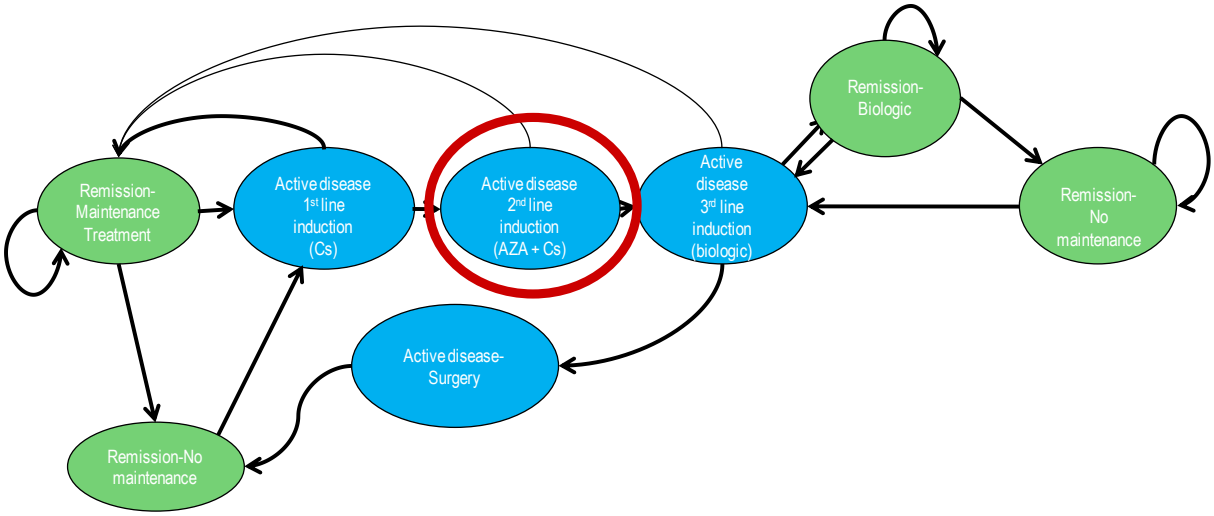
Due to the way withdrawals were reported in the RCTs, two separate analyses were conducted for the clinical review, a non-conservative analysis where only the 'relapse' outcome was analysed, and conservative analysis where 'relapse + withdrawals' was analysed. Treatment effects in the economic model were parameterised so as to account for these two different methods. For the non-conservative analysis in the economic model, withdrawals and relapses were treated separately so that people who withdrew from treatment were still assumed to be in remission (although from this point their risk of relapse reverts back to the risk associated with no treatment). For the conservative analysis in the economic model, people who withdrew were assumed to be in relapse.

The GDG advised that people in relapse should be treated with the induction sequence that was found to be most cost-effective in the induction of remission model (a glucocorticosteroid, followed by azathioprine + a glucocorticosteroid then a biologic). The GDG were uncertain as to what the induction sequence should be for people who relapse while on azathioprine maintenance treatment. People who relapse on azathioprine treatment are likely to have a glucocorticosteroid or biologic induction therapy *added* to their azathioprine regimen, and therefore initiation of azathioprine induction therapy in these people is not relevant as they are already taking azathioprine. One plausible alternative was to assume a three-line induction sequence for azathioprine (a glucocorticosteroid – a biologic – surgery) but a four-line sequence (a glucocorticosteroid – azathioprine + a glucocorticosteroid- a biologic – surgery) for the other maintenance strategies but this three-line sequence is less cost effective and this may potentially bias the assessment. This scenario was explored, but an analysis where there was a three-line induction sequence (a glucocorticosteroid – a biologic – surgery) for *all* maintenance strategies was also conducted in order to address this potential imbalance. In this analysis only the maintenance treatment varies between comparators and not the induction sequence but this is probably only a reasonable comparison for people who have had a recent history of severe disease and so would necessitate more urgent treatment.

- Conservative treatment effects - three lines of induction treatment (including surgery) for people relapsing on azathioprine, four lines of induction treatment for all other people (Cons 4L).
- Non- conservative treatment effects - three lines of induction treatment (including surgery) for people relapsing on azathioprine, four lines of induction treatment for all other people (Non-cons 4L).
- Conservative treatment effects - three lines of induction treatment (including surgery) for all people in relapse (Cons 3L).
- Non-conservative treatment effects - three lines of induction treatment (including surgery) for all people in relapse (Non-cons 3L).

The model structure is shown in Figure 7; note that in the first two analyses described above, the circled health state is omitted for people relapsing on azathioprine maintenance treatment. It is also omitted from the Cons 3L and Non-cons 3L models.

Figure 7- Health states in the maintenance of remission economic model



Key assumptions:

- People enter the model in the remission maintenance treatment state
- People who relapse enter the acute induction treatment sequence
- People in whom remission is successfully re-induced on first- or second-line induction treatment go back on their initial maintenance treatment
- People who fail induction on biologics undergo surgery
- If remission is successfully induced on biologics, people stay on biologics until either:
    - **Failure**: where they undergo dose escalation (equivalent to re-induction using biologics) and have then can either :
        - responding and being put again on maintenance dose or
        - not responding and go to surgery
    - **Completion of 12 months**: where they are reassessed and
        - if in remission they go on to no maintenance treatment
        - if not they undergo dose escalation (i.e. re-induction) and go back to the start of the sequence.

2.2.2.2 Uncertainty

One-way sensitivity analysis

One-way sensitivity analyses were also conducted in order to test the robustness of model results to changes in key parameters. In one way sensitivity analysis, one parameter is varied while all other parameters are kept constant and the effects of changing this parameter on model results are explored. The one-way sensitivity analyses conducted are described in Table 20.

Probabilistic analysis

A Monte Carlo simulation[16] was conducted to explore the uncertainty in model results. In Monte Carlo simulation, each parameter is assigned a distribution reflecting its uncertainty; random draws are then taken from this distribution and propagated through the model, to calculate costs and QALYs. This process is repeated 1,000 times and a model result which represents an average of the simulations is computed.

2.2.3 Model inputs

2.2.3.1 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. Summaries of the model inputs used in the base-case analysis are provided in Table 25, Table 26, Table 27 and Table 28. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

The costs and probabilities associated with induction treatments for people in relapse are those associated with the optimal strategy in the induction of remission model and can be found in the induction of remission model write-up.

Table 25: Cost inputs

Input	Data	Source
Drugs		
Cost per two-month cycle[(a)] of mesalazine maintenance treatment[(b)]	£109.71	BNF 63[25] and NHS reference costs[14]
Cost per two-month cycle[(a)] of budesonide maintenance treatment[(b)]	£103.20	BNF 63[25] and NHS reference costs[14]
Cost per two-month cycle[(a)] of glucocorticosteroid maintenance treatment[(b)]	£34.82	BNF 63[25] and NHS reference costs[14]
Cost per two-month cycle[(a)] of azathioprine maintenance treatment[(b)]	£75.29	BNF 63[25] and NHS reference costs[14]
Cost per two-month cycle[(a)] of olsalazine maintenance treatment[(b)]	£71.07	BNF 63[25] and NHS reference costs[14]
Cost per two-month cycle[(a)] of biologic maintenance treatment[(b)]	£1,681.46	BNF 63[25] and NHS reference costs[14]
Visits		
Yearly cost of Crohn's treatment while in remission (first year)	£230.72	Economic subgroup (see Table 11 for specific tests/consultations frequency)
Yearly cost of Crohn's treatment while in remission (second year)	£153.97	Economic subgroup (see Table 11 for specific tests/consultations frequency)
Yearly cost of Crohn's treatment while in remission (third year)	£88.56	Economic subgroup (see Table 11 for specific tests/consultations frequency)
Consultant gastroenterology outpatient visit	£113.58	NHS reference costs: Consultant led follow up attendance non admitted face to face "Medical gastroenterology" (code 301M)
Cost for 1/2 hour specialist nurse appointment	£28.50	PSSRU[11]
Cost for average length GP consultation	£41.00	PSSRU[11]
Non-consultant gastroenterology outpatient visit	£93.92	NHS reference costs[14]: Non-consultant

Input	Data	Source
		led follow-up attendance non-admitted face to face "Medical gastroenterology" (code 301M)
Phone call to IBD nurse	£5.70	NHS reference costs[14]
Tests		
DEXA scan	£72.00	NHS reference costs[14] (code RA15Z)
Microbiology/virology to test for chickenpox	£8.00	NHS reference costs[14] (DAP831)
Full blood count	£1.00	NHS reference costs[14] (DAP823)
Renal and liver function tests	£3.00	NHS reference costs[14] (DAP841)
Chest x-ray	£17.00	NICE TB guideline[35]
Interferon gamma test for latent TB	£22.00	NICE TB guideline[35]
Cost of diagnostic colonoscopy	£589.91	NHS reference costs[14]
Cost of MRI scan	£173.57	NHS reference costs[14]
Cost of surgery	£5,351.24	Induction of remission model write-up.

(a) One cycle = two months
(b) Including tests and consultations

Table 26- Clinical inputs- probabilities of relapse + withdrawal (conservative analysis) per cycle

Input	Probability of relapse + withdrawal
No treatment (placebo)	8.98%
Mesalazine	6.05%
Budesonide	7.92%
Glucocorticosteroid treatment	8.26%
Azathioprine	1.61%
Olsalazine	9.36%
Biologic (first two cycles)	13.93%
Biologic (next three cycles)	2.64%

Source: Clinical review

Table 27- Clinical inputs- probabilities of withdrawal and remission conditional on not withdrawing (non-conservative analysis)

Input	Probability of withdrawal due to adverse events	Probability of relapse conditional on non-withdrawal
No treatment (placebo)	2%	9%
Mesalazine	3%	6%
Budesonide	3%	8%
Glucocorticosteroids	3%	8%
Azathioprine	2%	2%
Olsalazine	4%	9%

Source: Studies used in clinical review

Table 28- Utility weights in the model

Input	Data	Source
Disease remission	0.89	Stark et al[54]
Active disease	0.61	Stark et al[54]

Note: Same as induction of remission model

2.2.3.2 Baseline events (withdrawal, relapse and relapse + withdrawal)

Baseline events were modelled in WinBUGS using a random effects logistic regression on the placebo arms of the RCTs from the clinical review. The aim of the logistic regression was to calculate the baseline log odds of withdrawals due to adverse events and remission conditional on non withdrawal.

2.2.3.3 Relative treatment effects (withdrawal, relapse and relapse + withdrawal)

Relative treatment effects were calculated so as to reflect the clinical review as closely as possible in terms of pooling of studies. As described above, treatment effects were parameterised in two

different ways, to facilitate a conservative and non-conservative analysis. Calculation of these treatment effects is described in the following section.

Conservative analysis

For the conservative analysis, with the exception of 5-ASA treatment and glucocorticosteroid treatment, all of the treatment effects could be extracted directly from the clinical review. As discussed previously in the induction of remission model write-up,5-ASA compounds are treated separately for economic analysis within this guideline due to differences in costs and side-effect profile. For glucocorticosteroid treatment, only one trial [53] reported withdrawals and was used to obtain a relative risk for relapse + withdrawal of 1.15 at one year. In the meta-analysis for the clinical review, five mesalazine studies [1,2,45,53,57,62] and one olsalazine [29] study were pooled. These were separated and a new meta-analysis was conducted using the mesalazine studies from the clinical review to obtain a relative risk of 0.81 at one year for relapse + withdrawal with mesalazine. The olsalazine study [29] was then used to calculate a relative risk 1.23 for relapse + withdrawal.

Baseline log odds were converted to the natural scale to obtain a baseline risk of relapse + withdrawal of 52% at one year using the following equation:

$$p_{pl} = \frac{e^{(\theta_{pl})}}{1 + e^{(\theta_{pl})}}$$

where θ_{pl} and p_{pl} denote the baseline log odds and risk of relapse + withdrawal respectively, on placebo.

All the relative risks, the baseline risk and associated confidence intervals for relapse + withdrawal are shown in Table 29. Note that in the model these are converted from yearly to two-monthly probabilities to reflect the cycle length.

Table 29- Conservative analysis treatment effects

Treatment	**Baseline risk (95% CI)**
No treatment (placebo)	0.52 (0.43 to 0.61)
Treatment	**Relative risk (95% CI)**
Mesalazine	0.81 (0.69 to 0.97)
Budesonide	0.87 (0.70 to 1.08)
Glucocorticosteroid treatment	1.15 (0.62 to 2.15)
Azathioprine	0.58 (0.29 to 1.15)
Olsalazine	1.23 (1.03 to 1.48)

Non-conservative analysis

For the non-conservative analysis, with the exception of 5-ASA treatment all of the treatment effects for relapse could be extracted directly from the clinical review. Estimates of relative risk for relapse on mesalazine were obtained in the same way as described in 0, yielding relative risks at one year of 0.69 and 0.9 for mesalazine and olsalazine respectively.

As described in 2.2.2, for the non-conservative analysis it was important to capture withdrawals from treatment. To achieve this, a series of pair wise meta-analyses were conducted on the withdrawal outcome and probabilities for relapse conditional on 'non withdrawal' were calculated, as follows:

1. Absolute risks of relapse were calculated using baseline log odds of relapse and relative risks.
2. Absolute probabilities of withdrawal were calculated as follows:

   Let $\mathbf{i}$ represent the number of studies reporting relapse and relapse + withdrawal

   Let $\boldsymbol{R_i}$ and $\boldsymbol{RW_i}$ represent the number of relapses, relapses + withdrawals and number at risk reported in study $\boldsymbol{i}$

   The number of withdrawals in study $\boldsymbol{i}$ was then calculated from the equation:

   $$\boldsymbol{W = RW_i - R_i}$$
3. Using these quantities, odds ratios for withdrawal were calculated and pooled across studies. Studies were pooled in the same way as in the clinical review. Treatment-specific odds ratios for withdrawal were then converted to absolute probabilities of withdrawal using methods previously described in the induction of remission model write-up. A probability of relapse conditional on not withdrawing was then calculated using the following equation:

Equation 1- Calculating probability of relapse conditional on non-withdrawal

$$\boldsymbol{P(R|W^c) = \frac{P(R)}{1 - P(W)}}$$

Treatment effects used in the non-conservative analysis are shown in Table 30. Please note that treatment effects for withdrawal were calculated as odds ratios.

Table 30- Non-conservative analysis treatment effects

Treatment	Baseline probability of relapse (95% CI)	Baseline probability of withdrawal (95% CI)
No treatment (Placebo)	0.39 (0.28 to 0.50)	0.10 (0.04 to 0.22)
Treatment	**Relative risk of relapse (95% CI)**	**Odds ratio for withdrawal (95% CI)**
Mesalazine	0.69 (0.55 to 0.87)	1.49 (1.05 to 2.11)
Budesonide	0.84 (0.68 to 1.03)	1.76 (0.61 to 5.45)
Glucocorticosteroids	0.88 (0.62 to 1.26)	1.63 (0.46 to 6.03)
Azathioprine	0.21 (0.06 to 0.68)	1.23 (0.43 to 3.61)
Olsalazine	0.90 (0.67 to 1.21)	2.46 (1.46 to 4.18)

Once the probabilities of relapse, withdrawal and relapse conditional on non withdrawal had been calculated, yearly probabilities were calculated as described in this section, and then transformed to two- monthly probabilities using the equation:

$$p_{2month} = 1 - \exp\left[-\frac{1}{6}\left(-\ln\left(1 - p_{1year}\right)\right)\right]$$

All of the probabilities calculated using the methods described in this section can be found in Table 26 and Table 27.

Figure 8- Conservative and non-conservative analysis

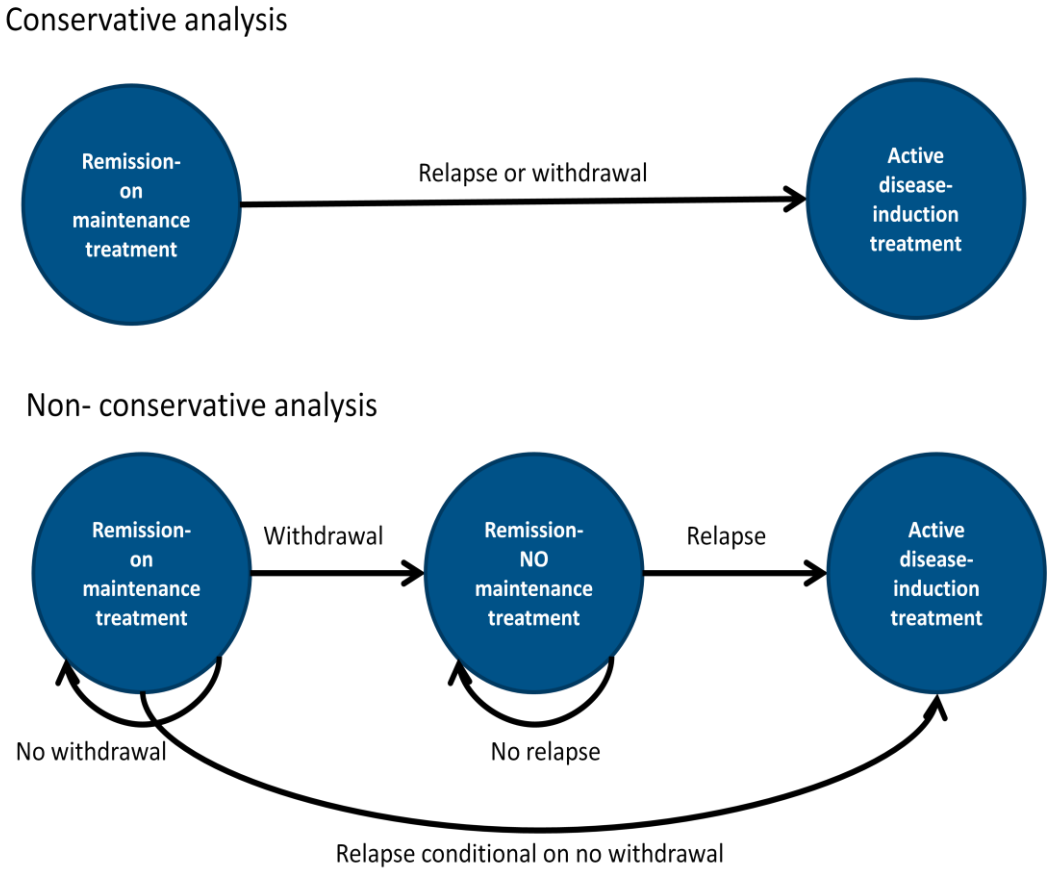


Figure 4 shows how the probabilities described above and shown in Table 26 and Table 27 operate in the model for the conservative and non-conservative analyses. Note that Figure 8 describes only the patient pathway up to relapse, and a full representation of the patient pathway can be found in Figure 7.

In the conservative analysis, people who either relapse or withdraw are assumed to have active disease and move into the active disease health states where they receive treatment for induction of remission.

In the non-conservative analysis, people who withdraw from treatment are still assumed to be in remission, but not receiving drugs for maintenance of remission; their probability of relapse is then equal to the baseline relapse probability- i.e. the same as people in the no treatment arm. People who do not withdraw from treatment may relapse according to the probability calculated in Equation 1. People relapsing from either the remission- maintenance treatment or remission- no maintenance treatment health states move into the active disease health states where they receive treatment for induction of remission.

2.2.3.4 Utilities

For economic evaluation, a specific measure of HRQoL known as utility is required to calculate QALYs. Utilities indicate the preference for health states on a scale from 0 (death) to 1 (perfect health). The NICE reference case[36] specifies that the preferred way for this to be assessed is by the EQ-5D instrument.

The utility weights used in the model for people with active disease and people in remission were the same as those used in the induction model and are shown in Table 28. The rationale for selecting these utility weights can be found in the induction model write-up.

2.2.3.5 Resource use and cost

Please note that all of the drug-specific information in this section refers to people undergoing treatment for maintenance of remission. For information pertaining to induction of remission please see the induction of remission model write-up.

The GDG advised that, as well as the treatment-specific tests and consultations, people in remission of Crohn's disease would have regular consultations and tests regardless of treatment. The GDG noted that these consultations would differ according to how long people were in remission for, and agreed on yearly frequencies of consultations for people who have been in one, two and three years of remission. This was accounted for in two different ways in the model. In the base case, the two-year frequencies were used and an overall cost of £25.75 applied per cycle to people in remission over the two-year time horizon. In a sensitivity analysis, an average cost of consultations over three years was calculated, and a cost of £26.51 applied per cycle to people in remission over the two-year time horizon. These consultations and tests are summarised in Table 31.

Table 31- Consultations and tests for people not in remission (regardless of induction treatment)

Type of consultation	Unit cost	Year one frequency	Year two frequency	Year three frequency
Consultant	£113.58	One per year (all people)	One per year (HALF of all people)	One per year (HALF of all people)
Specialist Registrar	£93.92	One per year (all people)	One per year (HALF of all people)	One per year (HALF of all people)
GP	£41.00	One per year (all people)	Two per year (all people)	One per year (all people)
IBD nurse	£28.50	One per year (all people)	One per year (all people)	None
IBD nurse (phone)	£5.70	Two per year (all people)	One per year (all people)	One per year (HALF of all people)

Drug acquisition costs

Drug costs in the model were calculated based on weighted average drug acquisition costs were calculated based on prescribing patterns for all preparations[39]. This can be seen in Table 32.Error! Reference source not found.

Table 32- Base case weekly drug acquisition costs in the model

Treatment	Dosage	Drug name	Cost per tab	Weekly Cost	Prescriptions (1,000s)[39]	Weight	Weighted average weekly cost
Azathioprine	2.5 mg/kg per day	Azathioprine 25 mg (28-tab pack = £6.02)	£0.22	£11.73	154	21%	**£5.04**
		Azathioprine 50 mg (56-tab pack = £5.04)	£0.09	£2.45	559	75%	
Mercaptopurine	1.5 mg/kg/day	Asacol MR 400 mg (25-tab pack = £22.54)	£0.90	£14.75	37	5%	
Mesalazine	2 g daily	100 pack Pentasa 500 mg (90-tab pack = £29.41)	£0.33	£11.44	351	56%	**£9.38**
	2 g daily	Salofalk E/C 250 mg (100-tab pack = £24.21)	£0.24	£8.47	272	43%	
	1.5 g daily	Asacol MR 400 mg (100-tab pack = £16.19)	£0.16	£6.80	5.73	1%	
Budesonide	4.5 mg daily	Entocort 3 mg (100 tab pack = £75.05)	£0.75	£7.88	4.96	100%	**£8.82**
		Budenofalk 3 mg (100 tab pack = £99.00)	£0.99	£10.40	2.95	0%	
Glucocorticosteroid	5 mg	Prednisolone 5 mg (28 tab pack = £1.21)	£0.04	£0.30	696	65%	**£0.96**
		Prednisolone 5 mg E/C (28 tab pack = £9.86)	£0.31	£2.17	374	35%	
Olsalazine	1000 mg daily	Dipentum 500 mg (60-tab pack = £21.18)	£0.35	£4.94	2.5	49%	**£4.94**
		Dipentum 250 mg (112-cap pack = £19.77)	£0.18	£4.94	2.6	51%	

Drug-specific tests

Drug-specific tests were decided by the GDG economic subgroup and chair. The GDG noted that the frequency of these drug specific tests would differ according to how long people were in remission

for, and agreed on yearly frequencies of consultations for people who have been in one, and two years of remission. This was accounted for in two different ways in the model. In the base case, the two-year frequencies were used and an overall cost applied per cycle to people in remission over the two-year time horizon. In a sensitivity analysis, an average cost of tests over the two years was calculated, and a cost applied per cycle to people in remission over the two-year time horizon. These consultations and tests are summarised in Table 33, Table 34 and Table 35. Note that the consultations are expressed in two-monthly frequencies, so as to reflect the cycle length in the model.

Table 33- Drug-specific tests for mesalazine and olsalazine in the model

Type of test	Unit cost	Year one frequency	Year two frequency
Full blood count	£3.00	56 tests per 100 people every two months	42 tests per 100 people every two months
Liver function test	£1.00	47 tests per 100 people every two months	39 tests per 100 people every two months
Renal function test	£1.00	42 tests per 100 people every two months	33 tests per 100 people every two months

Table 34- Drug-specific tests for glucocorticosteroid treatment and budesonide in the model

Type of test	Unit cost	Year one frequency	Year two frequency
Full blood count	£3.00	13 tests per 100 people every two months	13 tests per 100 people every two months
Liver function test	£1.00	13 tests per 100 people every two months	13 tests per 100 people every two months
Renal function test	£1.00	13 tests per 100 people every two months	13 tests per 100 people every two months

Table 35- Drug-specific tests for azathioprine in the model

Type of test	Unit cost	Year one frequency	Year two frequency
Full blood count	£3.00	200 tests per 100 people every two months[(a)]	97 tests per 100 people every two months
Liver function test	£3.00	174 tests per 100 people every two months[(a)]	97 tests per 100 people every two months
Renal function test	£1.00	174 tests per 100 people every two months[(a)]	97 tests per 100 people every two months
TPMT assay	£26.00	14 tests per 100 people every two months	0 tests per 100 people every two months
Virology tests	£8.00	50 tests per 100 people every two months	0 tests per 100 people every two months

(a) Please note that number of tests exceeds number of people since some people may have more than one test. In the case of full blood count, all people are assumed to have – on average- one test per month.

2.2.4 Computations

The mean cost and effectiveness of the competing strategies were calculated using Microsoft Office Excel 2007.

2.2.4.1 Calculating QALYs

In order to calculate the QALYs associated with a given treatment, for each cycle the prevalence of people in each health state was multiplied by the utility weight associated with that health state and divided by an adjustment factor to reflect the cycle length. A worked example of the utility calculation is shown below; please note this is a simplified calculation and the full calculation would take account of all the health states shown in Figure 7.

Table 36- Example calculation for model QALYs

	Remission	Active disease
Number of people in health state	560	440
Utility weight (Table 28)	0.89	0.61
Contribution to QALYs per patient (2 months)	$\frac{560 \times 0.89}{1000} \times \frac{2}{12} = 0.083$	$\frac{440 \times 0.61}{1000} \times \frac{2}{12} = 0.045$

Thus the total QALY for the cycle described above would be 0.083 + 0.045 = 0.128. These QALY contributions were then aggregated over the two-year model time horizon to calculate the total number of QALYs associated with each treatment.

2.2.4.2 Probabilistic analysis in the model

In the probabilistic analysis, distributions were assigned to treatment effects, utilities and, where possible, costs in order to account for the uncertainty in model inputs and capture the effect of this uncertainty on model outputs. Please see the induction of remission model write-up for more details on how inputs pertaining to induction of remission were made probabilistic.

Treatment effects:

Treatment effects were sampled probabilistically by assigning lognormal distributions as described elsewhere to quantities in Table 25 and Table 27.

Reference costs:

In order to assign a distribution to reference costs, it was assumed that they followed a lognormal distribution and the interquartile range was used to calculate an approximate standard error on the log scale.

Let $\boldsymbol{X}$ be the cost assigned to a distribution to, i.e. $\ln(\boldsymbol{X}) \sim \boldsymbol{Normal}(\boldsymbol{\mu}, \boldsymbol{\sigma^2})$

Let M be the mean associated with the cost.

Let $\boldsymbol{IQR}$ be the interquartile range associated with the cost.

Note that for normally distributed data:

$$IQR \approx 1.35\sigma$$

And noting that the standard error $\boldsymbol{s}$, is related to the standard deviation by:

$$s = \frac{\sigma}{\sqrt{n}}$$

Then the standard error on the log scale can be calculated as:

$$\sigma = \frac{\ln(IQR)}{1.35 \times \sqrt{n}}$$

And therefore random draws from the distribution can be taken:

$$\ln(X) \sim Normal\left(ln\left(\mu - \frac{\sigma^2}{2}\right), \left(\frac{\ln(IQR)}{1.35 \times \sqrt{n}}\right)^2\right)$$

Utilities:

Utilities were sampled probabilistically by assigning lognormal distributions to utility decrements as described elsewhere [6]. Normal distribution parameters were converted to lognormal parameters by method of moments, as defined below:

Let $E[X]$ and $Var[X]$ be the mean and variance respectively, of the utility decrement U

Then the parameters of the lognormal distribution, μ and σ^2 are found by:

$$\mu = \ln(E[X]) - \frac{\ln\left(1 + \frac{Var[X]}{E[X]^2}\right)}{2}$$

$$\sigma^2 = \ln\left(1 + \frac{Var[X]}{E[X]^2}\right)$$

2.2.4.3 Calculating cost effectiveness

It is possible, for a particular cost-effectiveness threshold, to express cost-effectiveness results in terms of net benefit (NB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs. The decision rule then applied is that the comparator with the highest NB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation NB is used to identify the optimal strategy in the probabilistic analysis simulations.

Let $\mathrm{C_t}$ and $\mathrm{Q_t}$ denote the mean costs and mean QALYs respectively, associated with a given treatment. Then the mean net benefit is then calculated as $\mathrm{NB_t}$:

$$\mathrm{NB_t} = \mathrm{C_t} - (20{,}000 \times \mathrm{Q_t})$$

Where £20,000 per QALY represents the cost-effectiveness threshold in the NICE reference case.

This net benefit is calculated for each of the 1000 simulations in the probabilistic analysis. This means that the probability that a given treatment would be optimal, can be estimated based on the number of times it has the highest net benefit.

However, the strategy that is optimal overall is the one that has the highest net benefit calculated using the mean costs and QALYs, where means were the average of the 1,000 simulated estimates.

2.2.5 Sensitivity analyses

The results of the model were tested by changing the parameters which were most uncertain, as described in Table 37.

Table 37- One-way sensitivity analyses in the model

Sensitivity analysis	Description	Value in base case	Value or range in sensitivity analysis
1- Time horizon	Time horizon increased	Two years	10 years
2- QALY discount rate	QALY discount rate decreased	3.5%	1.5%
3- Tests	Average number of drug-specific tests over two years used. Please see 0.	Year two	Average
4- Consultations	As described in 1.2.4.6, a sensitivity analysis was conducted whereby the average estimated resource use over three years was calculated and used in the model instead of the estimated year two resource use.	Year two	Average
5- Utility decrements	Since data were not available to inform a model based on varying levels of patient severity, it was decided to explore the effects of a utility decrement for each stage of failed induction therapy.	0%	10%
6- High baseline risk	A higher baseline risk for relapse and relapse + withdrawal was explored in the non-conservative and conservative analyses respectively.	Non-conservative: Relapse = 39% Conservative: Relapse + withdrawal = 52%	90%
7- Low baseline risk	A lower baseline risk for relapse and relapse + withdrawal was explored in the non-conservative and conservative analyses respectively.	Non-conservative: Relapse = 39% Conservative: Relapse + withdrawal = 52%	10%

2.2.6 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 the model formulae and calculations. The model parameters and results were also assessed against the content of this appendix.

2.2.7 Interpreting results

The strategy with the highest mean net benefit is the one that should be recommended[20], though the uncertainty around costs and QALYs should also be taken into consideration; the reasons for this have been detailed elsewhere. Since the disutilities of treatment-specific adverse events could not be

captured explicitly, caution should be exercised in recommending strategies containing treatments with high withdrawal rates.

2.3 Results

2.3.1 Conservative analysis

2.3.1.1 Conservative analysis- four-line model

Base case results

The results for the model run with conservative treatment effects and with relapses from all treatments (except azathioprine) being treated with four lines of induction therapy- a glucocorticosteroid, azathioprine + a glucocorticosteroid, a biologic, surgery- are shown in this section. In this analysis, the induction sequence for people relapsing from azathioprine is: a glucocorticosteroid, a biologic, surgery.

Table 38- Mean clinical outcomes in the base case (per patient)

Maintenance treatment	Time in weeks								QALYs
	On medical maintenance treatment	On no maintenance treatment	On biologic	**Total in remission**	On glucocorticosteroid	On biologic	In surgery	**Total with active disease**	
No treatment	0.00	19.71	0.59	**20.30**	2.29	0.38	0.15	**3.68**	1.67
Mesalazine	20.16	0.44	0.46	**21.07**	1.82	0.30	0.12	**2.91**	1.68
Budesonide	19.84	0.48	0.50	**20.83**	1.96	0.32	0.13	**3.15**	1.68
Glucocorticosteroid	18.26	0.68	0.70	**19.64**	2.70	0.44	0.18	**4.34**	1.65
Azathioprine/ mercaptopurine	20.08	0.95	0.91	**21.94**	1.26	0.56	0.22	**2.04**	1.71
Olsalazine	17.78	0.74	0.77	**19.29**	2.92	0.48	0.19	**4.69**	1.64

Table 38 shows that, in the base case conservative analysis where relapses from all treatments except azathioprine are treated with four lines of induction therapy, azathioprine was associated with the most weeks in remission and hence the highest number of QALYs.

Table 39- Mean costs in the base case (per patient)

Treatment	Drugs	Tests	Consultations	Surgery	Total
No treatment	£865	£51	£898	£385	£2,198
Mesalazine	£1,489	£63	£773	£303	£2,628
Budesonide	£1,485	£51	£812	£328	£2,675
Glucocorticosteroid	£1,100	£67	£1,004	£456	£2,627
Azathioprine/mercaptopurine	£1,686	£99	£657	£579	£3,021
Olsalazine	£1,489	£86	£1,062	£495	£3,131

Table 39 shows that, in the base case conservative analysis where relapses from all treatments except azathioprine are treated with four lines of induction therapy, the 'no treatment' arm was associated with the lowest costs for maintenance of remission- £2,200 per patient.

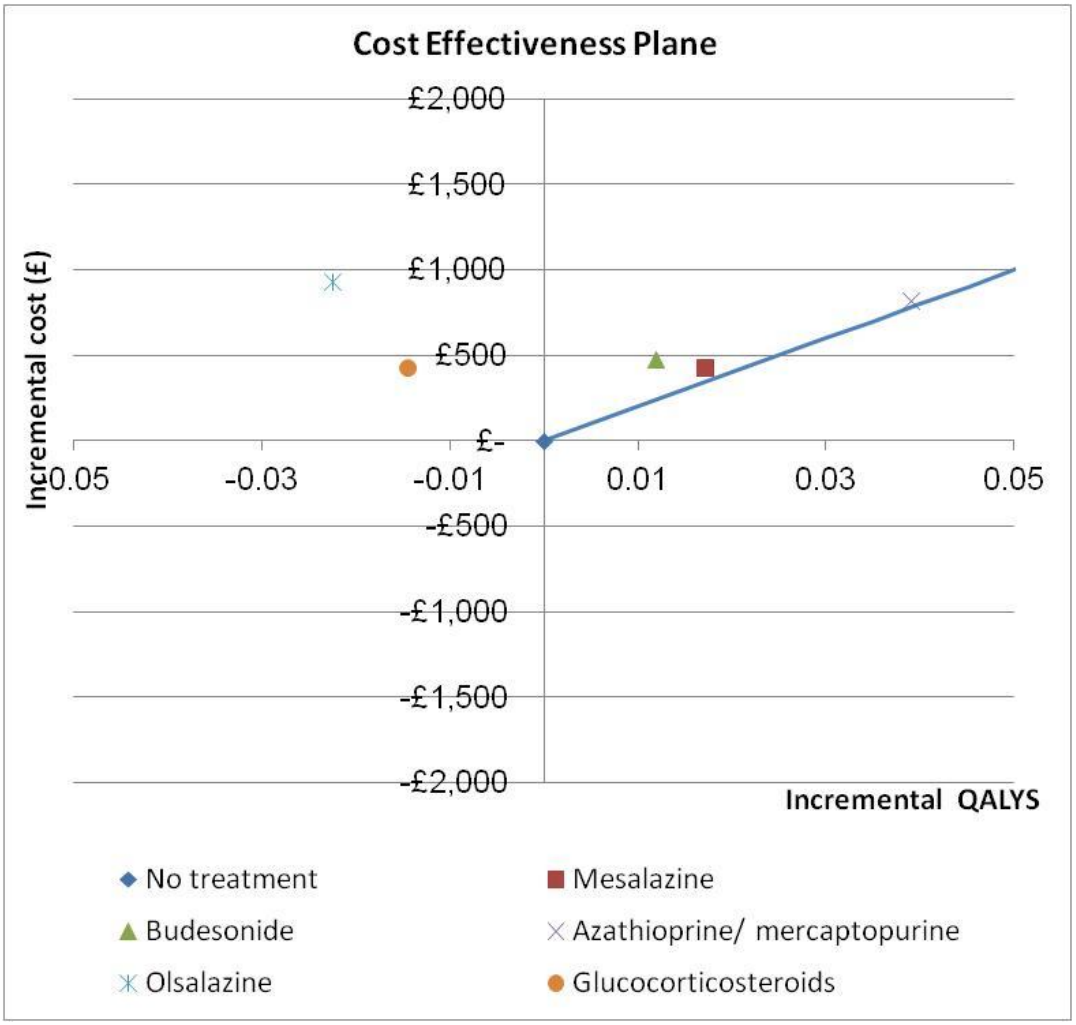
Table 40- Cost-effectiveness in the base case (mean)

First-line remission treatment	QALYs gained (vs NT) per patient	Incremental Cost (vs NT) per patient	Incremental net benefit* (vs NT) per patient	Cost-effectiveness rank*	ICER vs no treatment
No treatment (NT)	0	£0	£0	1	Comparator
Mesalazine	0.017	£430	-£88	3	£25,133
Budesonide	0.012	£477	-£241	4	£40,392
Glucocorticosteroid	-0.015	£429	-£721	5	Dominated
Azathioprine/mercaptopurine	0.039	£823	-£44	2	£20,319
Olsalazine	-0.023	£933	-£1,384	6	Dominated

* Using a willingness-to-pay threshold of £20,000 per QALY.

Table 40 shows that in the base case conservative analysis where relapses from all treatments except azathioprine are treated with four lines of induction therapy, the 'no treatment' arm was most cost effective at a willingness-to-pay threshold of £20,000 per QALY. Olsalazine and glucocorticosteroid treatment were dominated by no treatment. Budesonide, mesalazine and azathioprine were associated with ICERs of £40,000, £25,000 and £21,000 per QALY gained respectively compared with no treatment. This is represented visually in Figure 9, the cost-effectiveness plane depicting the mean costs and QALYs associated with each treatment. Note that in this diagram, the blue line represents a willingness-to-pay threshold of £20,000 per QALY and therefore any treatments that fall to the right of the line are cost effective compared to no treatment at this threshold.

Figure 9- Cost-effectiveness plane conservative four-line analysis



One-way sensitivity analysis

A description of the sensitivity analyses run in the model can be found in Table 20. This section only reports the sensitivity analyses in which the cost-effectiveness ranking changed.

- Sensitivity analysis one: ten year time horizon
    - Mesalazine ranked first, No treatment ranked second, budesonide ranked third.

In this sensitivity analysis, azathioprine is overtaken in cost-effectiveness by mesalazine and budesonide and mesalazine becomes the most cost-effective treatment. This is because as the time horizon gets longer more people relapse and thus the cost of induction treatment gets higher in less effective maintenance treatments. Azathioprine is the most effective maintenance treatment, but

due to the shorter induction sequence for azathioprine in this analysis, the cost of induction increases more in the azathioprine arm than in the mesalazine arm, which leads to mesalazine appearing more cost-effective over time.

- Sensitivity analysis seven: yearly baseline risk of relapse = 90%
    - Mesalazine ranked 1st, azathioprine ranked 2nd , budesonide ranked 3rd

  In this sensitivity analysis, mesalazine becomes the highest ranked treatment and no treatment is no longer ranked as one of the three most cost-effective treatments. This occurs because at a higher baseline relapse risk the effectiveness of maintenance treatment is much greater relative to no treatment leading to more people remaining in remission and hence greater cost effectiveness. Mesalazine becomes more cost effective than azathioprine because of the fact that azathioprine has a shorter induction sequence in this analysis, and thus the higher number of relapses generates higher costs than in the mesalazine arm, which offsets the higher maintenance efficacy of azathioprine. A threshold analysis showed that this change occurred when the baseline relapse risk was set to 60%

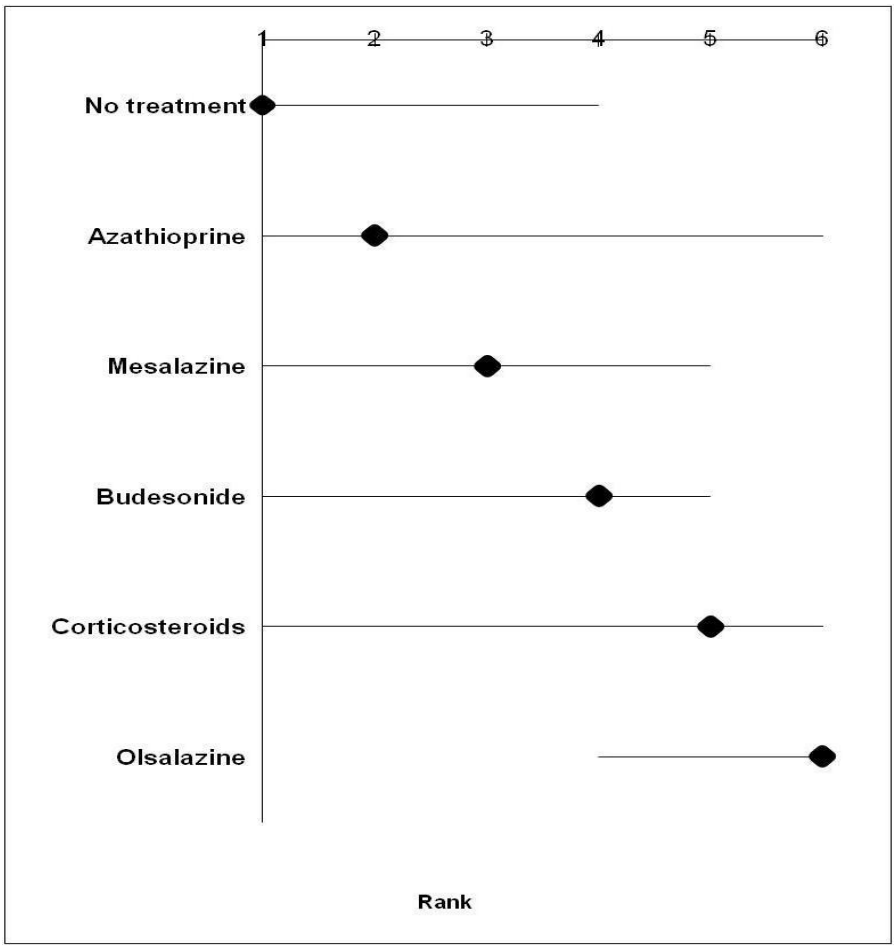
- Sensitivity analysis eight: yearly baseline risk of relapse = 10%
    - no treatment ranked first, glucocorticosteroid treatment ranked second, azathioprine ranked third

  In this sensitivity analysis, glucocorticosteroid treatment moves ahead of azathioprine, in terms of cost effectiveness. This is because at a lower baseline risk of relapse, the differences between effectiveness of maintenance treatments becomes relatively less. This leads to fewer additional remissions being induced among the more effective treatments and therefore lowers their cost-effectiveness. This change occurred when the baseline risk of relapse was lowered from 38% to 26%.

Probabilistic sensitivity analysis

Cost effectiveness ranks at £20,000 per QALY and their associated 95% confidence intervals were calculated by Monte-Carlo simulation. These are shown in Figure 10.

Figure 10- Conservative four-line model, forest plot of cost-effectiveness rankings



It can be seen from Figure 10 that although no treatment is most cost-effective in this case- as shown in the deterministic analysis- there is a lot of uncertainty around the relative ranks of the different treatments. The probability that each treatment was the most cost-effective in terms if incremental net benefit at a willingness to pay of £20,000 per QALY is shown in Table 41.

Table 41- Probability of each treatment being most cost-effective

Treatment	Probability of being most cost-effective
Placebo	22%
Mesalazine	7%
Budesonide	8%
Glucocorticosteroid	23%
Azathioprine	41%
Olsalazine	0%

2.3.1.2 Conservative analysis - three-line model

The results for the model run with conservative treatment effects and with all treatments having three lines of induction therapy- a glucocorticosteroid, a biologic and surgery- are shown in this section.

Table 42- Mean clinical outcomes in the base case (per patient)

Maintenance treatment	Time in weeks								QALYs
	On medical maintenance	On no maintenance treatment	On biologic	**Total in remission**	On glucocorticosteroid	On biologic	In surgery	**Total with active disease**	
No treatment	0.00	18.81	1.62	20.43	2.18	0.98	0.39	3.55	1.67
Mesalazine	18.46	1.37	1.29	21.12	1.76	0.79	0.31	2.86	1.69
Budesonide	18.03	1.48	1.39	20.90	1.89	0.85	0.34	3.08	1.68
Glucocorticosteroid	15.89	2.07	1.90	19.86	2.52	1.14	0.46	4.12	1.66
Azathioprine/ mercaptopurine	20.08	0.95	0.91	21.94	1.26	0.56	0.22	2.04	1.71
Olsalazine	15.26	2.24	2.06	19.56	2.70	1.23	0.49	4.42	1.66

Table 42 shows that, in the base case conservative analysis where relapses from all treatments are treated with three lines of induction therapy, azathioprine was associated with the greatest number of weeks in remission and hence the highest number of QALYs.

Table 43- Mean costs in the base case (per patient)

Treatment	Drugs	Tests	Consultations	Surgery	Total
No treatment	£2,162	£77	£922	£1,025	£4,185
Mesalazine	£2,466	£82	£800	£819	£4,168
Budesonide	£2,541	£73	£838	£883	£4,335
Glucocorticosteroid	£2,593	£96	£1,022	£1,196	£4,908
Azathioprine/mercaptopurine	£1,686	£99	£657	£579	£3,021
Olsalazine	£3,047	£115	£1,075	£1,288	£5,525

Table 43 shows that, in the base case conservative analysis where relapses from all treatments are treated with three lines of induction therapy, azathioprine was associated with the lowest costs for maintenance of remission- £3,021 per patient.

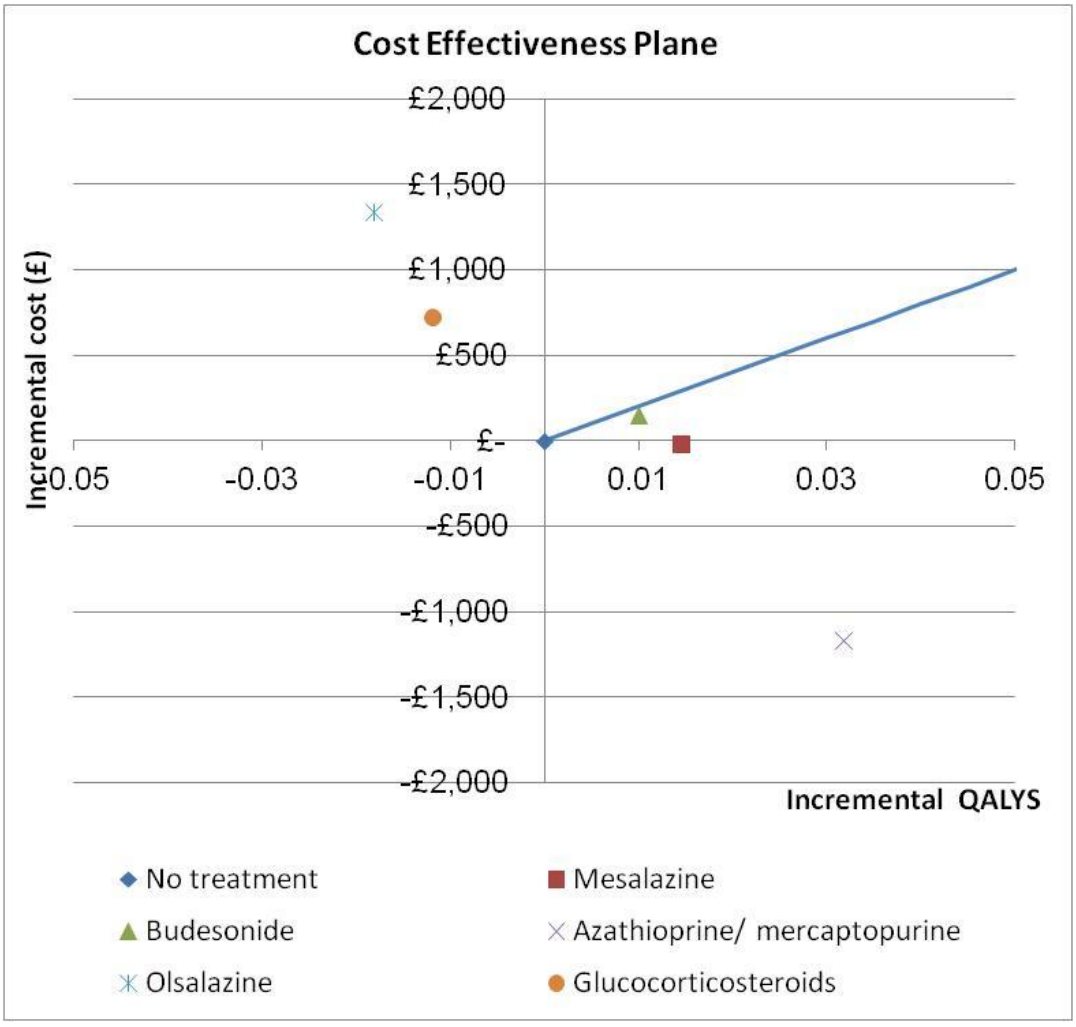
Table 44- Cost-effectiveness in the base case (mean)

First-line remission treatment	QALYs gained (vs NT) per patient	Incremental Cost (vs NT) per patient	Incremental net benefit* (vs NT) per patient	Cost-effectiveness rank*	Cost per QALY gained (vs NT)
No treatment	0	£0	£0	*4*	Comparator
Mesalazine	0.015	-£17	£307	*2*	Dominates
Budesonide	0.010	£150	£49	*3*	£15,070
Glucocorticosteroid	-0.012	£723	-£961	*5*	Dominated
Azathioprine/mercaptopurine	0.032	-£1,164	£1,798	*1*	Dominates
Olsalazine	-0.018	£1,340	-£1,703	*6*	Dominated

* Using a willingness-to-pay threshold of £20,000 per QALY.

Table 44 shows that in the base case conservative analysis where relapses from all treatments are treated with three lines of induction therapy, azathioprine was the most cost-effective treatment at a willingness–to-pay threshold of £20,000 per QALY. Olsalazine and glucocorticosteroid were dominated by no treatment. Budesonide was associated with an ICER of £15,000 per QALY gained compared with no treatment and both mesalazine and azathioprine were dominant vs no treatment. Note that even though mesalazine and budesonide were cost-effective vs no treatment, they were still substantially dominated by azathioprine in terms of costs and QALYs. This is represented visually in Figure 11, the cost-effectiveness plane depicting the mean costs and QALYs associated with each treatment. Note that in this diagram, the blue line represents a willingness-to-pay threshold of £20,000 per QALY and therefore any treatments that fall to the right of the line are cost effective at this threshold.

Figure 11- Cost-effectiveness plane conservative three-line analysis



One way sensitivity analysis

- Sensitivity analysis eight-yearly baseline risk of relapse = 10%
  - no treatment ranked first azathioprine ranked second, glucocorticosteroid treatment ranked third

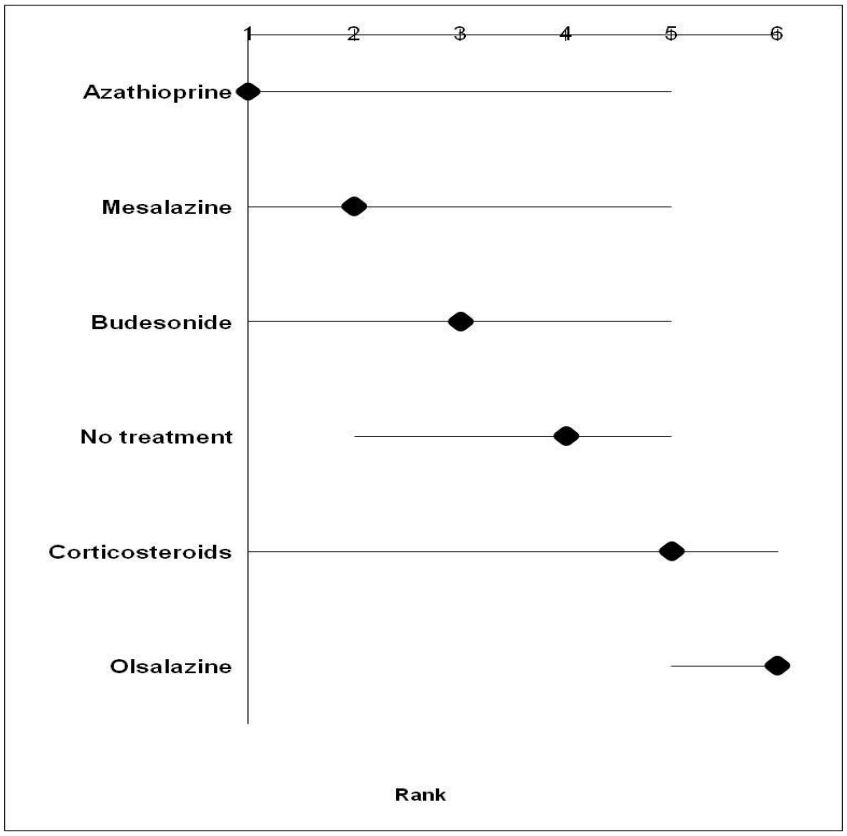
In this sensitivity analysis, no treatment and glucocorticosteroid treatment move into the top three treatments in terms of cost effectiveness. This is because at a lower baseline risk of relapse, the effectiveness of maintenance treatment becomes relatively less. This leads to fewer additional

remissions being induced among the more effective treatments and therefore lowers their cost-effectiveness. This change occurred when the baseline risk of relapse was lowered from 52% to 14%.

Probabilistic sensitivity analysis

Cost-effectiveness ranks at £20,000 per QALY and their associated 95% confidence intervals were calculated by Monte-Carlo simulation. These are shown in Figure 12.

Figure 12- Conservative three-line model, forest plot of cost-effectiveness rankings



It can be seen from Figure 12 that, although azathioprine is most cost effective in this case- as shown in the deterministic analysis- there is a lot of uncertainty around the relative ranks of the different treatments.

The probability that each treatment was the most cost-effective in terms if incremental net benefit at a willingness to pay of £20,000 per QALY is shown in Table 41.

Table 45- Probability of each treatment being most cost-effective

Treatment	Probability of being most cost-effective
Placebo	1%
Mesalazine	4%
Budesonide	3%
Glucocorticosteroid	9%
Azathioprine	82%
Olsalazine	0%

2.3.2 Non-conservative analysis

2.3.2.1 Non-conservative analysis- four-line model

The results for the model run with non-conservative treatment effects and with relapses from all treatments except azathioprine being treated with four lines of induction therapy- glucocorticosteroid treatment, azathioprine + a glucocorticosteroid, a biologic, surgery- are shown in this section. In this analysis, the induction sequence for people relapsing from azathioprine is: a glucocorticosteroid, a biologic, surgery.

Table 46- Mean clinical outcomes in the base case (per patient)

Maintenance treatment	Time in weeks								QALYs
	On medical maintenance	On no maintenance treatment	On biologic	**Total weeks in remission**	On glucocorticosteroid	On biologic	In surgery	**Total weeks with active disease**	
No treatment	0.00	20.51	0.48	20.99	1.86	0.30	0.12	2.99	1.68
Mesalazine	18.63	2.80	0.34	21.78	1.38	0.22	0.09	2.20	1.70
Budesonide	17.64	3.19	0.43	21.26	1.70	0.27	0.11	2.72	1.69
Glucocorticosteroid	17.70	3.03	0.45	21.18	1.75	0.28	0.11	2.80	1.69
Azathioprine/ mercaptopurine	20.23	2.56	0.34	23.14	0.53	0.22	0.09	0.84	1.73
Olsalazine	16.37	4.03	0.49	20.90	1.92	0.31	0.12	3.08	1.68

Table 46 shows that in the base case non-conservative analysis where relapses from all treatments except azathioprine are treated with four lines of induction therapy, azathioprine was associated with the greatest number of weeks in remission and hence the highest number of QALYs.

Table 47- Mean costs in the base case (per patient)

Treatment	Drugs	Tests	Consultations	Surgery	Total
No treatment	£698	£41	£786	£311	£1,836
Mesalazine	£1,255	£51	£658	£226	£2,190
Budesonide	£1,298	£44	£742	£281	£2,364
Glucocorticosteroid	£725	£45	£756	£291	£1,817
Azathioprine/mercaptopurine	£924	£73	£447	£227	£1,671
Olsalazine	£1,068	£61	£801	£321	£2,250

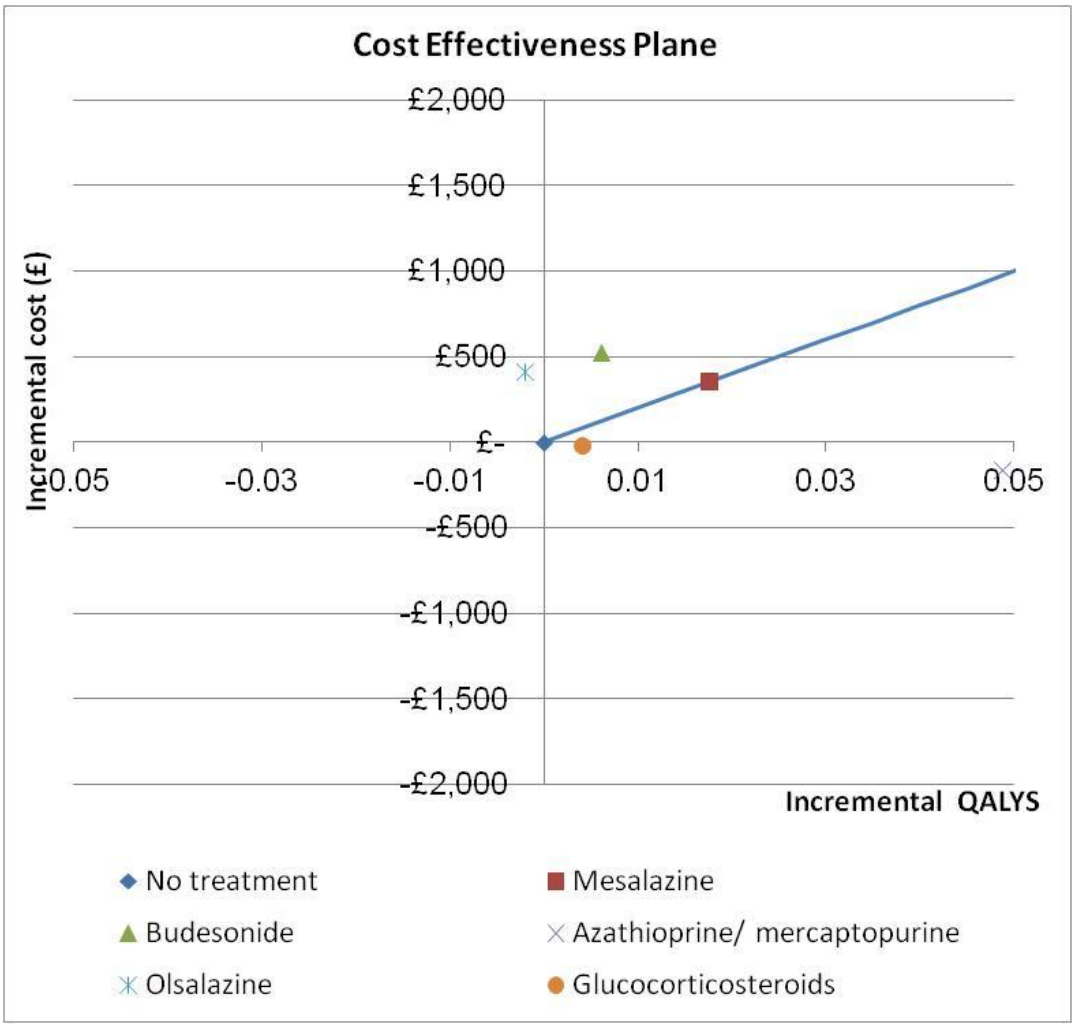
Table 47 shows that in the base case non-conservative analysis where relapses from all treatments except azathioprine are treated with four lines of induction therapy, azathioprine was associated with the lowest costs for maintenance of remission- £1,671 per patient.

Table 48- Cost effectiveness in the base case (mean)

First-line remission treatment	QALYs gained (vs NT) per patient	Incremental Cost (vs NT) per patient	Incremental net benefit* (vs NT) per patient	Cost-effectiveness rank*	Cost per QALY gained (vs NT)
No treatment	0	£0	£0	*3*	Comparator
Mesalazine	0.017	£355	-£6	*4*	£20,319
Budesonide	0.006	£528	-£408	*5*	£87,610
Glucocorticosteroid	0.004	-£19	£101	*2*	Dominates
Azathioprine/ mercaptopurine	0.049	-£164	£1,140	*1*	Dominates
Olsalazine	-0.002	£415	-£456	*6*	Dominated

* Using a willingness-to-pay threshold of £20,000 per QALY. Table 48 shows that in the base case non-conservative analysis where relapses from all treatments except azathioprine are treated with four lines of induction therapy, azathioprine was the most cost-effective treatment at a willingness-to-pay threshold of £20,000 per QALY. Olsalazine was dominated by no treatment. Budesonide and mesalazine were associated with ICERs of £20,000 and £88,000 per QALY gained respectively compared with no treatment and glucocorticosteroid treatment and azathioprine were dominant vs no treatment. This is represented visually in Figure 13, the cost-effectiveness plane depicting the mean costs and QALYs associated with each treatment. Note that in this diagram, the blue line represents a willingness-to-pay threshold of £20,000 per QALY and therefore any treatments that fall to the right of the line are cost effective at this threshold.

Figure 13- Cost-effectiveness plane non-conservative four-line analysis



One-way sensitivity analysis

A description of the sensitivity analyses run in the model can be found in Table 20. This section, only reports the sensitivity analyses in which the cost-effectiveness ranking changed significantly.

- Sensitivity analysis seven-yearly baseline risk of relapse = 90%
    - Azathioprine ranked first, mesalazine ranked second, budesonide ranked third

In this sensitivity analysis, mesalazine and budesonide move ahead of glucocorticosteroid treatment in the cost-effectiveness rankings. This is because at a higher baseline risk of relapse, the effectiveness of maintenance treatments increases relative to no treatment leading to more people in remission and therefore greater cost effectiveness. This occurred when the baseline risk of relapse was increased from 52% to 60%

- Sensitivity analysis eight-yearly baseline risk of relapse = 10%
    - No treatment ranked first, glucocorticosteroid treatment ranked second, azathioprine ranked third

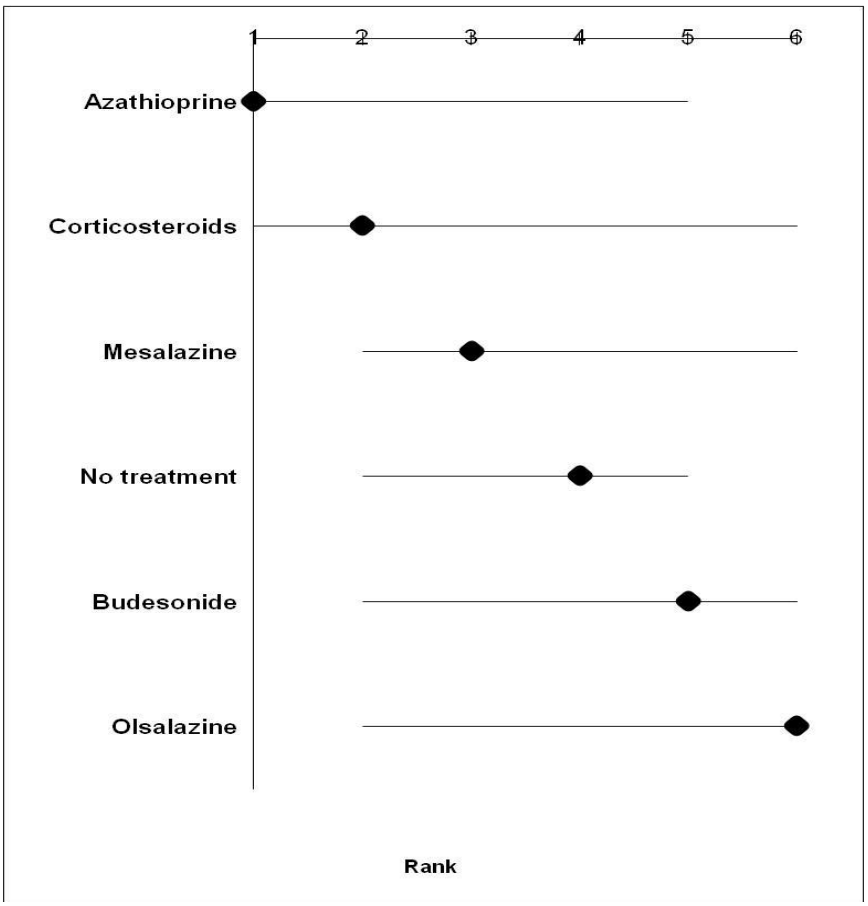
In this sensitivity analysis, no treatment and glucocorticosteroid treatment move ahead of azathioprine in terms of cost-effectiveness. This is because at a lower baseline risk of relapse, the effectiveness of maintenance treatments becomes less, and therefore the extra people that remain in remission on more effective treatments is reduced. This leads to fewer additional remissions

among the more effective treatments and therefore lowers their cost-effectiveness. This change occurred when the baseline risk was lowered from 39% to 11%.

Probabilistic-sensitivity analysis

Cost effectiveness ranks at £20,000 per QALY and their associated 95% confidence intervals were calculated by Monte-Carlo simulation. These are shown in Figure 14.

Figure 14-Non-conservative four-line model, forest plot of cost-effectiveness rankings



It can be seen from Figure 14 that, although azathioprine is most cost-effective in this case- as shown in the deterministic analysis- there is a lot of uncertainty around the relative ranks of the different treatments.

The probability that each treatment was the most cost-effective in terms if incremental net benefit at a willingness-to-pay of £20,000 per QALY is shown in Table 41.

Table 49- Probability of each treatment being most cost-effective

Treatment	Probability of being most cost-effective
Placebo	2%
Mesalazine	2%
Budesonide	0%
Glucocorticosteroid	9%
Azathioprine	87%
Olsalazine	0%

2.3.2.2 Non-conservative analysis- three-line model

The results for the model run with non- conservative treatment effects and with all treatments having three lines of induction therapy- a glucocorticosteroid, a biologic, surgery- are shown in this section.

Table 50- Mean clinical outcomes in the base case (per patient)

Maintenance treatment	Time in weeks								QALYs
	On medical maintenance treatment	On no maintenance treatment	On biologic	**Total in remission**	On glucocorticosteroid	On biologic	In surgery	**Total with active disease**	
No treatment	0.00	19.76	1.32	21.07	1.79	0.80	0.32	2.91	1.69
Mesalazine	17.39	3.44	0.97	21.80	1.35	0.60	0.24	2.18	1.70
Budesonide	16.15	3.98	1.20	21.32	1.64	0.73	0.29	2.66	1.69
Glucocorticosteroid	16.16	3.85	1.24	21.24	1.69	0.75	0.30	2.74	1.69
Azathioprine/ mercaptopurine	20.23	2.56	0.34	23.14	0.53	0.22	0.09	0.84	1.73
Olsalazine	14.75	4.88	1.36	20.99	1.84	0.82	0.33	2.99	1.69

Table 50 shows that in the base case non-conservative analysis where relapses from all treatments are treated with four lines of induction therapy, azathioprine was associated with the greatest number of weeks in remission and hence the highest number of QALYs.

Table 51- Mean costs in the base case (per patient)

Treatment	Drugs	Tests	Consultations	Surgery	Total
No treatment	£1,756	£63	£809	£833	£3,460
Mesalazine	£1,996	£66	£682	£617	£3,361
Budesonide	£2,209	£63	£765	£759	£3,796
Glucocorticosteroid	£1,715	£65	£779	£783	£3,342
Azathioprine/ mercaptopurine	£924	£73	£447	£227	£1,671
Olsalazine	£2,122	£81	£824	£858	£3,885

Table 51 shows that in the base case non-conservative analysis where relapses from all treatments are treated with three lines of induction therapy, azathioprine was associated with the lowest costs for maintenance of remission- £1,671 per patient.

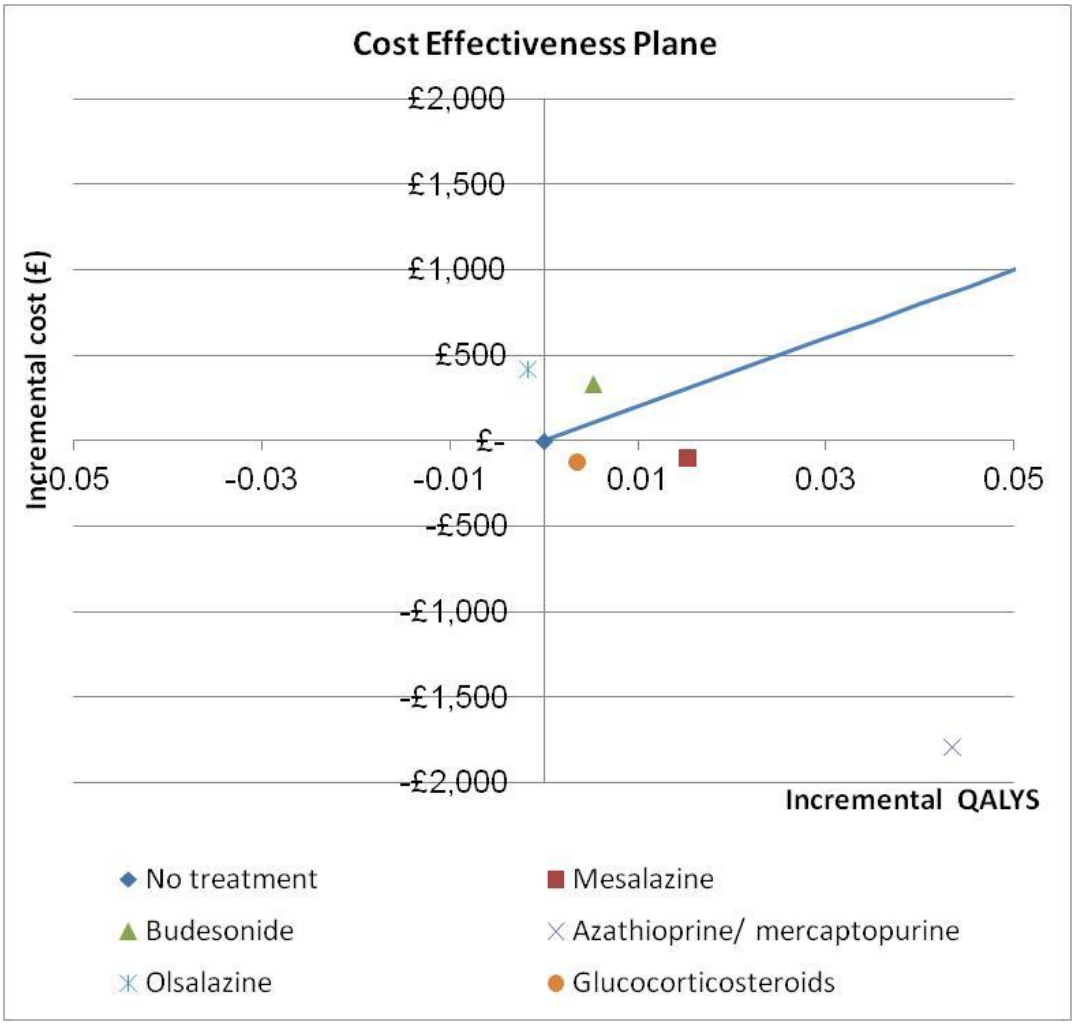
Table 52- Cost effectiveness in the base case (mean)

First-line remission treatment	QALYs gained (vs NT) per patient	Incremental Cost (vs NT) per patient	Incremental net benefit* (vs NT) per patient	Cost-effectiveness rank*	Cost per QALY gained (vs NT)
No treatment	0	£0	£0	*4*	comparator
Mesalazine	0.015	-£99	£403	*2*	Dominates
Budesonide	0.005	£336	-£232	*5*	£65,013
Glucocorticosteroid	0.003	-£118	£188	*3*	Dominates
Azathioprine/ mercaptopurine	0.043	-£1,789	£2,656	*1*	Dominates
Olsalazine	-0.002	£425	-£460	*6*	Dominated

* Using a willingness-to-pay threshold of £20,000 per QALY.

Table 52 shows that in the base case non-conservative analysis where relapses from all treatments are treated with three lines of induction therapy, azathioprine was the most cost-effective treatment at a willingness-to-pay threshold of £20,000 per QALY. Olsalazine was dominated by no treatment. Budesonide was associated with an ICER of £65,000 per QALY gained compared with no treatment and glucocorticosteroid treatment, mesalazine and azathioprine were dominant vs no treatment. Note that even though the ICERs associated with mesalazine and glucocorticosteroid treatment are under the cost-effectiveness threshold of £20,000 per QALY, both are significantly dominated by azathioprine. This is represented visually in Figure 15, the cost-effectiveness plane depicting the mean costs and QALYs associated with each treatment. Note that in this diagram, the blue line represents a willingness-to-pay threshold of £20,000 per QALY and therefore any treatments that fall to the right of the line are cost effective at this threshold.

Figure 15- Cost-effectiveness plane non-conservative three-line analysis



One-way sensitivity analysis

- Sensitivity analysis eight- yearly baseline risk of relapse = 10%
    - azathioprine ranked first, no treatment ranked second, glucocorticosteroid treatment ranked third

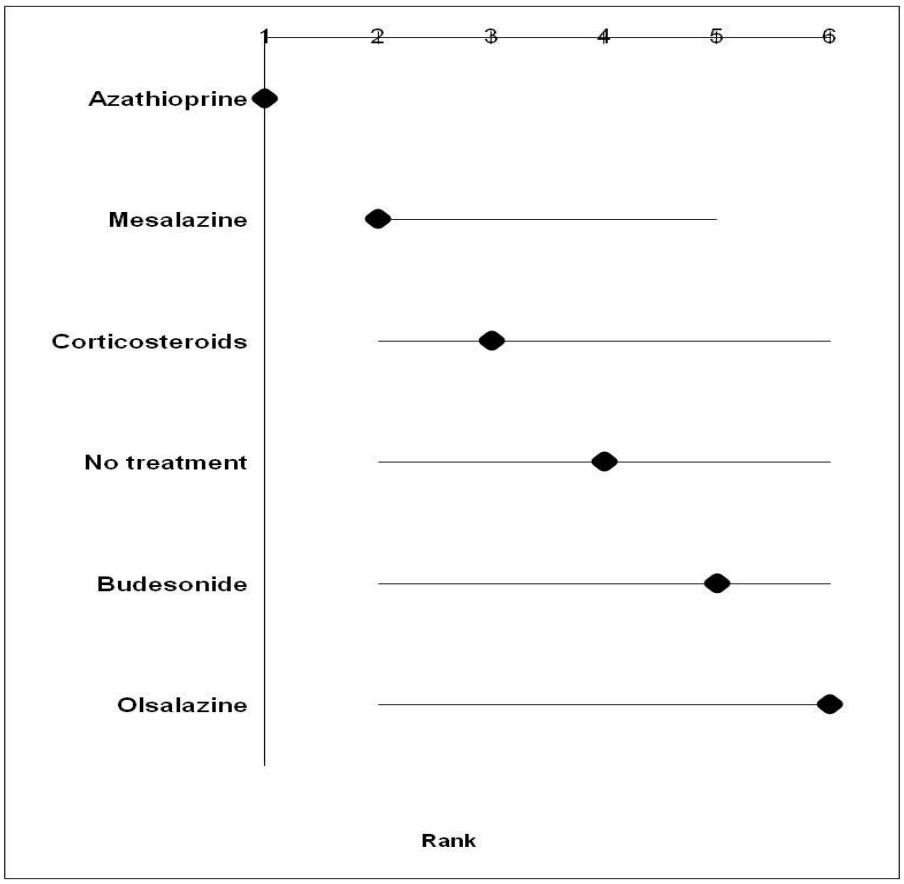
In this sensitivity analysis, no treatment and glucocorticosteroid treatment move into the top three treatments in terms of cost effectiveness. This is because at a lower baseline risk of relapse, the effectiveness of maintenance treatments becomes less, and therefore the extra people that remain in remission on more effective treatments is reduced. This leads to fewer additional remissions

among the more effective treatments and therefore lowers their cost-effectiveness. However, in spite of the lower number of remissions induced at this low risk of relapse, azathioprine is still the most cost-effective treatment in this analysis. This change occurred when the baseline risk of relapse was lowered from 39% to 13%.

Probabilistic sensitivity analysis

Cost effectiveness ranks at £20,000 per QALY and their associated 95% confidence intervals were calculated by Monte-Carlo simulation. These are shown in Figure 16.

Figure 16-Non-conservative four-line model, forest plot of cost-effectiveness rankings



It can be seen from Figure 16 that azathioprine is most cost-effective in this case- as shown in the deterministic analysis. In addition, there is much more certainty around its cost-effectiveness ranking.

The probability that each treatment was the most cost-effective in terms if incremental net benefit at a willingness-to-pay of £20,000 per QALY is shown in Table 53.

Table 53- Probability of each treatment being most cost-effective

Treatment	Probability of being most cost-effective
Placebo	0%
Mesalazine	1%
Budesonide	0%
Glucocorticosteroid	1%
Azathioprine	98%
Olsalazine	0%

2.4 Discussion

2.4.1 Summary of results

The analysis shows that in the base case:

- Azathioprine was dominant and ranked as the most cost-effective treatment option in all cases apart from the conservative four-line induction analysis where it was associated with an ICER of £20,000 per QALY gained compared with no treatment.
- The ICER for mesalazine ranged from being dominant to £25,000 per QALY gained in non-conservative and conservative analyses respectively.
- The ICER for budesonide ranged from £15,000 to £88,000 per QALY gained in non-conservative and conservative analyses respectively.
- Glucocorticosteroid treatment ranged from being dominant to dominated in conservative and non-conservative analyses respectively, showing there is a large amount of uncertainty in its cost-effectiveness.
- Olsalazine was dominated in all analyses.
- Excluding the azathioprine ranking in the non-conservative three-line induction model, there was a lot of uncertainty around cost-effectiveness rankings. This is due to the uncertainty in treatment effects propagated through the model.

2.4.2 Limitations and interpretation

This model is based on findings from RCTs included in the clinical review of the guideline and therefore any issues concerning interpretation in the clinical review also apply to interpretation of the economic analysis. Limitations of the model include:

- The utility loss and treatment cost associated with treatment-related adverse events have not been explicitly incorporated. This is likely to mean the cost effectiveness of all the treatment strategies has been over-estimated in the economic analysis, though since each treatment is likely to have a different side-effect profile, it is unlikely that ICERs have been underestimated by the same magnitude for all treatment strategies. For treatment strategies with more severe side-effects, the over estimation of the ICER is likely to be higher than in treatment strategies with less severe side-effect profiles.
- No clinical review was conducted on the efficacy of biologic treatments as this was outside of the Crohn's disease guideline remit therefore efficacy data have been derived from the two studies from within the NICE Technology Appraisal 187.
- Efficacy for azathioprine in the model is based on withdrawal trials and thus any conclusions regarding its cost effectiveness should be made in this context. The participants in these trials were, by definition those who had already achieved a stable remission with azathioprine, and therefore more likely to experience continued remission if randomised to azathioprine than a patient who has not previously tried the drug.
- It is difficult to incorporate severity of disease with precision, since both the trial and utility evidence tends to dichotomise outcomes to active disease and remission, whereas in reality there is a blurred line between active disease and remission. Furthermore relapses vary in terms of their severity.
- The conclusions from this model relate to which maintenance treatment to use once it has been decided to offer maintenance treatment to a person with Crohn's disease. The model is not designed to answer the question of when a patient should be put on maintenance treatment.

2.4.3 Generalisability to other populations and settings

It should be noted that all of the findings from this cost-effectiveness analysis relate to an adult population and the conclusions may not apply to treatment of Crohn's disease in childhood. It was not possible to conduct a separate model for children due to the paucity of both clinical and quality of life studies conducted in this area.

2.4.4 Conclusion and evidence statement

The original cost-effectiveness analysis conducted for this guideline suggests that azathioprine is the most cost-effective treatment for maintenance of remission in Crohn's disease, although there was considerable uncertainty related to interpretation of withdrawals in the trials and the induction sequence assumed for people that relapse.

2.5 Reference List

1 Coated oral 5-aminosalicylic acid versus placebo in maintaining remission of inactive Crohn's disease. International Mesalazine Study Group. Alimentary Pharmacology and Therapeutics. 1990; 1990 Feb;4(1):55-64

2 Arber N, Odes HS, Fireman Z, Lavie A, Broide E, Bujanover Y et al. A controlled double blind multicenter study of the effectiveness of 5-aminosalicylic acid in patients with Crohn's disease in remission. Journal of Clinical Gastroenterology. 1995; 20(3):203-206

3 Ardizzone S, Bollani S, Manzionna G, Imbesi V, Colombo E, Bianchi Porro G. Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. Digestive and Liver Disease. 2003; 35(9):619-627

4 Arora S, Katkov W, Cooley J, Kemp JA, Johnston DE, Schapiro RH et al. Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. Hepato-Gastroenterology. 1999; 46(27):1724-1729

5 Bar-Meir S, Chowers Y, Lavy A, Abramovitch D, Sternberg A, Leichtmann G et al. Budesonide versus prednisone in the treatment of active Crohn's disease. The Israeli Budesonide Study Group. Gastroenterology. 1998; 115(4):835-840

6 Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluation. Oxford: OUP; 2006

7 Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of Clinical Epidemiology. 1997; 50(6):683-691

8 Candy S, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. Gut. 1995; 37(5):674-678

9 Casellas F, Arenas JI, Baudet JS, Fabregas S, Garcia N, Gelabert J et al. Impairment of health-related quality of life in patients with inflammatory bowel disease: a Spanish multicenter study. Inflammatory Bowel Diseases. 2005; 11(5):488-496

10 Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007; 132(1):52-65

11 Curtis L. Unit costs of health and social care. Canterbury: Personal Social Services Reseach Unit, University of Kent; 2010. Available from: http://www.pssru.ac.uk/pdf/uc/uc2010/uc2010.pdf

12 De Vries F, Bracke M, Leufkens HG, Lammers JW, Cooper C, Van Staa TP. Fracture risk with intermittent high-dose oral glucocorticoid therapy. Arthritis and Rheumatism. 2007; 56(1):208-214

13 Department of Health. NHS reference costs 2009-2010. 2011. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459 [Last accessed: 1 August 2011]

14 Department of Health. NHS reference costs 2010-11. 2012. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_131140 [Last accessed: 27 March 2012]

15 Dias, S, Welton, NJ, Sutton, AJ, Caldwell, DM, Lu, G, and Ades, AE. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 2011 Available from: http://www.nicedsu.org.uk

16 Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. Mecial Decision Making. 1985; 5(2):157-177

17 Escher JC, European Collaborative Research Group on Budesonide in Paediatric IBD. Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled, multicentre trial. European Journal of Gastroenterology and Hepatology. 2004; 16(1):47-54

18 Ewe K, Press AG, Singe CC, Stufler M, Ueberschaer B, Hommel G et al. Azathioprine combined with prednisolone or monotherapy with prednisolone in active Crohn's disease. Gastroenterology. 1993; 105(2):367-372

19 Feagan BG, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. New England Journal of Medicine. 1995; 332(5):292-297

20 Fenwick E, Briggs A. Cost-effectiveness acceptability curves in the dock: case not proven? Mecial Decision Making. 2007; 27(2):93-95

21 Gibson PR, Weston AR, Shann A, Florin TH, Lawrance IC, Macrae FA et al. Relationship between disease severity, quality of life and health-care resource use in a cross-section of Australian patients with Crohn's disease. Journal of Gastroenterology and Hepatology. 2007; 22(8):1306-1312

22 Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN et al. Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. New England Journal of Medicine. 1994; 331(13):836-841

23 Gregor JC, McDonald JWD, Klar N, Wall R, Atkinson K, Lamda B et al. An evaluation of utility measurement in Crohn's disease. Inflammatory Bowel Diseases. 1997; 3(4):265-276

24 Gross V, Andus T, Caesar I, Bischoff S, Lochs H, Tromm A et al. Oral pH-modified release budesonide versus 6-methylprednisolone in active Crohn's disease. German/Austrian Budesonide Study Group. European Journal of Gastroenterology and Hepatology. 1996; 8(9):905-909

25 Joint Formulary Committee. British National Formulary (BNF). 62nd edition. London: British Medical Association and The Royal Pharmaceutical Society of Great Britain; 2011. Available from: http://www.bnf.org.uk

26 Joint Formulary Committee. British National Formulary (BNF). 63rd edition. London: British Medical Association and The Royal Pharmaceutical Society of Great Britain; 2012. Available from: http://www.bnf.org.uk

27 Klein M, Binder HJ, Mitchell M, Aaronson R, Spiro H. Treatment of Crohn's disease with azathioprine: a controlled evaluation. Gastroenterology. 1974; 66(5):916-922

28 Mahida YR, Jewell DP. Slow-release 5-amino-salicylic acid (Pentasa) for the treatment of active Crohn's disease. Digestion. 1990; 45(2):88-92

29 Mahmud NB, Kamm MA, Dupas JL, Jewell DP, O'Morain CA, Weir DG et al. Olsalazine is not superior to placebo in maintaining remission of inactive Crohn's colitis and ileocolitis: a double blind, parallel, randomised, multicentre study. Gut. 2001; 49(4):552-556

30 Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. Gastroenterology. 1984; 86(2):249-266

31 Martin F, Sutherland L, Beck IT, Anderson AH, Williams CN, Saibil F et al. Oral 5-ASA versus prednisone in short term treatment of Crohn's disease: A multicentre controlled trial. Canadian Journal of Gastroenterology. 1990; 4(7):452-457

32 Mate-Jimenez J, Hermida C, Cantero-Perona J, Moreno-Otero R. 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. European Journal of Gastroenterology and Hepatology. 2000; 12(11):1227-1233

33 National Clinical Guideline Centre. Hypertension: the clinical managment of primary hypertension in adults. London: Royal College of Physicians, 2011 Available from: http://guidance.nice.org.uk/CG127

34 National Clinical Guideline Centre. The management of hip fracture in adults. London: Royal College of Physicians, 2011 Available from: http://guidance.nice.org.uk/CG127

35 National Institute for Clinical Excellence. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. NICE clinical guideline CG117. London: National Institute for Health and Clinical Excellence, 2011 Available from: http://guidance.nice.org.uk/CG117

36 National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London: National Institute for Health and Clinical Excellence, 2008 Available from: http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp

37 National Institute for Health and Clinical Excellence. NICE technology appraisal guidance 187. Infliximab (review) and adalimumab for the treatment of Crohn's disease. Includes a review of NICE technology appraisal guidance 40. 2010 Available from: http://guidance.nice.org.uk/TA187

38 National Institute for Health and Clinical Excellence. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. (CG117). London: NICE, 2011

39 NHS Information Centre. Quarterly Prescription Cost Analysis, England (January - March 2011). 2011. Available from: http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/quarterly-prescription-cost-analysis-england--january--march-2011 [Last accessed: 29 March 2012]

40 NHS Information Centre. Health survey for England. 2012. Available from: http://www.ic.nhs.uk/hse [Last accessed: 29 March 2012]

41 NHS Information Centre. Monthly Hospital Episodes Statistics (HES) data. 2012. Available from: http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=1132 [Last accessed: 29 March 2012]

42 Office for National Statistics. 2011 Census, Population and Household Estimates for England and Wales. 2012. Available from: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-257414 [Last accessed: 19 July 2012]

43 Oren R, Moshkowitz M, Odes S, Becker S, Keter D, Pomeranz I et al. Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. American Journal of Gastroenterology. 1997; 92(12):2203-2209

44 Prantera C, Cottone M, Pallone F, Annese V, Franze A, Cerutti R et al. Mesalamine in the treatment of mild to moderate active Crohn's ileitis: results of a randomized, multicenter trial. Gastroenterology. 1999; 116(3):521-526

45 Prantera C, Pallone F, Brunetti G, Cottone M, Miglioli M. Oral 5-aminosalicylic acid (Asacol) in the maintenance treatment of Crohn's disease. The Italian IBD Study Group. Gastroenterology. 1992; 103(2):363-368

46 Present DH, Korelitz BI, Wisch N. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. New England Journal of Medicine. 1980; 302(18):981-987

47 Punekar YS, Sunderland T, Hawkins N, Lindsay J. Cost-effectiveness of scheduled maintenance treatment with infliximab for pediatric Crohn's disease. Value in Health. 2010; 13(2):185-195

48 Rasmussen SN, Lauritsen K, Tage-Jensen U, Nielsen OH, Bytzer P, Jacobsen O et al. 5-Aminosalicylic acid in the treatment of Crohn's disease. A 16-week double-blind, placebo-controlled, multicentre study with Pentasa. Scandinavian Journal of Gastroenterology. 1987; 22(7):877-883

49 Rutgeerts P, Lofberg R, Malchow H, Lamers C, Olaison G, Jewell D et al. A comparison of budesonide with prednisolone for active Crohn's disease. New England Journal of Medicine. 1994; 331(13):842-845

50 Scholmerich J, Jenss H, Hartmann F, Dopfer H. Oral 5-aminosalicylic acid versus 6-methylprednisolone in active Crohn's disease. Canadian Journal of Gastroenterology. 1990; 4(7):446-451

51 Singleton JW, Hanauer SB, Gitnick GL, Peppercorn MA, Robinson MG, Wruble LD et al. Mesalamine capsules for the treatment of active Crohn's disease: Results of a 16-week trial. Gastroenterology. 1993; 104(5):1293-1301

52 Singleton JW, Law DH, Kelley ML, Jr., Mekhjian HS, Sturdevant RA. National Cooperative Crohn's Disease Study: adverse reactions to study drugs. Gastroenterology. 1979; 77(4 Pt 2):870-882

53 Smith RC, Rhodes J, Heatley RV, Hughes LE, Crosby DL, Rees BI et al. Low dose steroids and clinical relapse in Crohn's disease: a controlled trial. Gut. 1978; 19(7):606-610

54 Stark RG, Reitmeir P, Leidl R, Konig HH. Validity, reliability, and responsiveness of the EQ-5D in inflammatory bowel disease in Germany. Inflammatory Bowel Diseases. 2010; 16(1):42-51

55 The Health and Social Care Information Centre. HESonline: Hospital Episode Statistics. 2012. Available from: http://www.hesonline.nhs.uk [Last accessed: 19 July 2012]

56 Thomsen OO, Cortot A, Jewell D, Wright JP, Winter T, Veloso FT et al. A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. New England Journal of Medicine. 1998; 339(6):370-374

57 Thomson AB, Wright JP, Vatn M, Bailey RJ, Rachmilewitz D, Adler M et al. Mesalazine (Mesasal/Claversal) 1.5 g b.d. vs. placebo in the maintenance of remission of patients with Crohn's disease. Alimentary Pharmacology and Therapeutics. 1995; 9(6):673-683

58 Tremaine WJ, Schroeder KW, Harrison JM, Zinsmeister AR. A randomized, double-blind, placebo-controlled trial of the oral mesalamine (5-ASA) preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. Journal of Clinical Gastroenterology. 1994; 19(4):278-282

59 Tromm A, Bunganic I, Tomsova E, Tulassay Z, Luka M, Kykal J et al. Budesonide (9mg) is at Least as Effective as Mesalamine (4.5g) in Patients with Mildly to Moderately Active Crohn's disease. Gastroenterology. 2010; 140(2):425-434

60 Tursi A, Giorgetti GM, Brandimarte G, Elisei W, Aiello F. Beclomethasone dipropionate for the treatment of mild-to-moderate Crohn's disease: an open-label, budesonide-controlled, randomized study. Medical Science Monitor. 2006; 12(6):I29-I32

61 Varas-Lorenzo C, Rodriguez LA, Maguire A, Castellsague J, Perez-Gutthann S. Use of oral corticosteroids and the risk of acute myocardial infarction. Atherosclerosis. 2007; 192(2):376-383

62 Wellmann W, Schroder U. New oral preparations for maintenance therapy in Crohn's disease. Canadian Journal of Gastroenterology. 1988; 2(SUPPL. A):71A-72A

63 Willoughby JM, Kumar P, Beckett J, Dawson AM. A double-blind trial of azathioprine in Crohn's disease. Gut. 1971; 12(10):864