NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Infliximab for the treatment of acute exacerbations of ulcerative colitis

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to:

- provide further information on completed randomised controlled trials (RCTs) and ongoing trials
- supply more data on mixed treatment comparisons (MTCs)
- provide more information on a number of cost-effectiveness assumptions that underpin the economic model
- discuss further the role of observational studies in medium-term effectiveness (late surgery).

Licensed indication

Infliximab (Remicade, Schering-Plough Ltd) has a marketing authorisation for the treatment of moderately to severely active ulcerative colitis. Infliximab is indicated for intravenous use in adults whose ulcerative colitis has responded inadequately to conventional therapy (including corticosteroids and 6-mercaptopurine or azathioprine), or who are intolerant to or have medical contraindications to such therapies. The recommended posology and method of administration in patients with ulcerative colitis is 5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5-mg/kg

infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Key issues for consideration

Clinical effectiveness

- Are there sufficient clinical data to form conclusions on the clinical effectiveness of infliximab in comparison with ciclosporin?
- How should the information from case series of infliximab be taken into account, given that identification of this kind of evidence was not attempted for the main comparator of interest, ciclosporin?
- Does the treatment population of the analysis reflect that indicated in the licence?
- Should the study by D'Haens and coworkers (D'Haens et al. 2001) be included in the MTC, given that it was conducted in a different population and used a different comparator from the other studies?
- Are the rates of colectomy for ciclosporin, estimated by the MTC model, appropriate for use in the economic model?

Cost effectiveness

- Does the economic model fully represent the uncertainty in the evidence? In particular with regard to:
  - predicted probabilities of colectomy rates
  - time horizon
  - adverse effects
  - mortality/morbidity (adverse events).

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Adults with acute exacerbations of severely active ulcerative colitis whose ulcerative colitis has responded inadequately to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications to such therapies, and whose clinical management requires hospitalisation.
Intervention	Infliximab 5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5-mg/kg infusions at 2 and 6 weeks after the first infusion and every 8 weeks thereafter.
Comparators	• Standard clinical management, which may be followed by surgical intervention • Ciclosporin, which may be followed by surgical intervention • Surgical intervention
Outcomes	• Health-related quality of life • Rates of surgical intervention • Survival • Measures of disease activity • Adverse effects of treatment including mortality
Economic evaluation	The cost effectiveness was expressed in terms of incremental cost per quality-adjusted life year (QALY). The treatment goals for ulcerative colitis patients with an acute flare are: • avoiding surgery • avoiding prolonged hospitalisation • reduction in disease activity resulting in remission. Costs were considered from an NHS and personal Social Services perspective.

1.2 Evidence Review Group comments

1.2.1 Population

The ERG stated that the MS addressed the population in the scope. However, it felt that it might have been worth clarifying that in the UK context, unless

contraindicated, the initial management of a patient hospitalised with acute ulcerative colitis would be intravenous corticosteroids for at least 3 days. Ulcerative colitis that does not respond to such treatment is deemed to be 'steroid refractory'. Infliximab, ciclosporin and surgery are options for the treatment of steroid-refractory ulcerative colitis.

1.2.2 Intervention

In the MS evidence relating to the licensed infliximab dose of 5 mg/kg is included. The MS did not appraise data on unlicensed higher doses of infliximab. The ERG has raised concerns about how research evaluating unlicensed higher doses such as 10 mg/kg and 20 mg/kg should be treated, and whether excluding such research is unnecessarily restrictive.

1.2.3 Comparators

The comparators included in the analysis were: standard clinical management which may be followed by surgical intervention; ciclosporin which may be followed by surgical intervention; and surgical intervention.

1.2.4 Outcomes

With regard to the manufacturer's clinical-effectiveness evidence, the ERG stated that the MS focuses on clinical response/induction of remission, colectomy rates and adverse events. The ERG stated that duration of hospitalisation and health-related quality of life would have been preferred. However, this information was not available from the four main studies that were included in the MS.

1.2.5 Economic evaluation

The ERG considered that the manufacturer's economic model appropriately addressed the acute phase of the disease. The main evidence used to estimate the key probabilities in the model were derived from the main trials. Data on resource use and costs were only available from an expert panel.

Utility data were taken from an observational cohort. Probabilistic and univariate sensitivity analyses were performed.

1.2.6 Timeframe

In the MS the base case analysis had a 1-year time horizon. The justification for the time horizon was both the nature of the decision problem (rescue therapy for avoidance/delay of colectomy) and the lack of any longer-term data. The ERG found this argument reasonable. However, the ERG noted the sensitivity analyses, in which the time horizon was extended. Some extreme scenarios were modelled; that is, all patients received colectomies at 12 months, and no further colectomies beyond 12 months were assumed.

1.3 Statements from professional/patient groups and nominated experts

The professional groups stated that moderate to severe active ulcerative colitis is treated with oral prednisolone or intravenous hydrocortisone/methylprednisolone. Ciclosporin or infliximab are considered in the inpatient setting if there is no clinical response by day three of intravenous corticosteroids. The condition is treated according to best practice and evidence-based guidelines, which have been published both in the UK and internationally.

2 Clinical-effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer developed a systematic review of the literature on the use of infliximab and comparator medicines in the target population. The searches identified a Cochrane review (Lawson et al. 2006), two other systematic reviews (Gisbert et al. 2007, Rahimi et al. 2007) and one smaller review (Rossetti et al. 2004) of infliximab for ulcerative colitis, and one Cochrane review of ciclosporin trials (Shibolet et al. 2005). Seven RCTs of infliximab

were found to begin with; however, five of them were excluded because of inappropriate patient populations. The two RCTs that were included are Jarnerot and coworkers (2005), and Sands and coworkers (2001). Similarly, seven ciclosporin RCTs were found, but only two of them (Lichtiger et al. 1994, D'Haens et al. 2001) were used in the MS, as the rest did not meet the inclusion criteria.

Both infliximab RCTs that were included were double-blind, multi-centre, parallel group trials of infliximab compared with placebo for the treatment of severe ulcerative colitis unresponsive to corticosteroids. Patient numbers in both studies were small. The Lichtiger and coworkers study was a randomised, double-blind, placebo-controlled prospective study which was followed by an open-label period (Lichtiger et al. 1994). The D'Haens and coworkers study was a randomised double-blind, single-centre prospective study (D'Haens et al. 2001). The methodology of these trials is presented in table 1.

Table 1 Summary of clinical effectiveness RCTs included in the MS

	Study	Population	Intervention	Comparator	Outcomes
Infliximab	Jarnerot et al. 2005	Acute severe/ moderately severe UC unresponsive to i/v corticosteroids for at least 4 days (n = 45)	Infliximab 4 mg/kg or 5 mg/kg plus intensive i/v corticosteroid therapy (n = 24)	Placebo plus intensive i/v corticosteroid therapy (n = 21)	*Primary:* colectomy or death within 3 months. *Secondary:* clinical and endoscopic remission at 1 and 3 months. Analyses undertaken early due to slow enrolment.
	Sands et al. 2001	Acute severe UC unresponsive to 7 days of corticosteroid therapy (of which ≥ 5 days used i/v administration) (n = 11)	Infliximab 5 mg/kg (n = 3), infliximab 10mg/kg (n = 3), infliximab 20 mg/kg (n = 2)	Placebo (n = 3)	*Primary:* treatment failure at 2 weeks after infusion. *Secondary:* change from baseline in modified Truelove & Witts score, physician's and patient's global response evaluation, ESR, CRP levels, sigmoidoscopic ratings, and histological disease scores. Enrolment terminated early due to slow accrual.
Ciclosporin	Lichtiger et al. 1994	Acute severe UC refractory to i/v corticosteroids after ≥ 7 days (n = 20)	Ciclosporin (n = 11)	Placebo (n = 9)	*Primary:* clinical activity score, response (clinical activity score of < 10 on two consecutive days) within 14 days of starting treatment.
	D'Haens et al. 2001	Patients hospitalised with severe UC (clinical activity score ≥ 10) (n = 30)	Ciclosporin (n = 15)	Methylprednisolone (n = 15)	*Primary:* improvement in clinical activity score, response (clinical activity score of < 10 on days 7 and 8 with a drop in the score from day 1 to 8 of at least 3 points and the possibility of discharge to the patients' home).

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; i/v, intravenous;
MS, manufacturer's submission; RCT, randomised controlled trial; UC, ulcerative colitis.

The primary outcome in the MS and economic evaluations was the avoidance of colectomies. Jarnerot and coworkers reported a significant reduction in the primary outcome of colectomy rates in favour of infliximab with an odds ratio of 4.9 (95% confidence interval, 1.4 to 17) (Jarnerot et al. 2005). Median time to colectomy was 8 days (range, 2–22 days) in the infliximab group and 4 days (range, 1–13 days) in the placebo group. In the study by Sands and coworkers, of the non-responding patients treated with infliximab, one patient received an increased corticosteroid dose and subsequent ciclosporin, and one patient underwent elective colectomy (Sands et al. 2001). There were no responders amongst patients treated with placebo and all three underwent colectomy by 2 weeks. Statistical analyses were not conducted in this study, due to small sample size.

In the study by Lichtiger and coworkers, a total of 9 out of 11 patients in the intravenous ciclosporin group had a response to therapy compared with no patients in the placebo group ($p < 0.001$) (Lichtiger et al. 1994). Also, at the end of the study the mean decline in the clinical activity score in the ciclosporin group was significantly greater than that in the placebo group ($p < 0.001$). One patient in the ciclosporin group who had a response to therapy elected to undergo colectomy. In the study by D'Haens and coworkers, 9 out of 14 patients had a response to ciclosporin compared with 8 out of 15 in the comparator group ($p = 0.4$). Mean decline in the clinical activity score was 5.4 (range, –1 to 14) with ciclosporin and 4.4 (range, -1 to 9) with methylprednisolone for all patients who completed the trial and 7.7 (range, 3 to 14) versus (vs) 6.1 (range, 4 to 9) in the responders. The mean time to response was 5.2 days (range, 2 to 8) in the ciclosporin group vs 4.3 days (range, 2 to 8) in the comparator group. The colectomy rates are summarised in table 2.

Table 2 Summary of colectomy outcomes from studies included in the MS

Study	Infliximab	Ciclosporin	Placebo or corticosteroids
Colectomy at 3 months			
Jarnerot et al. 2005	7/24 (29%)	–	14/21 (67%)
Sands et al. 2001	0/3 (0%)	–	3/3 (100%)
Lichtiger et al. 1994	–	3/11 (27%)	4/9 (44%)
D'Haens et al. 2001	–	3/14 (21%)	3/15 (20%)
Colectomy at 12 months			
Jarnerot et al. 2005	10/24 (42%)	–	15/21 (71%)
D'Haens et al. 2001	–	6/14 (36%)	6/15 (40%)
MS, manufacturer's submission.			

A Bayesian hierarchical model was used to synthesise the relative treatment effects in respect of colectomy outcomes observed within the trials. The objective was to develop probabilities of colectomy that could be used in an economic evaluation comparing infliximab with ciclosporin. These probabilities are shown in table 3.

Table 3 Predicted probabilities of colectomy

Treatment	Timepoint (months)	Mean	SD	2.5% CI	97.5% CI
Placebo	0–3	0.67	0.10	0.46	0.85
	3–12	0.14	0.12	0.00	0.47
Infliximab	0–3	0.23	0.13	0.05	0.56
	3–12	0.27	0.27	0.00	0.92
Ciclosporin	0–3	0.58	0.18	0.22	0.88
	3–12	0.18	0.19	0.00	0.70
CI, confidence interval; SD, standard deviation.					

Jarnerot and coworkers reported no deaths and the frequency of adverse events appeared to be comparable between the infliximab and placebo groups (Jarnerot et al. 2005). Sands and coworkers also reported no deaths

(Sands et al. 2001). Most adverse events were mild to moderate and no patients discontinued the infusion due to adverse events.

Lichtiger and coworkers reported no deaths (Lichtiger et al. 1994). Ciclosporin was associated with paresthesias, grand mal seizure, and headaches. No deaths were reported by D'Haens and coworkers, and no patients discontinued due to adverse events (D'Haens et al. 2001).

The manufacturer identified six more observational studies (Regueiro et al. 2006, Actis et al. 2002, Chey et al. 2001, Kohn et al. 2007, Kohn et al. 2002, Lees et al. 2007) that investigated the efficacy of infliximab in hospitalised patients with acute severe treatment history, but clinical data from these studies were not used to inform any efficacy estimates in the economic modelling. The manufacturer asserts that these observational studies support the assumption used in the economic model that infliximab is safe and effective as a 'rescue' therapy in preventing or delaying colectomy in acute severe ulcerative colitis patients. A summary of their methods and colectomy rates are presented in tables 4 and 5.

Table 4 Methodology of infliximab observational studies

Study	Design	n	Disease measure	Infliximab regimen
Actis et al. 2002	Prospective, open, uncontrolled	8	Disease activity index	Single dose 5 mg/kg
Chey et al. 2001	Open, uncontrolled	8	Disease activity index	Single dose 5 mg/kg
Kohn et al. 2002	Prospective, open, uncontrolled	13	Truelove and Witts	Single dose 5 mg/kg
Kohn et al. 2007	Retrospective and prospective	83	Modified Truelove and Witts	Single dose 5 mg/kg
Lees et al. 2007	Retrospective, open, uncontrolled	39	Truelove and Witts	Single dose 5 mg/kg
Regueiro et al. 2006	Retrospective, open, uncontrolled	12	Disease activity index	Single dose 5 mg/kg

Table 5 Colectomy results in infliximab observational studies

Study	Early colectomy assessment	Early colectomy	Late colectomy assessment	Late colectomy (cumulative)
Actis et al. 2002	7 months	4/8 (50%)	N/A	5/8 (63%)
Chey et al. 2001	5 months	0/8 (0%)	N/A	0/8 (0%)
Kohn et al. 2002	25.6 months	2/13 (15%)	N/A	3/13 (23%)
Kohn et al. 2007	23.4 months	12/83 (15%)	2 months	24/83 (30%)
Lees et al. 2007	203 days	13/39 (33%)	Admission	15/39 (38%)
Regueiro et al. 2006	5 months	2/12 (16%)	Admission	9/12 (75%)

2.2 Evidence Review Group comments

The ERG considered that the search strategies of both the MS and the underlying Cochrane review were strong with respect to published data, but limited with respect to unpublished data. For ciclosporin the search strategy was weaker and the terms used for the economic evaluation search strategy

were limited. Search strategies conducted by the ERG identified no additional RCTs for either infliximab or ciclosporin. The ERG was concerned about the small number of participants in the identified studies and stated that the amount of uncertainty has been understated in the MS.

The ERG pointed out that the MS only presented the results from observational studies investigating infliximab. It noted that the validity of the studies has not been rigorously assessed and the studies might overstate the effectiveness of infliximab relative to ciclosporin.

In the ERG's view it was not appropriate to include the study by D'Haens and coworkers (D'Haens et al. 2001) because this was a comparison of ciclosporin and intravenous corticosteroids in people with acute severe ulcerative colitis requiring hospitalisation who had **not yet** received any intensive treatment. Therefore neither the population nor the comparator treatment were in line with the rest of the infliximab and ciclosporin RCTs, which were comparisons with placebo in people who had not responded to initial treatment with intravenous corticosteroids. Therefore, including this study is likely to have led to an overestimation of the effect of infliximab relative to ciclosporin in the economic model.

The ERG re-ran the MTC model using the code provided by the manufacturer and obtained the same results. The ERG queried the face validity of the results, which bore little relation to actual estimates of effect obtained in the original trials. The ERG pointed out that it is likely that the MTC model does not appropriately estimate the true effects of the different treatment options; in particular with respect to the effectiveness of ciclosporin. The estimate of colectomy rate in the MTC was nearly twice that actually observed in the RCTs of ciclosporin.

The ERG re-ran the MTC model without the study by D'Haens and coworkers (D'Haens et al. 2001) as an exploratory analysis. This exclusion reduced the estimated colectomy rates for ciclosporin to some extent, but they were still

much higher than what would be expected in practice. Data from the re-run MTC model are presented in table 6.

Table 6 ERG re-run MTC model

Intervention	Manufacturer's MTC model for colectomy rates (0–3 months results)	ERG re-run MTC model without D'Haens et al. (0–3 months results)	ERG comments
Crude rates (%) [95% CI by Wilson's method]			
Infliximab	(0.23) [0.05, 0.56]	(0.24) [0.05, 0.56]	No change from original estimate
Ciclosporin	(0.58) [0.22, 0.88]	(0.48) [0.09, 0.89]	Change from 0.58 to 0.48
Placebo	(0.67) [0.46, 0.85]	(0.67) [0.46, 0.85]	No change from original estimate
Odds ratios [95% CI]			
Infliximab vs placebo	0.13 [0.03, 0.44]	0.13 [0.03, 0.44]	No change from original estimate
Ciclosporin vs placebo	0.70 [0.18, 2.69]	0.43 [0.06, 3.1]	Change from 0.70 to 0.43 (widening of 95% CI)
Infliximab vs ciclosporin	No direct comparisons		

CI, confidence interval; ERG, Evidence Review Group, MTC, mixed treatment comparison; vs, versus.

The ERG stated that the manufacturer did not indicate that there is similar or slightly less strong evidence that ciclosporin is clinically effective. The ERG obtained clinical opinion suggesting that the colectomy rate estimated for ciclosporin was 'completely inconsistent with the current evidence and with clinical experience.' Consequently, the ERG considered the assertion that infliximab has greater benefit than ciclosporin based on the indirect comparison to be unfounded.

2.3 Statements from professional/patient groups and nominated experts

Professional organisations stated that approximately 20–33% patients with acute severe ulcerative colitis require colectomy while in hospital. This requirement for colectomy is probably reduced by approximately 50% in the short term, and 25% in the long term, by the use of either ciclosporin or infliximab in patients whose disease is not showing a rapid response to corticosteroids. In the UK IBD Audit 2006, 28% patients with acute severe ulcerative colitis responded well to intravenous corticosteroids. In the remainder of cases with steroid-refractory disease, the treatments used were surgery (42%), ciclosporin (28%) and infliximab (4%). Intravenous ciclosporin has been used for steroid-refractory acute severe ulcerative colitis for approximately 12 years with an acute response rate, measured by avoidance of colectomy, of approximately 70%. However, up to 60% of patients 'rescued' with ciclosporin have colectomy within a year of this episode. Ciclosporin is associated with several serious side effects, including opportunistic infection, neuropsychiatric disturbances including fits, renal malfunction, hypertension, electrolyte disturbances and drug interactions. These side effects are more common in older people but in large series have been associated with a mortality of approximately 3% (mainly due to infection).

The other accepted treatment option is urgent sub-total colectomy with illeostomy and, in most patients, subsequent formation of an illeoanal pouch anastomosis. Surgery of this sort carries a small risk of mortality, particularly in the case of acute severe ulcerative colitis.

It was stated by professional groups that there are subgroups of patients with the condition who have a different prognosis from the typical patient. These include those with previous malignancy, young children and patients with a history of tuberculosis. All of these are at greater risk of potentially fatal complications following treatment with infliximab or ciclosporin. Younger patients are at greater risk overall in terms of immunogenicity and developing

other morbidity and mortality. The elderly are less likely to develop severe reactions and there may be less risk of complications when treating this group of patients with infliximab or ciclosporin.

The clinical specialists stated that one potential benefit of infliximab is that surgery can be delayed until patients are in better health. This reduces the risk of complications after surgery, rather than not having the treatment and having an emergency colectomy which carries a higher risk of sepsis. For this purpose, ciclosporin may be slightly faster acting than infliximab, but has potential toxicity and must be given within an inpatient unit with frequent blood monitoring. The clinical specialists stated that when patients are acutely ill with ulcerative colitis, treatment decisions need to be made quickly because if treatment is ineffective, surgery must be performed as soon as possible.

With regard to concomitant drug use during treatment with infliximab, it was stated that it is often recommended that patients also receive azathioprine or methotrexate for immunosuppression, to try to maintain subsequent remission in patients whose ulcerative colitis responds to infliximab.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The analysis submitted by the manufacturer was specifically related to the acute presentation of severe ulcerative colitis. A decision analytical model was used to simulate the progression of hypothetical cohorts of patients. The structure of this model was informed by the infliximab and ciclosporin RCTs, information on current UK clinical practice and expert opinion. People with severe active ulcerative colitis hospitalised for an acute exacerbation of the disease were considered in the economic evaluation. These patients were tracked as they received one of the four treatment strategies – infliximab, ciclosporin, standard care or surgical intervention in the first treatment cycle (0 to 3 months) and the second treatment cycle (4 to 12 months). The time

horizon used in the base case was 1 year. An extrapolated analysis extending up to 10 years was conducted to address the long-term treatment effect.

The parameter estimates used in the model were obtained from clinical studies of infliximab and ciclosporin, published literature sources and data on file. Although the baseline risk of disease progression was estimated using the placebo (standard care) arm from the study by Jarnerot and coworkers (Jarnerot et al.2005) this was inconsistently stated in the MS. The base-case utilities were derived mainly from the Health Outcomes Data Repository (HODaR) study, which was conducted using the EQ-5D instrument in patients with ulcerative colitis in south Wales. These were supplemented with utilities from the study by Arseneau and coworkers in which utilities were estimated using the time trade-off method (Arseneau et al. 2006). An average of utilities for ileoanal pouch anal anastomosis (IPAA) and ileostomy reported on both the HODaR study and that by Arseneau coworkers (Arseneau et al. 2006) was used for the post-surgery remission health state. Estimates of healthcare resource use and concomitant medication use were based on a panel of UK gastroenterologists opinions. The cost of all drugs was calculated based on the average doses used in the clinical trials and on pack sizes in the BNF. Drug administration costs were obtained from the NHS reference costs.

The model represented the disease progression of ulcerative colitis patients for a year after the point of hospital admission following an acute exacerbation. The course of the disease was represented by post-hospitalisation outcomes including medical remission, surgical remission and surgical complications.

The initial model cohort consisted of hypothetical individuals with acute severe ulcerative colitis that did not respond to 72 hours of intravenous corticosteroid therapy. These patients were assumed to receive one of the four treatment strategies under consideration, that is, infliximab, ciclosporin, standard care, or surgical intervention. Treatment outcomes were characterised in the model

as short-term outcomes (0–3 months), medium-term outcomes (4–12 months) and long-term outcomes (2–10 years).

Table 7 Incremental base-case analysis results

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Surgery	17,067	0.58	–	–	–
Ciclosporin	18,162	0.70	1,095	0.12	9,374
Standard care	18,550	0.68	388	–0.02	Dominated
Infliximab	19,890	0.80	1,729	0.10	18,425
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; vs, versus.					

Univariate sensitivity analyses were performed considering variations in treatment effect, patient weight, utility estimates, infliximab administration cost, hospitalisation period, and infliximab infusion doses. Probabilistic sensitivity analyses were conducted to assess the uncertainty of the cost-effectiveness estimates by assigning distributions around the primary outcome (colectomy), secondary outcome (post-surgery complications), utility estimates and unit costs. For results and a full discussion on the sensitivity analyses performed, see sections 6.3.3 and 5.4 of the ERG's report and point B5 and B6 in the manufacturer's response to the clarification request.

At the request of NICE's technical team, the manufacturer submitted the results of the economic evaluation in a disaggregated format. As a result, a breakdown of treatment outcomes, at every time cycle of the model, for a cohort of 100 patients and their contributions to the final QALYs was presented.

3.2 Evidence Review Group comments

The ERG considered that the structure of the manufacturer's economic model appropriately addressed the acute phase of the disease. However, the model did not take into account any costs or disutilities associated with adverse events. The ERG noted this was especially important when trials of infliximab

in patients with ulcerative colitis described 'serious adverse events'. Similarly, adverse events associated with other treatments were ignored. Mortality issues were also ignored.

The sensitivity analyses explored the importance of patient weight and the timeframe of the analysis, in particular when long-term data for the clinical effectiveness of infliximab were not available. However, the colectomy rates associated with the alternative treatment arms were not varied as part of the univariate analyses. The incremental cost-effectiveness ratios (ICERs) were shown by the ERG to be most sensitive to these colectomy rates. Also, the probabilistic sensitivity analysis placed distributions around selected parameters only.

On the basis of the total costs and total QALYs for standard care and ciclosporin, as shown in table 7, it was concluded that the move from standard care to ciclosporin is highly cost effective. As a result, the ERG suggested that the only appropriate comparator for infliximab is ciclosporin. When the ERG used the revised 0–3 months colectomy rate for the ciclosporin study, as shown in table 8, the ICER for infliximab versus ciclosporin increased considerably from £19,922 to £48,367.

Table 8 Revised cost-effectiveness results

Treatment comparisons	Incremental costs (£)	Incremental QALYs	ICER (£)
Infliximab vs standard care	1,230	0.107	11,503
Infliximab vs ciclosporin	2,895	0.060	48,367
Infliximab vs surgery	2,692	0.192	13,998

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; vs, versus.

4 Authors

George Vamvakas and Prashanth Kandaswamy with input from the lead team (Paul Ewings and Norman Vetter).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by: West Midlands Health Technology Assessment Collaboration, Department of Public Health and Epidemiology, University of Birmingham

- Bryan S et al. Infliximab for the treatment of acute exacerbations of ulcerative colitis, June 2008

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- Schering-Plough Ltd

II Professional/specialist, patient/carer and other groups:

- Nahal J. Clinical Nurse Specialist (gastroenterology), Royal College of Nursing
- Grevenson K. Inflammatory Bowel Disease Nurse, Royal College of Nursing
- Burnham R. Registar, Royal College of Physicians
- Lynch J. Medway PCT sponsoring Health Priority Setting Unit

Appendix B: Ongoing research

The manufacturer and the ERG identified two additional ongoing trials comparing infliximab with ciclosporin in steroid-refractory acute severe ulcerative colitis in hospitalised patients. This might be very useful in improving the evidence base for clinical decisions on the management of acute severe flares of ulcerative colitis, as currently the amount of rigorous evidence is so limited.