REMICADE®
(*infliximab*)

Infliximab for the treatment of acute exacerbations of ulcerative colitis

A Submission to the National Institute for Health and Clinical Excellence

Schering-Plough Ltd

Date of Report: 8 may 2007

Section A

1 Description of technology under assessment

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

Remicade®, Infliximab – TNF-α inhibitor

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

Yes; 28th February 2006

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

Rheumatoid arthritis:

Remicade, in combination with methotrexate, is indicated for: the reduction of signs and symptoms as well as the improvement in physical function in:

• patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate.

• patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by x-ray, has been demonstrated.

Crohn's disease:

Remicade is indicated for:

• treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

• treatment of fistulising, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Ulcerative colitis:

Remicade is indicated for: Treatment of moderately to severely active ulcerative colitis in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

Ankylosing spondylitis:

Remicade is indicated for: Treatment of ankylosing spondylitis, in patients who have severe axial symptoms, elevated serological markers of inflammatory activity and who have responded inadequately to conventional therapy.

Psoriatic arthritis:

Remicade is indicated for: Treatment of active and progressive psoriatic arthritis in patients who have responded inadequately to disease-modifying anti-rheumatic drugs. Remicade should be administered

- in combination with methotrexate

- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated

Psoriasis:
Remicade is indicated for: Treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Product launched and currently used in NHS

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

Infliximab has regulatory approval following a positive opinion granted on 28th February 2006, by the European Union's (EU) Committee for Medicinal Products for Human Use (CHMP), for the European Agency for the Evaluation of Medicines Agency (EMEA). The Commission approval results in Marketing Authorization with unified labelling valid in all EU-member states (current 25 members), as well as Iceland and Norway.
Infliximab has been approved by US FDA for moderate to severely active UC patients on 15th September 2005.

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

Moderate to severe chronic ulcerative colitis
Negative guidance in Scotland due to non submission. Submission not made pending outcome of several ongoing studies. Submission planned on completion of these studies. Currently undergoing a separate single technology appraisal by NICE in the population mentioned above.

Acute exacerbation of ulcerative colitis
The technology has not been subjected to any assessment in UK for this population.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

100 mg vial containing powder for concentrate for solution for infusion

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

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. Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. three doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

£419.62 per vial of Remicade

1.10 What is the setting for the use of the technology?

Secondary care

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

None

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with acute exacerbations of severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies, and whose clinical management require hospitalisation.	The submission will address the licensed indication of infliximab as outlined in the final scope.
Intervention	Infliximab	Infliximab 5 mg/kg given as an intravenous infusion over a 2 hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion.
Comparator(s)	The standard comparators to be considered include: standard clinical management which may include surgical intervention ciclosporin	Current clinical management in UK for an acute exacerbation of UC not responding to 72 hours iv steroids consists of treatment with infliximab, ciclosporin, up to 1 week iv steroids as a bridge to maintenance immunomodulatory therapy or surgery. All the treatment options including infliximab upon failure may result in surgical intervention. Therefore the proposed submission will focus on surgical intervention as an outcome of inadequate response to treatment as well as a comparator. Therefore, the comparators will be ▪ standard clinical management which may result in surgical intervention ▪ ciclosporin which may result in surgical intervention ▪ Surgical intervention
Outcomes	The outcome measures to be considered include: 1. health-related quality of life 2. survival 3. rates of and duration of response, relapse and remission 4. rates of surgical intervention measures of disease activity adverse effects of treatment	The submission will focus on • health-related quality of life • rates of surgical intervention • survival • measures of disease activity • adverse effects of treatment including mortality
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Time horizon should be long enough to allow reasonable estimation of expected costs (including adverse events if applicable) and benefits for the intervention, but should also account for the disease specific	The cost effectiveness will be expressed in terms of incremental cost per QALY. Time horizon The treatment goals for UC patients with an acute exacerbation are • Avoiding surgery • Avoiding prolonged hospitalisation • Reduction in disease activity resulting in remission Therefore, outcomes over a shorter time

	feature, particularly fluctuation and unpredictability of symptoms. Costs will be considered from an NHS and Personal Social Services perspective.	horizon such as 3 months (immediate) and 12 months (short-term) are considered to be significant. The current evidence for infliximab and its competitors in this setting is also restricted for a shorter time horizon. Therefore, a base case analysis of 12 months with a sensitivity analysis of 3 months will be provided. Costs will be considered from an NHS and Personal Social Services perspective.
Special considerations and other issues	Where evidence permits, the appraisal of infliximab for the acute exacerbation of severely active UC should identify patient subgroups for whom the technology is most appropriate. Where evidence permits, the appraisal of infliximab for the acute exacerbation of severely active UC should consider different posology or methods of administration, treatment continuation strategies and lengths of treatment required when patients have responded to infliximab. Guidance will only be issued in accordance with the Summary of Product Characteristics	Depending on the availability of evidence a sub-group analysis for newly diagnosed UC patients contraindicated to immunomodulators will be provided. The submission will focus on a full induction dose of infliximab (weeks 0, 2 & 6) followed by 'bridge' to immunomodulator therapy.

Section B

3 Executive summary

Ulcerative colitis (UC) is estimated to affect up to 90,000 people in the UK, with an annual incidence of 5,000 – 10,000 new cases per year (Calculation based on BSG Guidelines). It is a lifelong condition characterised by diffuse inflammation primarily involving the colon mucosa (BSG Guidelines). The primary symptoms of UC are bloody diarrhoea and abdominal pain and other symptoms include anaemia, weight loss, rectal bleeding and skin lesions. Patients with UC often have recurrent exacerbations of the disease resulting in hospitalisation and an increased risk of surgery. It is estimated that 20% of all UC patients will have such acute attacks at any given time (Jarnerot, 1985).

For UC patients hospitalised with an acute exacerbation, the goal of treatment is to avoid colectomy and induce remission. Current standard care for these patients comprises the addition of intravenous corticosteroids (for up to 72 hours) to their existing immunomodulator therapy. However, 30-40% of these patients are likely to fail IV steroids and require further medical intervention (Truelove, 1974; Jarnerot, 1985).

The primary treatment options for such moderate/severe UC patients are surgery or ciclosporin (ECCO guidelines, 2007; UK IBD audit 2006). Surgery is associated with important risks in particular patient groups (e.g. women of child-bearing age, young males, and patients with co-morbid conditions), will lead to significant post-surgical complications in a proportion of patients, and may also impact negatively upon quality of life. On account of the various risks and outcomes of surgical intervention, certain patients will be defined unsuitable for surgical intervention, expressed either as a patient preference not to undergo surgery or as a clinical judgement. Ciclosporin, the other treatment alternative not licensed but often used, is also associated with side effects and excess mortality (Sandborn, 1995; Arts, 2005). As a result of the risks and outcomes of existing treatment alternatives and the preference for some patients to avoid surgical intervention, there is a substantial unmet need in this patient population.

The biological therapy, infliximab (Remicade®), is an inhibitor of tumour necrosis factor (TNF), a cytokine that plays a major role in the pathogenesis of UC. Infliximab is the only TNF inhibitor licensed for treatment of UC with its primary competitor being standard care. Infliximab received marketing authorisation in the UK in February 2006 for the treatment of moderately or severely active UC patients who have had an inadequate response to standard care. The current evidence indicates that the clinical response is usually achieved after three doses of infliximab i.e. week 0, 2 and 6 (the induction dose).

The efficacy of infliximab in the treatment of moderate/severe sub-acute UC patients has been demonstrated in two randomised controlled trials, ACT I and ACT II. Randomised studies by Jarnerot et al and Sands et al have also looked at infliximab use as a rescue therapy for UC patients with an acute exacerbation who have failed IV steroids. Both studies demonstrated infliximab to be a safe and efficacious treatment option to avoid surgery in acute UC patients. Several other studies have found infliximab to be an effective treatment in avoiding surgery in an acute inpatient setting (Jakobovits, 2007; Lees, 2007; Kohn, 2007).

Infliximab is available in vials containing 100mg powder to be prepared into a solution for infusion. Each vial costs £419.62. The cost of infliximab treatment for an 80 kg patient is

estimated at £5,223 for the full induction dose (3 infusions) including the cost of administration.

A decision analytic model was constructed to estimate the costs and benefits associated with infliximab, ciclosporin, surgery and standard care. The model structure and design reflects the clinical practice in England and Wales. On account of both the acute nature of UC and the available clinical evidence base, a one year time horizon was modelled in the base case. One way and probabilistic sensitivity analyses were performed to address the uncertainty around important parameters.

Four treatment strategies were compared – induction with infliximab followed by immunomodulator therapy, one week intravenous ciclosporin followed by oral ciclosporin and immunomodulator therapy, surgical intervention, or current standard care comprising intravenous steroid therapy. In the base case results for the 1 year model, the infliximab strategy was associated with expected costs of £19,890 and 0.80 QALYs. Base case results for the comparator treatment strategies were £18,162 and 0.70 QALYs (ciclosporin), £17,067 and 0.58 QALYs (surgery) and £18,550 and 0.68 QALYs (standard care). In the base case, incremental cost effectiveness ratios for infliximab were estimated at £11,589 compared to standard care, £18,425 compared to ciclosporin and £13,407 compared to surgery. Univariate sensitivity analyses demonstrated that the base case ICERs were most sensitive to assumptions regarding patient weight, long term treatment effect and resource utilisation during hospital stay. However, in majority of sensitivity analyses infliximab remained cost-effective at conventional willingness to pay thresholds.

In conclusion, infliximab is a highly effective and well-tolerated therapy for the management of UC patients with an acute exacerbation and provides significant clinical benefit over standard care. Economic analyses demonstrate that the incremental costs associated with achieving these clinical benefits are acceptable, and that infliximab is a cost-effective treatment option compared to the existing treatment alternatives.

4 Context

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Ulcerative Colitis

Ulcerative colitis (UC) is a severe form of inflammatory bowel disease (IBD) characterised by chronic inflammation of the mucosa of the intestine, specifically the large intestine (colon). The symptoms of UC vary according to the extent and severity of the inflammation. The classic symptom of UC is bloody diarrhoea that may be accompanied by abdominal pain. Other symptoms include anaemia, fatigue, weight loss, rectal bleeding, and loss of appetite. The quality of life for UC patients is detrimentally affected by both the symptoms associated with disease and by treatments and related adverse effects (Feagan 2007).

The extent of UC can be classified as either 'distal' or more extensive disease (Carter 2004). 'Distal' disease includes proctitis (rectum), proctosigmoiditis (rectum and sigmoid colon). More extensive disease involves left-sided colitis (up to splenic fixture), extensive colitis (up to hepatic fixture), and pancolitis (entire colon) (Carter 2004, Kornbluth 2004). The severity of disease is often classified using Truelove and Witts criteria (Truelove 1955) (Table 4.1.1). Mildly active UC is defined as less than four bowel movements daily. Moderately active UC is defined as more than four daily bowel movements but without systemic illness. Severe UC is defined as an attack in which the patient has more than six bowel movements daily, and who is systemically ill as shown by tachycardia, fever and anaemia. Fulminant disease is characterised by more than ten bowel movements daily, continuous bleeding, abdominal tenderness and distension, and the need for blood transfusions.

Table 4.1.1 Truelove & Witts Criteria

Activity	Mild	Moderate	Severe
Number of bloody stools	<4	4-6	>6
Temperature (C)	Afebrile	Intermediate	>37.8
Heart rate (beats per min)	Normal	Intermediate	>90
Haemoglobin (g/dl)	>11	10.5-11	<10.5
Erythrocyte sedimentation rate (mm/h)	<20	20-30	>30

Acute Exacerbations of Severe Ulcerative Colitis

Guidelines for the treatment of patients who have failed to respond to maximal oral treatment with a combination of mesalazine and/or corticosteroids and those who present with severe disease defined by the Truelove and Witts' criteria recommend that patients be admitted to hospital for intensive intravenous therapy (Carter 2004). It has been estimated that 15-19% of all UC patients will experience an acute attack sometime during the course of their disease (Kohn 2007).

Jakobovits and Travis (Jakobovits 2006) suggest that failure to respond to intensive treatment can be predicted at presentation (low abumin, high CRP, short duration of illness and prior steroid use) (Lindgren 1998). On day 1 (fever, stool frequency >9, albumin <30g/l and pulse rate >90 beats per minute (Lenard-Jones 1975), and on day 3 of intravenous therapy (stool frequency >8 and CRP >45mg/l) (Travis 1996). Estimates on the proportion of patients with a severe attack that fail to respond to intravenous corticosteroid therapy vary from 30-40% (Truelove 1974, Jarnerot 1985) up to 60% (Jakobovits 2006).

Current Treatment Options

Treatment options for patients refractory to intensive intravenous therapy are typically limited to intravenous ciclosporin or surgical intervention (colectomy) (Regueiro 2006).

Ciclosporin

Ciclosporin may delay or prevent colectomy in some patients but has also been associated with multiple side effects (including hypertension, renal insufficiency, seizures and infection) (Knigge 2005).

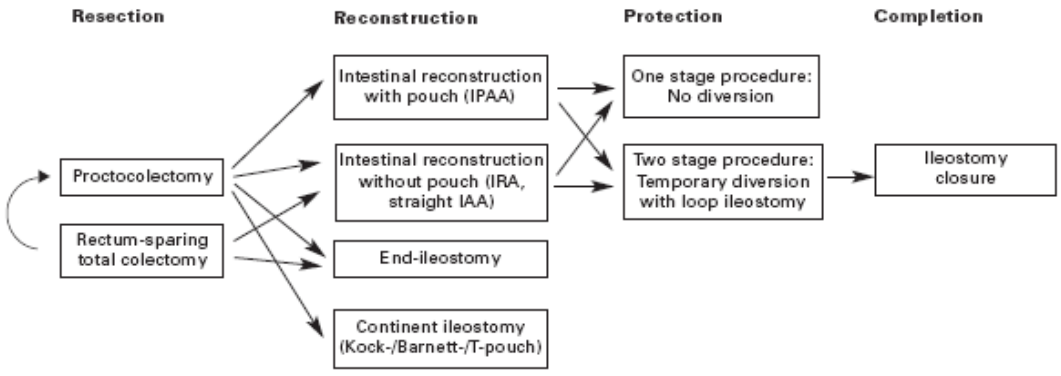
Surgery

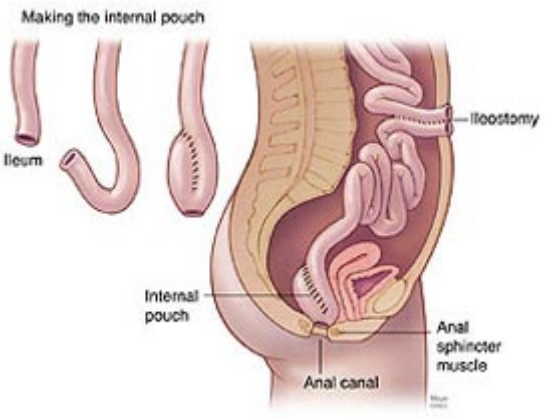
Surgery for UC is indicated as an emergency therapy in the event of life-threatening complications, and more as a therapy in "unacceptable" disease characterized by refractoriness to corticosteroid therapy.

Colectomy (usually proctocolectomy) with ileostomy or an ileoanal pouch anal anastomosis (IPAA) offers a cure for ulcerative colitis but may have significant long term psychological effects as well as an obvious physical impact (CCFA surgery guidelines).

Another reason for surgery is related to presence of epithelial dysplasia in biopsies or proven cancer. Whatever the indication the surgery aims to remove the diseased colon completely and reconstruct the remaining bowel. The set of procedures required to treat UC are given in the following figure.

Figure 4.1.1 Overview of surgical procedures in management of UC





Proctocolectomy is the surgical procedure to remove the colon and rectum. The small intestine is formed into a pouch and attached to the anus to reestablish the continuity of the digestive tract. This new pouch, called the ileoanal pouch, serves as a reservoir for waste. Its emptying is controlled by the anal and rectal muscles.

Since the ileoanal pouch requires more than a month to heal, a temporary ileostomy is formed. The ileostomy is an opening in the abdominal wall, where waste exits the small intestine. The temporary exit is upstream to the newly formed ileoanal pouch. After a couple of months, the patient will return to have the ileostomy reversed.

Proctocolectomy has evolved as the resection of choice in about 90% of patients with ulcerative colitis. This resection eliminates all possibly afffected colon from the caecum to the distal rectum and therefore involves a pelvic dissection down to the anus.

The most significant advance in surgical technique and management of ulcerative colitis involves reconstruction after a resection. In the past, end-ileostomy was the only surgical option for treatment of ulcerative colitis, yet was at the same time often unacceptable for many patients. Nowadays, a spectrum of choices with or without a permanent ileostomy are offered.

4.2 What was the rationale for the development of the new technology?

Infliximab is an established technology whose efficacy and safety in other indications have already been evaluated in NICE and SMC technology appraisals. Infliximab was developed to address clinical findings about the immunopathogenesis of several diseases including ulcerative colitis, where which the inflammatory cytokine TNF-α is thought to play a crucial role. For a recent review of this research in ulcerative colitis see Sands et al 2007 (*Clin Pharmacol*).

Infliximab belongs to a novel class of parenteral therapies which target T-cell functions and/or molecular signaling pathways to mediate particular inflammation symptoms. Broadly these therapies are called biologics. In the UK infliximab is the only licensed biologic treatment for ulcerative colitis.

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

Infliximab (Remicade) is a chimeric human-murine monoclonal antibody, which binds to both soluble and transmembrane forms of the human tumour necrosis factor (TNF)α and inhibits the functional activity of TNFα. TNFα is a cytokine involved in the inflammatory response characteristics of UC. Infliximab is administered as an intravenous infusion with 5 mg/kg given over a 2 hour period followed by additional 5 mg/kg infusion at 2 and 6 weeks, and every 8 weeks thereafter (Remicade® SPC).

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

In the UK, infliximab is indicated for the treatment of moderately to severely active UC in patients who have had an inadequate response to conventional therapy including corticosteroids, 6-mercaptopurine, andazathioprine or who are intolerant or have medical contraindications for such therapies. Infliximab is contraindicated in patients with tuberculosis or other severe infections such as sepsis, abscesses, or opportunistic infections, in patients with moderate or severe heart failure, or with a history of hypersensitivity to infliximab or to other murine proteins (Remicade® SPC).

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

In current clinical practice, infliximab is most commonly given as “rescue” therapy to patients presenting with an acute, severe UC flare which is refractory to other treatments and for which urgent surgery may be needed. Current practice is to give a single or induction dose of infliximab to such patients, typically involving 1 infusion or the infliximab induction regimen.

Ciclosporin

Ciclosporin is also commonly often used in "rescue" therapy. According to expert opinion, the use of ciclosporin in clinical practice is sporadic and declining, with only a few centres regularly using the drug in UC. This low level of use in the NHS is thought to be due to three factors:

1. the lack of a license for ciclosporin in UC
2. the lack of compelling efficacy data; a recent Cochrane Review of all available ciclosporin RCTs (Shibolet 2005) found only limited evidence that ciclosporin is more effective than standard treatment.
3. difficulties with its use, especially around toxicity and side-effect profile

However, since ciclosporin is the only alternative available for acute, steroid-refractory UC, we have treated it as an active comparator in this submission’s clinical report and in our cost effectiveness evaluation.

4.6 Provide details of any relevant guidelines or protocols.

The British Society of Gastroenterology has published Guidelines for the management of IBD including Crohn’s disease and UC. Infliximab is recommended as a treatment option for Crohn’s disease in these guidelines, but it is not mentioned as a UC therapy because at the time of the guideline’s publication the product was not licensed for the treatment of UC. NICE has also produced guidelines for the use of infliximab in the management of Crohn’s disease (www.nice.org.uk Guideline 40).

5 Clinical evidence

5.1 Identification of studies

Scope

Consistent with the 2007 re-definition of the infliximab UC Single Technology Appraisal into two separate appraisals, we developed a systematic review and analysis specifically to address the use of infliximab and comparator medicines in hospitalised patients with severe UC refractory, intolerant, or contraindicated to conventional treatment as presented in the scope for the ongoing NICE appraisal.

The scope for this work follows the decision problem set out at the beginning of this submission and can be summarised as follows:

Table 5.1.1 Scope of systematic review and analysis

Population(s)	Adult patients diagnosed with acute exacerbations of severe ulcerative colitis, with either • Inadequate response to conventional therapy (corticosteroids, 6-mercaptopurine, azathioprine) or • Intolerance to or medical contraindications to such therapies, and • Are hospitalised for treatment
Intervention(s)	Infliximab
Comparator(s)	• Standard clinical management (including surgical intervention) • Ciclosporin • Placebo (or steroids)
Outcomes of interest	• Survival • Rates of surgical intervention • Measures of disease activity • Rates of and duration of response, relapse and remission • Adverse effects of treatment • Health-related quality of life

Searches

Systematic searches were undertaken in order to identify systematic reviews, reports of RCTs, and relevant observational studies. Each study was reviewed for eligibility based on specified inclusion criteria developed from the study objective. Separate searches were performed to identify infliximab and ciclosporin studies. The full search terms and details allowing replication of our evidence review can be found in Appendix 9.2.

5.2 Study selection

5.2.1 Complete list of RCTs

Systematic reviews

Three systematic reviews of infliximab for UC were identified (Lawson 2006, Gisbert 2007, Rahimi 2007). Lawson et al and Rahimi et al included only RCTs (Lawson 2006, Rahimi 2007). Gisbert et al (2007) included all studies evaluating the efficacy of infliximab in ulcerative colitis. Although the reviews included patients with mild, moderate, as well as severe disease, they were an important source of potential references. All included and excluded references were checked for relevant information on infliximab for acute severe disease. Details of all three reviews are presented in Appendix 9.7. A fourth review (Rossetti 2004) reported a limited search of a single database without further evidence of a systematic approach or efforts to minimise bias; its references were checked for additional information but this review is not discussed further in this submission.

Our literature search for relevant ciclosporin trials identified a recent Cochrane review (Shibolet 2005). This review presented results from two RCTs (Lichtiger 1994, D'Haens 2001) which met the selection criteria. The selection criteria in Shibolet's (2005) Cochrane review closely match those set out in our search of ciclosporin trials. Our search strategy (Appendix 9.2) failed to reveal any new evidence which had not already been identified and considered in the Cochrane review. Consequently, we selected the ciclosporin RCTs by Lichtiger (1994) and D'Haens (2001) for inclusion in our analysis.

RCTs

Seven RCTs of infliximab for ulcerative colitis were retrieved and reported by all three systematic reviews (Armuzzi 2004 [*Eur Rev Med Pharmacol & Gastroenterology*]), Jarnerot 2005, Ochsenkuhn 2004, Probert 2003, Rutgeerts 2005 [NEJM & Gastroenterology], Sands 2001). Five RCTs were excluded due to inappropriate patient populations. One trial included only steroid-dependent patients (Armuzzi 2004 [*Eur Rev Med Pharmacol*]), one trial included only steroid-naïve patients (Ochsenkuhn 2004), and three studies included patients with predominantly moderate disease or patients who did not require hospitalisation and/or colectomy (Probert 2003, Rutgeerts 2005 [NEJM & Gastroenterology]). The two included RCTs (Jarnerot 2005, Sands 2001) are summarised in the sections following.

As discussed in the previous section, the two ciclosporin RCTs (Lichtiger 1994, D'Haens 2001) identified in the 2005 Cochrane review (Shibolet 2005) were used in this submission. The Cochrane review identified but excluded five other ciclosporin RCTs because of: inappropriate patient populations (Kornbluth 1994, Sandborn 1994); lack of placebo/steroid arm, incomplete write-up and no randomisation (Svanoni 1998); inappropriate ciclosporin dosing and lack of placebo/steroid arm (Van Assche 2002, Van Assche 2003).

5.2.2 Inclusion and exclusion criteria

A detailed breakdown of the inclusion and exclusion criteria is provided in Appendix 9.2 along with a description of our search strategy and terms.

5.2.3 List of relevant RCTs

Infliximab

Both included infliximab RCTs were double-blind, parallel group trials of infliximab compared with placebo for the treatment of severe UC unresponsive to steroids. Both studies reported problems with the slow recruitment of patients leading to earlier than planned analysis or termination of recruitment. Patient numbers were small with a total of 56 patients randomised across both studies; 33 patients were treated with infliximab and 24 patients were treated with placebo. A brief summary of infliximab trials is given in Table 5.2.3.1 together with each RCT's quality score (Oxford score) which is discussed in further detail in section 5.3.6.

Ciclosporin

The two included ciclosporin RCTs, selected in the 2005 Cochrane review (Shibolet 2005), are summarised in Table 5.2.3.1.

Table 5.2.3.1 Summary of included RCTs

Design	Population	Comparator	Intervention	Endpoints & Notes
Jarnerot et al 2005				
Randomised, double blind, parallel groups AC: adequate Oxford score R 1/2 DB 1/2 WD 1/1 Total 3/5	Acute severe/ moderately severe UC unresponsive to IV corticosteroids for at least 4 days N=45	Placebo plus IIVT therapy N=21	Infliximab 4mg/kg or 5mg/kg plus IIVT therapy N=24	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				
Randomised, double blind, parallel groups AC: unclear Oxford score R 1/2 DB 2/2 WD 1 Total 4/5	Acute severe UC unresponsive to 7 days of corticosteroid therapy (of which 5+ days used intravenous admin) N=11	Placebo N=3	Infliximab 5mg/kg N=3 Infliximab 10mg/kg N=3 Infliximib 20mg/kg N=2	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 Enrollment terminated early due to slow accrual
Lichtiger 1994				
Randomised, double blind, placebo controlled Single centre prospective study AC: adequate Oxford score R 1/2 DB 1/2 WD 1/1 Total 3/5	Acute severe UC refractory to IV corticosteroids after 7 or more days	Placebo N=9	Ciclosporin N=11	Primary Clinical activity score Response (clinical activity score of <10 on two consecutive days) within 14 days of starting treatment. Secondary Not defined
D'Haens et al 2001				
Randomised, double blind Single-centre prospective study AC: adequate Oxford score R 2/2 DB 1/2 WD 1/1 Total 4/5	Patients hospitalised with severe attack of UC (clin. activity score ≥ 10)	Methylprednisolone N=15	Ciclosporin 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 day 8 of at least 3 points and the possibility of hospital discharge to the patients

Oxford quality score elements: R (randomisation) DB (double blinding) WD (withdrawals and dropouts)

5.2.4 List of relevant non-randomised controlled trials

There were no relevant non-randomised controlled trials identified. The only other relevant evidence source was observational trials, which are summarised in section 5.8.

5.2.5 Ongoing studies

'ulcerative colitis' for relevant on-going or planned studies (Feb 2008). Five studies of infliximab in ulcerative colitis were found to be either active but not yet recruiting or recruiting (NCT00336492; NCT00537316; NCT00586807; NCT00207688; NCT00542152).

Only one study was relevant to this review (NCT00542152); a phase IV, multicentre, randomised, open label study of infliximab compared with ciclosporin in steroid-refractory severe attacks of ulcerative colitis in adults (sponsored by Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives). Disease severity is defined as a severe acute flare of UC with a Lichtiger Index score > 10. Enrolled patients are to receive either infliximab 5mg/kg at weeks 0, 2, and 6 or ciclosporin 2mg/kg/day IV for 7 days followed by Neoral 4mg/kg/day orally for 3 months. This study is currently recruiting patients (target n=100).

The license holder, Centocor, was contacted by Schering-Plough with a request to search the company databases for any relevant ongoing trials. No trials were identified beyond those already revealed by our search of www.clinicaltrials.gov.

5.3 Summary of methodology of relevant RCTs

We have presented detailed tabular summaries of the methodology, design and results of the two relevant infliximab RCTs and two relevant ciclosporin RCTs in Appendix 9.8. The following sections give brief narrative descriptions only of each relevant RCT.

5.3.1 Methods

Infliximab: Jarnerot et al 2005

Jarnerot et al (2005 [*Gastroenterology & Evidence-Based Gastroenterology*]) conducted a randomised, parallel group, double blind, placebo controlled trial in patients from 10 centres in Sweden and Denmark.

Two treatment groups were included; 24 patients were randomised to additional treatment with a single dose of infliximab (5 mg/kg or a dose close to 5 mg/kg) plus IIVT therapy and 21 patients were randomised to placebo plus IIVT therapy.

Patients showing a response were switched to oral prednisone 40mg/day and tapered by 5 mg/day each week.

Infliximab: Sands et al 2001

Sands et al conducted a randomised, double-blind, parallel group trial of infliximab or placebo in 6 centers (5 in the US and 1 in Belguim).

Patients were randomly assigned to receive a single intravenous infusion of placebo or infliximab 5, 10, or 20mg/kg.

Ciclosporin: Lichtiger 1994

This was a randomised, double-blind, placebo-controlled prospective study which was followed by an open-label period.

Patients assigned to receive ciclosporin were given a dose of 4 mg/kg per day by continuous infusion for up to 14 days. The patients assigned to placebo received an identical-appearing intravenous solution of cremaphor and alcohol.

Ciclosporin: D'Haens 2001

This was a randomised double-blind, single-centre prospective study.

Patients assigned to receive ciclosporin were given a continuous infusion of 4 mg/kg body wt per day for 8 days. Patients assigned to receive glucocorticosteroids were given 40 mg methylprednisolone per day.

5.3.2 Participants

Infliximab: Jarnerot et al 2005

45 patients with acute severe or moderately severe UC unresponsive to intensive intravenous corticosteroids (IIVT [betamethasone 4 mg twice daily]) were recruited. All patients presented with a severe flare, and were at risk for urgent colectomy. Eligible patients had UC established by clinical history, endoscopy, and exclusion of infectious cause.

Infliximab: Sands et al 2001

The 11 recruited patients had active UC of at least 2 weeks duration diagnosed by clinical history, endoscopy, and histology. Disease severity was established using modified Truelove and Witts score, all patients had to have a score >10. Patients were excluded if their disease was so severe that endoscopy was contraindicated, or if they had toxic megacolon, perforation of the colon, or disease that did not extend beyond the rectum.

All patients had received at least 7 days of unsuccessful corticosteroid therapy (>40 to <60mg/day prednisone equivalent), of which at least 5 days included intravenous administration.

Ciclosporin: Lichtiger 1994

All 20 patients included had a disease activity index of 10 or higher and had demonstrated no response to intravenous corticosteroid therapy, equivalent to a daily dose of 300mg hydrocortisone. Patients were excluded if they had bacterial or parasitic pathogens in stools, a positive test for Clostridium difficile toxin, septicemia, perforation of the bowel, megacolon, active fungal or viral infection, uncontrolled hypertension, or elevated levels of hepatic enzymes, creatinine, or cholesterol. Patients were also excluded if they had received mercatopurine, azathioprine or any investigational drug within the previous two weeks.

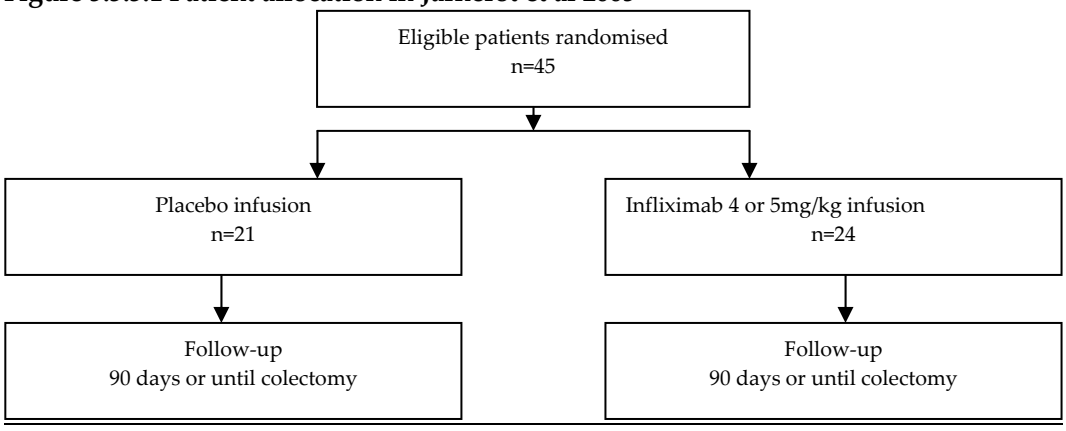
Ciclosporin: D'Haens 2001

All 30 patients were admitted to hospital with a severe attack of UC having a clinical disease activity score of 10 or more. Similar to Lichtiger, patients were exclueded if they had parasites or Clostridium difficile, enteropathogens, uncontrolled hypertension or elevated hepatic enzymes, creatinine, or cholesterol. Patients were also excluded if they had received azathioprine for less than 3 months or if the dose had been changed in the 4 weeks prior to admission, or if they had exhibited recent response on glucocorticoids.

5.3.3 Patient Numbers

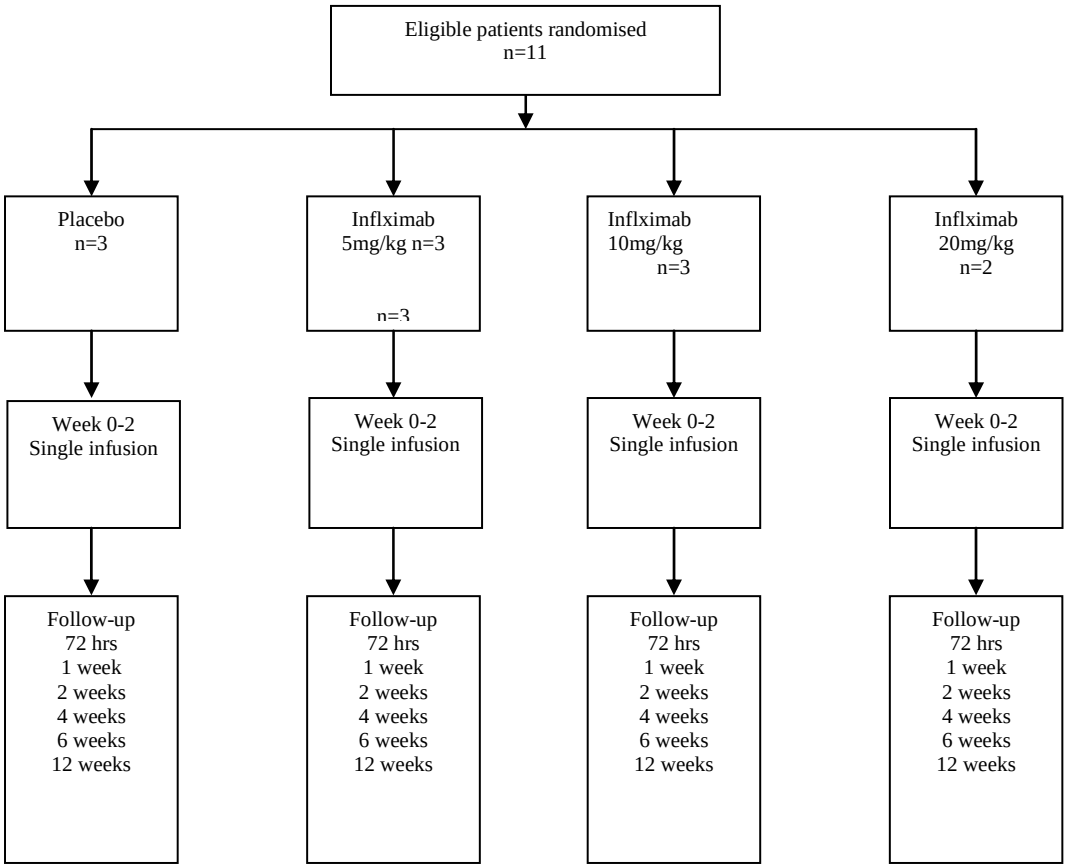
Infliximab: Jarnerot et al 2005

Figure 5.3.3.1 Patient allocation in Jarnerot et al 2005



Infliximab: Sands et al 2001

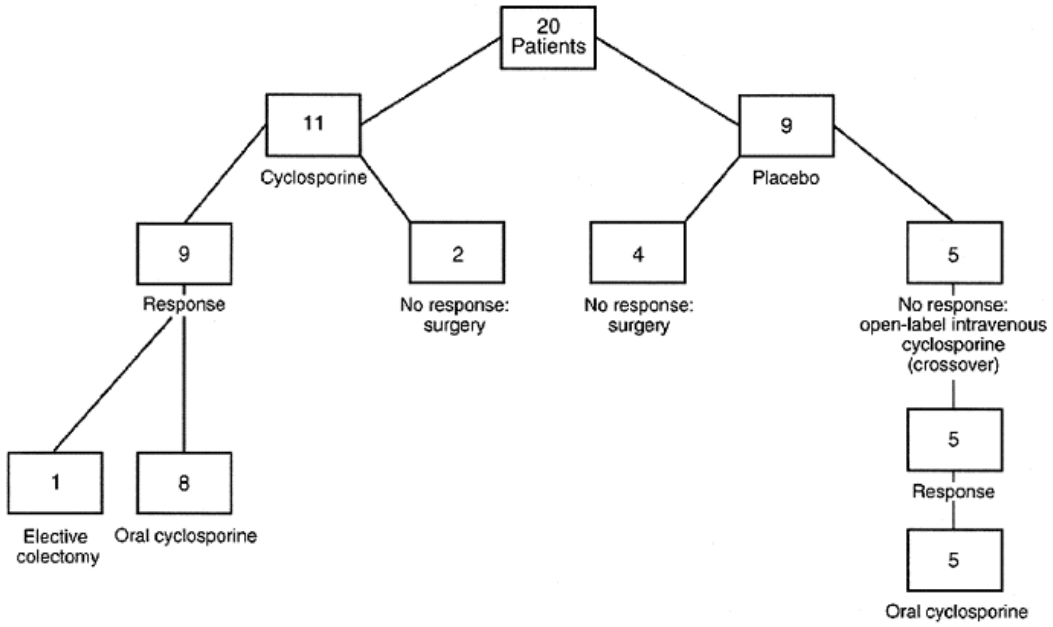
Figure 5.3.3.2 Patient allocation in Sands et al 2001



Ciclosporin: Lichtiger 1994

All patients were treated according to the protocol. One patient in the ciclosporin group who had a response to therapy elected to undergo colectomy. All remaining patients with an initial response to ciclosporin were treated with oral ciclosporin and discharged from the hospital 48 hours later.

Figure 5.3.3.3 Patient allocation in Lichtiger 1994



Ciclosporin: D'Haens 2001

Overall 30 sequential patients presenting at emergency at outpatient clinics were recruited. 15 patients were each randomised to either ciclosporin or methylprednisolone. One patient in the ciclosporin group was found to have C. difficile toxins in faeces and was withdrawn on day 2. A graphic showing patient disposition was not supplied in the write-up of this study.

5.3.4 Outcomes

Infliximab: Jarnerot et al 2005

The primary endpoint was colectomy or death within 3 months after randomisation.

Secondary endpoints included clinical remission (defined as Seo Index <150) and endoscopic remission at 1 and 3 months after the infusions.

Infliximab: Sands et al 2001

The primary endpoint was treatment failure at 2 weeks after infusion (defined as failing to achieve a clinical response as defined by a modified Truelove and Witts score of <10 and a 5-point reduction from baseline, a dosage of >60mg/day corticosteroids or Ciclosporin A or other immunomodulators due to worsening condition, a nonelective or elective colectomy, or if the patient died as a result of UC).

Secondary endpoints included a comparison of the individual components of treatment failure, change from baseline for the modified Truelove and Witts score, physician's and

patient's global response evaluation, ESR, CRP levels, sigmoidoscopic ratings, and histological disease activity scores.

Ciclosporin: Lichtiger 1994

The primary endpoint was defined as the clinical-activity score post treatment. A score of less than 10 on two consecutive days was considered to indicate a positive response to therapy. The score on the second of these two days was considered the final score. Patients whose clinical-activity scores did not fall below 10 for 2 consecutive days after 14 days of treatment or whose condition worsened were considered to have no response to treatment.

Secondary endpoints were not defined.

Ciclosporin: D'Haens 2001

The primary endpoint was defined as the level of improvement in clinical-activity score. Clinical 'response' was also assessed. This was defined as a score of <10 on days 7 and 8 with a drop in the score from day 1 to day 8 of at least 3 points and the possibility to discharge the patient.

Secondary endpoints were endoscopic and histologic response, urinary clearance, HMPAO white blood cell clearance.

5.3.5 Statistical analysis and definition of study groups

Infliximab: Jarnerot et al 2005

Forty-five patients were randomised: 24 to infliximab and 21 to placebo. Analyses were conducted on an intention-to-treat basis and included all 45 patients.

On the basis of published results, it was assumed that 35% in the infliximab group and 60% in the placebo group would have a colectomy. Seventy patients in each group would provide a statistical power of 80% and a significance level at 5%. It was planned that interim analysis would be performed and that the future of the study would be decided after 70 patients had been treated. The inclusion time was calculated as 1.5–2 years.

Categorical data were analyzed with the Fisher exact test (2-sided). The log-rank test, paired t test (2 sided), and logistic regression analysis were also used as appropriate.
Because this was an interim analysis, to reduce the risk of false- positive findings and to keep the overall significance level at 5%, a statistically significant P value should be <.029 instead of .05.

Infliximab: Sands et al 2001

Enrollment was terminated prematurely; 3 patients were randomised to placebo, 3 patients to infliximab 5mg/kg, 3 patients to 10mg/kg, and 2 patients to 20mg/kg

The study was designed to recruit 60 patients; however, enrolment was terminated prematurely because of slow accrual (11 patients were recruited in total)

Formal statistical analysis of results was not performed because of the small number of patients participating in the study

Ciclosporin: Lichtiger 1994

Two groups were defined – ciclosporin (n=11) and placebo (n=9).

The trial was terminated after 20 patients had been studied, when the physician who was aware of their treatment assignments noted a significant difference between the two groups, confirmed by the study monitor and two independent reviewers. No power calculations were reported.

Quantitative variables were compared with two-tailed Student's t-tests. Qualitative variables and differences between centers were compared with chi-square analysis with Yates' correction. All patients were assessed on an intention-to-treat basis.

Ciclosporin: D'Haens 2001

Sample size estimates showed that, with a sample size of 35 patients in each group, a 30% difference in the proportion of clinical responders could be demonstrated with 80% power (alpha 0.05), based on the assumption that 82% of patients would respond to 4 mg/kg and 50% to 2 mg/kg IV ciclosporin.

All patients were analyzed on an intention-to-treat basis. For quantitative data, statistical analysis was performed using 1-way analysis of variance for multiple comparisons, followed by a 2-tailed, paired t test for parametric, or Wilcoxon Rank sum test for nonparametric observations. Statistical signifi- cance was accepted at a P value 0.05. Mulivariate analysis with stepwise logistic regression was performed to test for parameters influencing clinical response.

5.3.6. Critical Appraisal of relevant RCTs

The methodological quality of included RCTs was assessed using the Oxford score (Jadad 1996). Results of this grading are shown in table 5.2.3.1 and described in more detail this section. The Oxford score (range 0-5) was calculated using the following items:

- Was the study described as randomised (e.g., randomly, random, and randomisation)? *0/1 point*
- Was the method used to generate the sequence of randomization described and appropriate (e.g., table of random numbers, computer-generated, etc)? *0/1point*
- Was the study described as double blind? *0/1 point*
- Was the method of double blinding described and appropriate (e.g., identical placebo, active placebo, dummy, etc)? *0/1 point*
- Was there a description of withdrawals and dropouts? *0/1 point*

One point was deducted if the method used to generate the sequence of randomisation was described but inappropriate (e.g. patients allocated alternately, or according to date of birth, hospital number). One point was also deducted if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).

Additionally, allocation concealment was assessed according to criteria described in the Cochrane Handbook (Higgins 2006). Concealment was reported as adequate if the participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:

- Centralised (e.g. allocation by a central office unaware of subject characteristics) or pharmacy-controlled randomisation
- Pre-numbered or coded identical containers which are administered serially to participants

- On-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered
- Sequentially numbered, sealed, opaque envelopes
- Other approaches achieving concealment along with reassurance that the person who generated the allocation scheme did not administer it.

Concealment was reported as inadequate if participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:

- Alternation
- Use of case record numbers, dates of birth or day of the week
- Any procedure that is entirely transparent before allocation (e.g., an open list of random numbers)

Allocation concealment was judged as unclear if the method of concealment was not described or lacked sufficient detail.

Infliximab: Jarnerot 2005

The study was of acceptable quality and scored 3/5 on the Oxford quality scale. Two points were withheld as there was insufficient information on how the random sequence had been generated or how double-blinding was achieved. Allocation concealment was regarded as adequate. Also of note was that interim analyses were performed earlier than planned in the protocol due to slow recruitment. For this reason and to reduce the risk of false-positive findings, a statistically significant P value was assumed when <0.29 instead of 0.05. The study is still likely to be underpowered. Despite randomisation, a skewed distribution was observed with more male patients and more patients with a first attack of UC were randomised to the placebo group.

Infliximab: Sands 2001

The study was of acceptable quality and scored 4/5 on the Oxford quality scale. One point was withheld, as there was insufficient information on how the random allocation sequence had been generated. A maximum two points were scored for double blinding as the use of an identical placebo was noted. Allocation concealment was regarded as unclear. Also of note is that recruitment was terminated early due to slow accrual. For this reason the authors did not undertake a formal statistical analyses of the results and the study is likely to be underpowered.

Ciclosporin: Lichtiger 1994 & D'Haens 2001

These two RCTs have previously been evaluated for quality in the Cochrane review (Shibolet 2005) which indicated that both trials had adequate concealment. The review did note that the two trials have divergent comparators: while Lichtiger 1994 was a placebo-controlled trial, D'Haens 2001 randomised patients to either steroids or ciclosporin. On the Oxford scale, Lichtiger 1994 was awarded 3/5 because no details are provided on the methods of randomisation, and because investigators were not blinded. D'Haens 2001 scored 4/5 on the Oxford scale, because investigator blinding was not maintained beyond 8 days, and was of acceptable quality.

Further details of the study designs and results of the ciclosporin trials can be found in Appendix 9.8.

5.4 Results of the relevant comparative RCTs

Detailed results for the relevant RCTs of infliximab and ciclosporin are presented in tabular format in Appendix 9.8. Table 5.4.1 summarises the outcome which is essential to the decision problem and which forms the primary basis of decision modelling in our economic evaluation, namely colectomy. This outcome was captured in all relevant RCTs. Following the colectomy table, narrative summaries are provided of all key findings from the included RCTs.

Table 5.4.1 Colectomy outcomes summary from included trials

Study	Placebo or Steroids	Infliximab	Ciclosporin
Colectomy at 3 months			
Järnerot 2005	14/21 (67%)	7/24 (29%)	-
Sands 2001	3/3 (100%)	0/3 (0%)	-
Lichtiger 1994	4/9 (44%)	-	3/11 (27%)
D'Haens 2001	3/15 (20%)	-	3/14 (21%)
Colectomy at 12 months			
Järnerot 2005	15/21 (71%)	10/24 (42%)	-
D'Haens 2001	6/15 (40%)	-	6/14 (36%)

Jarnerot et al 2005: results

There was a statistically significant reduction in the primary outcome of colectomy rates in favour of infliximab OR 4.9 (1.4 to 17). Median time to colectomy after infusion was 8 days (range, 2 – 22 days) in the infliximab group and 4 days (range, 1 – 13 days) in the placebo group. Despite the skewed distribution, multivariate logistic regression analyses still showed results in favour of infliximab for both earlier known UC or first attack OR 3.6 (95% CI 1.0 to 1.37) and sex OR 5.7 (95% CI 1.4 to 2.2).

The efficacy findings for the secondary outcomes did not show statistically significant benefit of infliximab over placebo for either clinical remission or endoscopic remission. The clinical course (0 to 3 months) according to the SEO index is described as being similar in both groups (and is presented together in the paper).

Sands et al 2001: results

Fifty percent of patients treated with infliximab were considered a treatment success at two weeks; two patients treated with infliximab 5mg/kg, one patient treated with infliximab 10mg, and one patient treated with infliximab 20mg/kg. Of the patients treated with infliximab who did not respond two patients did not meet modified Truelove and Witts criteria for response (one patient treated with 10mg/kg and the other 20mg/kg), one patient received an increased corticosteroid dose and subsequent Ciclosporin (5mg/kg), and one patient underwent elective colectomy (treated with 10mg/kg). There were no responders amongst patients treated with placebo and all three underwent colectomy by two weeks (one elective and two non-elective).

Ciclosporin: Lichtiger 1994

A total of 9 of 11 (82 percent) in the intravenous ciclosporin group had a response to therapy compared with 0/9 patients in the placebo group (P<0.001). The mean time to a response (second consecutive day on which the clinical-activity score was less than 10) was 7 days (range, 3 to 14). Mean clinical-activity score in the ciclosporin group fell from 13 (range, 10 to

16) to 6 (range, 2 to 8), and the mean score in the placebo group fell from 14 (range, 12 to 17) to 13 (range, 11 to 18). 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. All 14 patients with a response, except the 1 who chose to undergo colectomy, were treated with oral ciclosporin and discharged from the hospital 48 hours later.

Ciclosporin: D'Haens 2001

Nine of 14 patients (64%) had a response to ciclosporin therapy compared with 8 of 15 (53%) to methylprednisolone (P = 0.4). The mean dose of ciclosporin administered IV over the 8 days was 2.7 + 0.6 (range, 1.8 –3.5) mg/kg body wt per day, which corresponded to 196.7 + 18.1 (range, 91–263) mg/day; ciclosporin blood levels during IV treatment averaged 376 + 22 (range, 212– 488) ng/mL; concentrations in responders were not significantly different from those in nonresponders (means, 361 + 34 [212– 488] ng/mL vs. 385 + 30 [311– 482] ng/mL) (P = 0.6).

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, 3–14) vs. 6.1 (range, 4 –9) in the responders.

The mean time to response was 5.2 + 0.9 days (range, 2– 8) in the ciclosporin group vs. 4.3 + 0.7 days range, 2– 8) in the methylprednisolone group (P = 0.2).

After day 8, blinding ended and interpretation of response and/or failure may have been subject to investigator bias.

5.5 Meta-analysis

A meta-analysis was not appropriate given the lack of trials with similar designs. We have presented, however, an indirect comparison analysis which seeks to assess the relative efficacy of infliximab and ciclosporin in preventing colectomy.

5.6 Indirect/mixed treatment comparisons

Overview

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 which could be used in an economic evaluation comparing infliximab to ciclosporin. The common comparator for all trials was placebo or steroids. These two kinds of comparators were treated as equivalent since patients in trials which used a placebo arm had already been extensively exposed to I.V. steroids.

The model used Markov Chain Monte Carlo Methods (MCMC) and is described in detail in Appendix 9.6. We have presented the main results of the analysis in this section.

Main Results

The modelled log-Odds ratios of colectomy for infliximab and ciclosporin compared to placebo are shown in Table 5.6.1. Confidence intervals are wide for the 3-12 month time period as there were relatively few data points to inform the analysis here with a total n. at risk of only 7 in the Järnerot 2005 placebo arm.

Table 5.6.1 Log-Odds Ratios of Colectomy compared to Placebo

Treatment	Timepoint	Mean	SD	2.5% CI	97.5% CI
Infliximab	0-3 Months	-2.07	0.66	-3.40	-0.82
Infliximab	3-12 Months	0.65	1.55	-2.03	4.01
Ciclosporin	0-3 Months	-0.33	0.69	-1.70	1.01
Ciclosporin	3-12 Months	0.12	1.02	-1.92	2.16

The predicted probabilities which subsequently were used in economic modelling are shown in Table 5.6.2. The placebo arm of the Järnerot 2005 study was used to provide the baseline log-odds as this study included infliximab and reported colectomy outcomes at 3 and 12 months. Using this study for the baseline allowed us to develop predicted probabilities which could be validated against figures from the Järnerot 2005 publication.

Table 5.6.2 Predicted Probabilities of Colectomy

Treatment	Timepoint	Mean	SD	2.5% CI	97.5% CI
Placebo	0-3 Months	0.67	0.10	0.46	0.85
Placebo	3-12 Months	0.14	0.12	0.00	0.47
Infliximab	0-3 Months	0.23	0.13	0.05	0.56
Infliximab	3-12 Months	0.27	0.27	0.00	0.92
Ciclosporin	0-3 Months	0.58	0.18	0.22	0.88
Ciclosporin	3-12 Months	0.18	0.19	0.00	0.70

Key issues

The indirect comparison analysis is subject to uncertainty not only owing to its small sample sizes at some timepoints which affected the observed confidence intervals, but also due to methodological differences between the trials. While all of the included RCTs examined colectomy outcomes following a short, "rescue" therapy regimen, these trials varied in their choice of comparator. Lichtiger 1994, Jarnerot 2005, and Sands 2001 used placebo comarators whereas D'Haens used a steroid comparator. This difference is arguably of less importance to the decision problem since our main economic analysis seeks to model outcomes in patients for whom I.V. steroids are already in their treatment 'background'. Thus, patients in the placebo arms of Lichtiger 1994, Jarnerot 2005, and Sands 2001, who have already been exposed to I.V. steroids, might be considered sufficiently similar to the I.V. steroid group in D'Haens 2001.

5.7 Safety

Safety results from the main included RCTs are included below. See Appendix 9.8 for a tabular summary of the design, results and safety findings from the included RCTs. We have also provided in Appendix 9.10 a summary of the adverse events observed in the longer-term infliximab maintenance trials in UC, ACT I/II as well as long-term safety observations from infliximab's other indications. However, results from these trials may have limited relevance to the patient group in the decision problem, as the current submission is appraising efficacy and safety associated with brief 'rescue' interventions as opposed to drug maintenance.

Infliximab: Jarnerot et al 2005

No deaths were reported and the frequency of adverse events appeared to be comparable between the infliximab and placebo groups; 9 patients treated with infliximab reported general side effects and 4 patients reported adverse postoperative events whereas 8 patients treated with placebo reported 8 general side effects and 5 patients reported adverse postoperative events.

Infliximab: Sands et al 2001

No deaths were reported but all patients experienced at least one adverse event during the study. Most were mild to moderate and no patients discontinued the infusion due to adverse events. The events most frequently reported by infliximab patients were pruritus, headache and urinary tract infection (each occurring in two patients). Four patients reported five serious adverse events that required hospitalisation or prolonged the hospital stay, all resolved with appropriate treatment.

Ciclosporin: Lichtiger 1994

No deaths were reported. Four of 11 patients (36%) initially treated with cyclosporine had paresthesias compared with none of the patients in the placebo group. Hypertension, defined as a systolic blood pressure of more than 140 mm Hg or a diastolic blood pressure of more than 90 mm Hg for two consecutive days, was noted in 4/11 (36%) patients in the cyclosporine group, two of whom required treatment. Hypertension developed in one patient in the placebo group (11 percent). One patient in each group reported nausea and vomiting.

None of the patients had nephrotoxicity or hepatotoxicity. One patient treated with cyclosporine had a grand mal seizure after the initiation of therapy but had no more seizures after cyclosporine was discontinued. Headaches occurred as the only side effect in two of the patients who received cyclosporine after receiving placebo.

Ciclosporin: D'Haens 2001

No deaths were reported in the study. No patients discontinued due to adverse events and no dose reductions due to adverse events were necessary. Seizures did not occur, decreases in serum magnesium levels were observed in 2 and in serum potassium levels in 4 cyclosporine treated patients. For a detailed breakdown of AEs, see Appendix 9.8.

5.8 Non-RCT evidence

Nine observational studies (non RCTs) were identified in our literature search (Regueiro 2006, Actis 2002, Chey 2001 [*Inflamm Bowel Dis & Am J Gastroenterol*], Daperno 2004, Ferrante 2007, Jakobovits 2007, Kohn 2007, Kohn 2002, Kohn 2004, Lees 2007). One other observational study met the inclusion criteria but did not state whether patients were hospitalised for treatment and was excluded for this reason (Kaser 2001). Six studies recruited only hospitalised patients with acute severe treatment refractory UC (Regueiro 2006, Actis 2002, Chey 2001 [*Am J Gastroenterol*], Kohn 2007, Kohn 2002, Kohn 2004, Lees 2007).

Three studies included a mixed patient population (e.g., patients with mild or moderate disease) but separately reported data for a relevant subgroup (Daperno 2004, Ferrante 2007, Jakobovits 2007). These studies, summarised in Appendix 9.11, provided some limited information about our target population. All three studies were open and uncontrolled; two studies retrospectively identified a relevant cohort of patients using medical archives and case notes and spanning a 6 or 7 year period (Daperno 2004, Jakobovits 2007). The remaining study included the first 100 patients receiving infliximab at a single centre (Ferrante 2007). Two studies included a mixed population that included patients with moderate to severe disease (Ferrante 2007, Jakobovits 2007). Daperno et al included only severely affected patients but included data from first line treatment with corticosteroids as well as second line treatment with ciclosporin, infliximab, or colectomy (Daperno 2004).

Clinical data from these studies were not used to inform any efficacy estimates in our economic modelling. The papers we identified in this section are presented since they give

relevant reinforcement to our general assumption in the economic modelling that rescue therapy with infliximab is a safe and effective treatment.

5.8.1 Summary of methodology of relevant non-RCTs

Full summaries of both the methodology and results of the non-RCT evidence are given in the Appendix. Below we provide brief narrative summaries as well as a tabular overview of methods and common results.

Table 5.8.1.1 Methodology of relevant non-RCTs

Reference	Design	N	Disease measure	Early Colectomy assessment	Late Colectomy assessment	Infliximab dose and schedule
Actis et al 2002	Prospective, open, uncontrolled	8	Disease Activity Index	7 months	NA	Single dose 5mg/kg[1]
Chey et al 2001	Open, uncontrolled	8	Disease Activity Index	5 months	NA	Single dose 5mg/kg
Kohn et al 2002	Prospective, open, uncontrolled	13	Truelove and Witts	25.6 months	NA	Single dose 5mg/kg[1]
Kohn et al 2007	Retrospective + prospective	83	Modified Truelove and Witts	23.4 months	2 months	Single dose 5mg/kg[1]
Lees et al 2007	Retrospective, open, uncontrolled	39	Truelove and Witts	203 days	Admission	Single dose 5mg/kg[1]
Regueiro et al 2006	Retrospective, open, uncontrolled	12	Disease Activity Index	5 months	Admission	Single dose 5mg/kg[1]

Actis et al 2002

Actis et al 2002 conducted an uncontrolled open study of consecutive patients admitted to a referral clinic for severely active UC refractory to sequential medical treatments. Six patients were treated whilst in hospital for persistently active disease after a course of at least 7 days of parenteral steroids at the maximum dose. Two patients were treated in a day hospital unit; one had not responded to a daily oral dose of 50mg prednisone for the previous 15 days (and had required ciclosporin to control a steroid-refractory attack in 1997), the other patient had relapsed following a dose reduction in azathioprine treatment (100mg to 50mg/day). The patients in the study scored at least 10 prior to treatment on the Clinical Activity Index. Initial response to infliximab was expected to manifest as a decrease in stooling and faecal blood, yielding a 50% reduction or more in the Clinical Activity Index. Maintenance of response was also assessed.

Chey et al 2001

Chey et al 2001 report the results of treated in an uncontrolled open study of patients initially admitted for colectomy. Patients were considered to have failed maximal medical therapy; all had tried 5-aminosalicylates, intravenous corticosteroids, and most had also been treated with 6-mercaptopurine. All patients scored at least 15 on the Lichtinger disease activity score prior to treatment. Infliximab was administered as single intravenous infusion. Responses were determined by three parameters; clinical/subjective improvement, appearance on repeat endoscopy, and histological grade scoring of endoscopic biopsies. Scoring was done using a simple rating scale bya pathologist blind to the details of ulcerative colitis treatment. Repeat colonoscopy or flexible sigmoidoscopy was performed approximately 1 week after infusion whenever possible to assess response visually and histologically.

Kohn et al 2002 and follow-up

Kohn et al 2002 conducted an uncontrolled open study to evaluate the efficacy and safety of infliximab in the treatment of severe ulcerative colitis refractory to conventional therapy (methyl-prednisolone 60mg daily for 7+ days) The study was conducted at 2 hospitals in Italy between March 2000 to April 2001.
The diagnosis of UC was established by endoscopic and histological criteria. All patients presented endoscopic features of severe disease at basal proctosigmoidoscopy. A single infusion of 5mg/kg, patients were able to received further infusions at the treating clinician's discretion, all concomitant medications were continued if clinically indicated. Clinical response defined as CAI <10 on two consecutive days. Patients whose condition worsened or whose CAI score failed to fall below 10 for 2 consecutive days within 7 days of infliximab treatment were defined as nonresponders and underwent colectomy. 13 patients with severe UC refractory to methyl prednisolone 60mg/day for at least 7 days were included.

Kohn et al 2007

Kohn et al 2007 conducted a retrospective analysis of medical records and prospective data collection from 10 Italian gastroenterology units on patients admitted between May 2000 and January 2006. The aim of the study was to evaluate short- and long-term effectiveness and safety of infliximab in patients with acute severe or moderately severe UC. All patients were candidates for colectomy due to resistance to intensive intravenous glucocoticoid treatment for at least 7 days. Patients were recruited according to severe flare-up as defined by Truelove and Witts and modified by Chapman and all patients had UC diagnosis established by commonly accepted clinical, endoscopic, and histological criteria.

Patients received a single intravenous infusion of infliximab 5mg/kg and were able to receive a further one or two infusions based on individual physician's preferences (and not on clinical response). The primary endpoint was survival free from colectomy or death within 2 months from the first infliximab infusion. Colectomy performed within 2 months from the first infusion of infliximab was defined as early colectomy; any colectomy performed during the follow-up period was considered late colectomy. Secondary endpoints included clinical response and remission at 1 month after first infliximab infusion and during long-term follow-up. A CAI score of <10 on two consecutive days was considered a clinical response; clinical remission was defined as a CAI score of 4 or less. Time to clinical relapse defined as the need for a new steroid course and/or infliximab or surgery.

Lees et al 2007

Lees et al conducted a retrospective study of infliximab as a rescue therapy for hospitalised patients with acute severe UC unresponsive to intravenous corticosteroids. Data were collected retrospectively by case note review on a standardized data collection form between May 2005 and November 2006 at 8 Scottish hospitals. Patients were treated with intravenous infliximab 5mg/kg with the timing of administration at the physician's discretion. Patients were defined as initial responders if they were discharged from hospital without having surgery during the acute admission whereas late non-responders were defined as those having colectomy in the 90 days following infliximab treatment. Successful withdrawal of corticosteroid therapy at day 90 was also assessed.

Regueiro et al 2006

Regueiro et al 2006 conducted a retrospective uncontrolled study using medical archives and inpatient pharmacy database of patients treated between 2000 and 2004 at the University of Pittsburgh and Medical Centre Presbyterian/Montefoire Hospital. Data were extracted from physical, colonoscopy, and pathology reports, operative notes, discharge summary, outpatient clinic notes and inpatient pharmacy records.
Of the 62 patients admitted with severe UC, 12 patients were treated with infliximab after discussion of other medical and surgical options. All subjects had a confirmed diagnosis of UC by clinical, endoscopic, and pathology reports. All patients were refractory to oral and intravenous corticosteroids, had intractable diarrhoea and bleeding despite prednisone treatment for at least 2 week prior to admission. Patients received one dose of infliximab 5mg/kg administered as an intravenous infusion over 2 hours. An induction regimen (2 and 6 weeks) followed by a maintenance regimen (every 8 weeks after induction) was intended for patients who responded (response was defined as avoidance of colectomy by 6 months and cessation of corticosteroids). DAI was measured at baseline and two weeks after infusion and analysed using Wilcoxon signed-rank test.

5.8.2 Critical appraisal of relevant non-RCTs

No quality criteria were applied to included observational studies though potential sources of bias were noted (Higgins 2006). Data was collected using a standardised format summarising methods, participants, statistics, outcomes, efficacy and safety results as presented in Appendix 9.9.

5.8.3 Results of the relevant non- RCTs

We have given a tabular summary below of the common colectomy outcome from the relevant non-RCT studies of infliximab. It should be noted that these colectomy data are not used in the economic model. Rather, they are provided to support our general assumption about the efficacy of infliximab as a 'rescue' therapy to prevent or delay colectomy in acute UC patients.

Table 5.8.3.1 Results of relevant infliximab non-RCTs

Reference	Design	N	Early Colectomy assessment	Late Colectomy assessment	**Early colectomy**	**Late colectomy (cumulative)**
Actis et al 2002	Prospective, open, uncontrolled	8	7 months	NA	4/8 (50%)	5/8 (63%)
Chey et al 2001	Open, uncontrolled	8	5 months	NA	0/8 (0%)	0/8 (0%)
Kohn et al 2002	Prospective, open, uncontrolled	13	25.6 months	NA	2/13[1] (15%)	3/13 (23%)
Kohn et al 2007	Retrospective + prospective	83	23.4 months	2 months	12/83 (15%)	24/83 (30%)
Lees et al 2007	Retrospective, open, uncontrolled	39	203 days	Admission	13/39 (33%)	15/39 (38%)
Regueiro et al 2006	Retrospective, open, uncontrolled	12	5 months	Admission	2/12 (16%)	9/12 (75%)

1 One patient refused surgery and was lost to follow-up

Results: Actis et al 2002

A total 4/8 (50%) did not show an initial response to infliximab and were referred for immediate colectomy. Further, 4/8 (50%) responded with a reduction in CAI score of 50% (2 had universal disease, one had sub-total colitis, and in the other the left colon only was affected). Four patients responding to treatment were followed up for 1 to 7 months. One patient had had one injection, one had three, and the remaining two patients had two injections. The former two patients have maintained clinical remission and are steroid-free. One other patient relapsed needing elective colectomy at week 5 after the first injection. The fourth patient showed a >50% reduction in haemoglobin needing transfusions at day 56 in the absence of clinical haematochezia, an overt clinical relapse was noted at 6 months and the patient received a second injection which was followed by a slow improvement.

Results: Chey et al 2001

There was a statistically significant difference between the disease activity index scores of the 8 patients pre- and post- infliximab infusion ($p<0.01$ paired t test, $p=0.004$ Wilcoxon signed ranks test). At one week post infusion, histological grading scores showed a statistically significant improvement $p=0.0004$ and $p=0.0078$. Assessments were repeated at 4 and 8-16 weeks and also showed statistically significant improvement from baseline (1 patient lost to follow-up)
There was no statistically significant difference between means from week 1, week 4 and 8-16 weeks. No relapses were reported and no patient required colectomy

Results: Kohn et al 2002 and follow up

A total 10/13 (77%) had a clinical response to therapy on 2 consecutive days; 9/13 showed a dramatic clinical improvement after 48-72 hours and 1 patient had a clinical response after 6 days. Mean CAI score in responders fell from 14 (range 11-19) to 5.4 (3-10) after 3 days, to 3.5 (1-6) after 7 days. 2/13 (15%) underwent colectomy within 3 days due to clinical deterioration (another patient with no evidence of clinical response after 7 days refused surgery and was lost to follow-up. One patient relapsed at 5 months, the other 9 maintained clinical remission throughout the follow-up period. At a mean follow-up of 10.1 months all 10 responders were able to discontinue corticosteroid therapy. Seven of 10 continued on azathioprine or 6-MP alone or in combination with sulfasalazine or 5-acetylsalicylate acid. 2 patients discontinued immune modifiers due to intolerance and were kept on sulfasalazine and local treatment with steroids, 1 patient was maintained on sulfasalazine and local treatment with 5-acetylsalicylate acid.

Results: Kohn et al 2007

Overall colectomy rate (early and delayed) was 29%. 70/83 patients had avoided colectomy at 2 months. A total 12/83 patients were operated on in the absence of clinical response (2 patients within 4 days due to clinical deterioration). Median time to operation after infliximab infusion was 27 days; four and seven patients underwent colectomy within 15 and 30 days respectively
61 patients reached clinical remission (CAI <4) at 1 month. 27 patients (39%) relapsed after a median interval of 13.5 months (IQR 5 – 23). Of those who relapsed, 13 patients were treated successfully with oral/parenteral glucocorticoids, two patients received further infliximab infusions, and 12 patients required surgery.

Results: Lees et al 2007

A total 26/39 avoided urgent colectomy at the point of hospital discharge and were discharged as early responders. Further, 13/39 of patients underwent colectomy before hospital discharge (nonresponders) at a median of 5 days after infliximab therapy; there were

more urgent colectomies in patients with a first presentation and in patients treated with infliximab for 5 days or less after admission. At 90 days no additional patients had undergone colectomy; by a median follow-up of 203 days an additional 2 colectomies were reported.

Of 26 responders, 10 responders had more than 1 infliximab infusion; 5 patients had 3 doses (0, 2, 6 weeks), 1 patient went on to an 8 weekly maintenance schedule, and one had a second infusion at 26 weeks. Both of the 2 patients requiring colectomy during median follow-up had received only one dose of infliximab. 5 further patients had a second infusion to treat clinical relapse (2, 10, 12, 26 and 39 weeks after the first infusion). The patient re-treated at 39 weeks had a delayed hypersensitivity reaction to the second infusion.

At 90 days 17/24 had withdrawn corticosteroid therapy (rates comparable in those treated single or multiple infusions) and 20/24 (83.3%) were established on azathioprine/MP immunosuppression

Results: Reguiero et al 2006

At a median follow-up of 26 months, 3/12 patients responded to infliximab and were able to avoid colectomy and discontinue corticosteroids. 9/12 patients failed to respond and required colectomy (2 patients did not respond during hospitalisation and the other 7 within 5 months of hospitalisation). For the 3 responders, DAI scores did not significantly decrease from a baseline level of 9 2 weeks after the first dose of infliximab, but began to improve 2 weeks after the first infusion (score of 5, 7 and 9) and continued to improve after the second dose. By 4 weeks, DAI had dropped to 2, 3, and 4 respectively. For non-responders, DAI scores did not significantly decrease from a baseline level of 9 to 8, 2 weeks after the first dose of infliximab. All 3 responders had a re-staging colonoscopy within 1 year of hospitalisation and endoscopic response was found to correlate with clinical response (DAI 1, 0, and 3).

5.9 Interpretation of clinical evidence

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

Several studies included in other systematic reviews (e.g., Gisbert et al 2007) were excluded from the current study; largely this selection was a consequence of our report focussing only on severely affected hospitalised patients with refractory disease (several case reports, abstracts, and correspondence included in Gisbert et al 2007 were also excluded here). No other systematic review looking specifically at this patient population was found.

All studies summarised acute severe treatment refractory UC; no studies looked specifically at patients intolerant or contraindicated to corticosteroids, 6-mercaptopurine or azathioprine. Comparison with ciclosporin was only reported as a subgroup of a single observational study; few patients were treated (6 with infliximab and 15 with ciclosporin) and the differences were relatively small. High quality head-to-head RCTs were not found of infliximab and ciclosporin; all infliximab and ciclosporin RCTs compared the study drug to placebo or steroids.

The evidence identified from two small RCTs and nine largely small, open, uncontrolled observational studies (three of which reported subgroups only) suggest that infliximab provides clinical benefit to patients with acute severe, steroid-refractory UC and is well tolerated. Our indirect comparison against ciclosporin suggests that infliximab provides additional clinical benefit in terms of colectomy avoidance beyond that available with other, currently-used therapies.

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

We found no direct evidence which tests the efficacy of infliximab's licensed induction dose in preventing colectomy. Both infliximab trials included in this submission gave a single infusion of infliximab to patients, an off-label treatment which is not within the scope of this appraisal. Our efficacy analyses, however are based on these single-infusion trials and their outcomes data directly inform our economic model. It is asserted that currently the trials represent the best available evidence to address the decision problem set out in this appraisal, and that our economic analyses, which assume that patients receive the licensed induction dose of three infusions, are consequently likely to be conservative with respect to expected outcomes and price of infliximab. The relevance of the treatment methods seen in the clinical trials to current UK practice is addressed further in the economic section, where expert opinion was elicited to develop an appropriate model structure.

In respect of patient selection, we would suggest that the patient group for whom the decision problem is relevant can be readily identified owing to the acute symptoms which characterise their disease flare, and their prior treatment history will allow determination of their current refractoriness to other therapies.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.
[Response]

6.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.
[Response]

6.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Attribute	Reference case	Section in 'Guide to the methods of technology appraisal'
Comparator(s)	The comparator that has been specified in the decision problem	5.3.2
Perspective costs	NHS and Personal Social Services	5.3.3
Perspective benefits	All health effects on individuals	5.3.3
Form of economic evaluation	Cost-effectiveness analysis	5.3.4
Time horizon	Sufficient to capture differences in costs and outcomes	5.3.5
Synthesis of evidence	Systematic review	5.4.1
Outcome measure	Quality-adjusted life years (QALYs)	5.5

Health states for QALY measurement	Described using a standardised and validated instrument	5.5
Benefit valuation	Time trade-off or standard gamble	5.5
Source of preference data	Sample of public	5.5
Discount rate	Health benefits and costs – both 3.5%	5.7.2
Equity	No additional weighting to QALYs	5.9.7
Sensitivity analysis	Probabilistic sensitivity analysis	5.9.3

6.2.1 Technology

How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

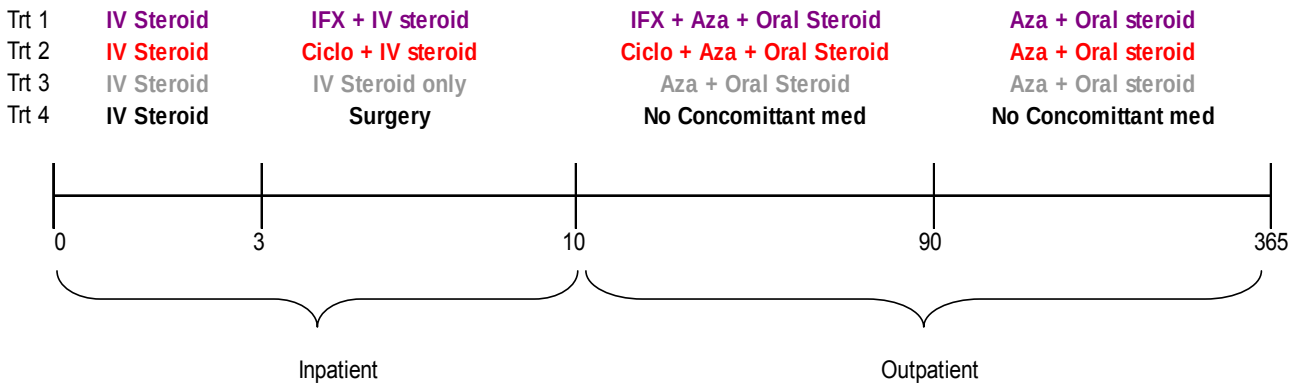
Indication
Within this economic evaluation, infliximab is considered for the treatment of acute exacerbations of severely active UC patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

Posology
Eligible patients receive the *full induction dose* of infliximab comprising of the first intravenous infusion of 5 mg/kg of infliximab on initiation of the treatment over a two hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion. Although, the current trial evidence suggests clinical benefit with a single infusion of infliximab, the licence holders' (Centocor Inc.) understanding of infliximab's licence in ulcerative colitis requires a full induction dose to be administered to all responders followed by further treatment at the discretion of the physician (Appendix 9.5).

The economic analysis presented in this submission assumes that the effectiveness of a full induction dose of infliximab is at least as effective as a single infusion of infliximab (efficacy estimates for the economic evaluation are derived from studies that investigated the effects of a single infusion of infliximab whereas drug acquisition costs included in the model assume a full induction dose comprising three infusions). There is some evidence that a full induction dose of infliximab is likely to be significantly more efficacious compared to a single infusion (Kohn, 2007). On this basis, we argue that the efficacy estimates used in the current analysis are likely to be conservative.

Treatment pathway
The current analysis assumes a defined treatment pathway during the timeframe of this analysis for all patients hospitalised with an acute exacerbation of ulcerative colitis. This treatment pathway was developed based on the clinical trial evidence and in consultation with UK clinical experts identified in Appendix 9.4. The treatment pathway is displayed in Figure 6.2.1.1.

Figure 6.2.1.1 Schematic representation of the treatment pathway



Initial treatment (Day 1-3): All patients will receive 72 hours of intravenous corticosteroid treatment. 400 mg/day of Hydrocortisone was assumed to be the choice of corticosteroid based on UK IBD audit.

Comparator treatment initiation (Day 4-10): All patients not responding to the initial treatment are assumed to receive one of the four identified treatment strategies comprising continued standard care, infliximab with standard care, ciclosporin with standard care or surgical intervention. Based on the clinical trials of infliximab and ciclosporin, patients are assumed to have a mean response time of 7 days following the initiation of treatment. Due to the observed variation in the clinical trials and the small number of patients in the trial it was not possible to make any conclusive judgement about the time to response/failure for individual treatments. Therefore, the 7 day response period was assumed to be identical for all the treatments under consideration.

Standard care - The standard care treatment included continuation of the intravenous corticosteroid treatment of 400 mg/day of Hydrocortisone for an additional 7 days.

Infliximab – Infliximab treatment included a first infusion of 5 mg/kg of infliximab on day 4. These patients also received concomitant standard care comprising of intravenous corticosteroid treatment for an additional 7 days during the hospital stay. As stated above, responders to infliximab were assumed to respond within 7 days of the first infusion.

Ciclosporin – Patients receiving ciclosporin are given a 4 mg/kg daily dose of intravenous ciclosporin starting on day 4 for a period of 7 days. These patients also receive standard care comprising of intravenous corticosteroid treatment during this period.

It is assumed that all patients are hospitalised until day 10. Responders to medical treatments are assumed to be discharged on day 10 and moved to an outpatient setting. Patients not responding to medical treatments on or before day 10 are assumed to progress to surgery.

Short term follow-up treatment (Day 11-90): Responders to medical treatments are assumed to receive the following short-term follow-up treatment.

Infliximab responders – Following discharge from hospital, all infliximab responders received oral corticosteroids (60 mg/day of Prednisolone) and Azathioprine (2 mg/kg) for 3 months. In addition, responders also received the two remaining doses of infliximab 5 mg/kg at weeks 2 and 6 following the first infusion.

Ciclosporin responders – Following discharge form hospital, ciclosporin responders are switched to oral ciclosporin (2 mg/kg/day) until the end of 3 months. In addition to oral ciclosporin, these patients also receive oral corticosteroids (60 mg/day of Prednisolone) and Azathioprine (2 mg/kg) during this period.
Standard care responders – Following discharge form hospital, responders to the standard care are switched to combination therapy comprising of oral corticosteroids (60 mg/day of Prednisolone) and Azathioprine (2 mg/kg) for 3 months.

Long term follow-up treatment (Day 91 onwards): Patients with continued response are assumed to 'bridge' onto combination therapy comprising of oral corticosteroids (60 mg/day of Prednisolone) and Azathioprine (2 mg/kg) and continue to receive this combination therapy for the remainder of the analysis timeframe. The base case analysis was conducted for a period of 1 year following hospitalisation for acute exacerbation of UC. A long-term analysis with a 10 year time horizon was carried out to explore uncertainty in long term outcomes.

Surgical intervention: Surgical intervention is also included as an alternative treatment strategy to reflect a scenario where patients choose to undergo colectomy following non-response to IV steroids (by day 3). Surgical intervention is also included in the economic evaluation as a treatment outcome for patients not responding to a medical treatments (Infliximab, ciclosporin or standard care; on or before day 10). Any patient undergoing surgical intervention and achieving post-surgical remission is assumed to have a hospitalised recovery period of 7 days. Subsequently, these patients are discharged from hospital and managed in an outpatient setting. Patients suffering from post-surgical complications are assumed to require an additional 10 days of hospitalisation.

6.2.2 Patients

6.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

As described above in section 6.2.1, severely active UC patients hospitalised with an acute exacerbation are considered in the economic evaluation. These patients represent a subgroup within the overall licensed population for infliximab which includes moderate to severe UC patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

The patient cohort was based on the Jarnerot et al study. Please refer to section 5.3 for detailed information on the inclusion and exclusion criteria.

6.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?

The analysis presented in this submission considers severe UC patients hospitalised with an acute exacerbation of the disease. This patient population is a subgroup of infliximab's license, which comprises all moderate to severe UC patients. However, within the decision problem specified for this appraisal, no sub-group analysis was conducted.

6.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

The subgroup of patients for whom the acute exacerbation is their first presentation of UC was not considered. Such patients are unlikely to have been prescribed azathioprine previously and therefore cannot be categorised as non-responders to azathioprine. Treatment with infliximab for these patients would therefore be off-license (appendix 9.5) and falls outside the remit for this appraisal.

6.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

The treatment pathway outlined in section 6.2.1 suggests that all patients with an acute exacerbation of UC are hospitalised. For the purpose of this analysis the day of hospitalisation is considered as Day 1. Therefore, all patients 'enter' the current evaluation at the time they are offered treatment to IV steroids, which for the purpose of this analysis is assumed to occur on the day of hospitalisation.
The base case analysis was conducted for a period of one year. Therefore, all patients 'exit' the evaluation one year following their first admission for an acute UC exacerbation or if they die during this time period.
The 'entry' and 'exit' points are identical between all the treatment options that were considered in this analysis.

6.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).
Following three treatment options were compared with infliximab in this analysis.

1. Standard care : This treatment option consisted of continued administration of IV steroids following the initial treatment with IV steroids. This option was selected as a treatment of choice for patients not suitable for infliximab or ciclosporin. Here, the primary outcome for responders is symptom free remission and for non-responders, it is surgical intervention such as colectomy. Responders achieving remission are further 'bridged' and maintained on immunomodulators such as Azathioprine with concomitant administration of oral steroids which may or may not be tapered down in future.
2. Ciclosporin : Clinical trials of ciclosporin have demonstrated its efficacy in achieving response and avoiding colectomy among UC patients hospitalised with an acute exacerbation. Ciclosporin is intermittently used as a rescue therapy in UC patients in current clinical practice in the UK. Therefore, ciclosporin was selected as a comparator in the current analysis. The treatment with ciclosporin is initiated with its IV formulation till the point of achieving a response and stabilising the patient, and subsequently switched to oral administration in an outpatient setting.
3. Surgical intervention : Surgical intervention such as colectomy was also considered as a treatment alternative for patients not responding to initial treatment with IV steroids. Non-responders may choose to undergo colectomy following consent from their physician instead of continuing on standard care (which they have already failed), ciclosporin (due to its side effects) or infliximab. Although not a common current clinical practice in the UK, surgical intervention was included as a comparator as it can be a treatment option offered to the patients. Surgical intervention is therefore considered as both a treatment outcome and as a comparator treatment strategy.

6.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.
The economic analysis was conducted using NHS and PPS perspective which is in accordance with NICE's reference case.

6.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?
The time horizon used in the base case was one year. The time horizon was selected based on the decision problem and the availability of the evidence.

- The decision problem is focussed on rescue therapy for hospitalised patients with an acute exacerbation of UC. In this setting, the goal of the treatment is to avoid or delay surgery and to achieve symptom free remission. Therefore, a short time horizon was considered appropriate for the base case analysis. This rationale was verified with a panel of UK gastroenterologists.
- The primary evidence for this analysis was derived from the Jarnerot et al and Sands et al studies for infliximab and from the D'Haens et al and Lichtiger et al studies for ciclosporin. Evidence for the primary outcome of avoidance of surgery is available from studies with a maximum duration of 1 year (Jarnerot et al. and D'Haens et al.). None of the available studies had evidence for longer-term outcomes (one year or beyond) in relation to the maintenance of remission or the recurrence of UC symptoms among responders. Therefore, a one year time horizon was considered appropriate for this analysis.

An extrapolated analysis extending up to 10 years was conducted to address the uncertainty around the long term treatment effect.

6.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

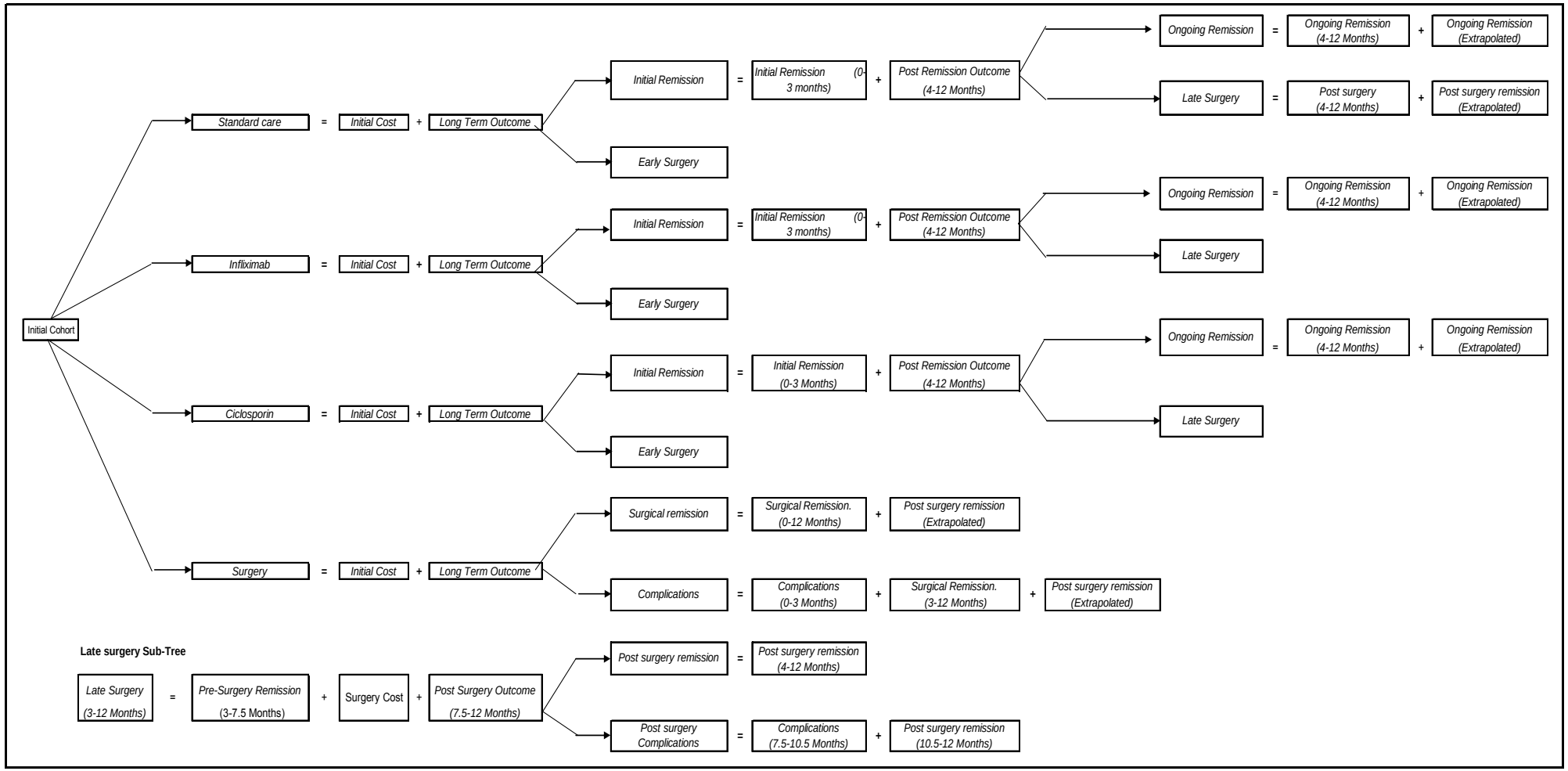
a) Model-based evaluations

6.2.6.1 Please provide the following.

1. A description of the model type.
2. A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.
3. A list of all variables that includes their value, range (distribution) and source.
4. A separate list of all assumptions and a justification for each assumption.

A decision analytic model was used to simulate the progression of hypothetical cohorts of patients with an exacerbation of UC receiving different treatment strategies and to track associated costs and outcomes (QALYs) over 1 year. This model was developed using Microsoft Excel. A schematic representation of the model is provided below.

Figure 6.2.6.1.1: Schema of the economic model for moderate/severe UC patients



The initial model cohort consists of acute severe UC patients not responding to 72 hours of IV steroid therapy. These patients are assumed to receive one of the four treatment strategies under consideration – infliximab, ciclosporin, standard care or surgical intervention. The base case time horizon of 12 months was divided into two treatment cycles (0-3 months and 4-12 months). Further analyses were conducted over a 10 year time horizon. Treatment outcomes were characterised in the model as short term outcomes (1st cycle; 0-3 months), medium term outcomes ; 4-12 months) and long term outcomes (2-10 years).

Short term outcomes
Patients treated with infliximab, ciclosporin or standard care either responded to treatment and achieved remission or failed treatment and underwent colectomy. In the absence of evidence regarding the variable course of disease severity for responders following different treatment interventions, all responders were assumed to achieve and maintain a symptom free remission for the first 3 months.

Medium term outcomes
Patients achieving initial remission either maintained the remission for the rest of the base case analysis period or lost response and underwent a colectomy. For patients undergoing colectomy after the first 3 months (1st cycle), no information was available on the time to colectomy. Therefore, it was assumed that in the medium term outcomes, colectomies occurred mid-cycle i.e. at 7.5 months.

Long term follow-up (2-10 years)
Long-term follow-up analysis was conducted as part of the sensitivity analysis to address the uncertainty around the choice of time horizon. In order to estimate the long term outcomes, probability of colectomy estimated in the medium term (4-12 months) was repeated using a Markov model beyond the first year. Long-term follow-up analysis was conducted with a time horizon of up to 10 years.

Surgery
Patients undergoing surgery either achieved post-surgery remission and maintained it throughout the time frame of this analysis or suffered from immediate post-surgery complications. It was assumed that post surgery complications would occur immediately following surgery and therefore in the same cycle as surgery. Patients treated for post surgical complications are assumed to recover in the next cycle, achieve post-surgical remission and remain in remission for the rest of the analysis. Due to the shorter timeframe of this base-case analysis, long term complications such as pouchitis and pouch failure were not considered. This is likely to favour surgery as a treatment option and adversely affect the ICERs for medical treatments such as infliximab compared to surgery.

Parameter Estimates
The efficacy estimates used in the model were obtained from clinical studies of infliximab (Jarnerot and Sands) and ciclosporin (D'Haens and Lichtiger), published literature sources and data on file. The list of parameters along with their estimated values and ranges is listed below.

Table 6.2.6.1: Parameter estimates

Parameter	Estimate	Range used for SA
Short term outcomes (0-3 months)		
Colectomy rate		
Infliximab	0.23	0.01-0.84
Ciclosporin	0.58	0.03-0.98
Standard care	0.67	0.24-0.96
Medium term outcomes (4-12 months)		
Colectomy rate	0.27	0.0-1.0
Infliximab	0.18	0.0-0.97
Ciclosporin	0.14	0.0-0.80
Standard care		
Surgical complications†	23.49%	
Post operative wound infection	8.95%	
Post-operative rectal stump complications	1.12%	
Post operative bleeding	1.54%	
Post operative sepsis	4.2%	
Anastomical leakage	1.7%	
Small bowel obstruction	3.0%	
Stoma complications	3.0%	
Patient weight	80 kg	60-80 kg
Time Horizon	1 year	1-10 years

†UK IBD Audit 2006 data. (Combined complications from emergency & elective surgeries)

6.2.6.2 Why was this particular type of model used?

The model structure used was a decision analytic model. Literature review and expert opinion indicated that patient progression in acute severe UC can be suitably captured using a decision analytic model. For extrapolation beyond the trial period, a Markov model was used.

6.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

This model represented the disease progression of UC patients from the point of hospital admission following an acute exacerbation through to end of first year. The chosen structure allowed incorporation of the clinical trial efficacy data within the clinical trial framework into effectiveness estimates within UK clinical practice. The course of the disease was represented by post hospitalisation outcomes including medical remission, surgical remission and surgical complications. Other possible structures such as a Markov model with several health states were deemed inappropriate to incorporate trial data and parameter estimates from literature.

6.2.6.4 What were the sources of information used to develop and inform the structure of the model?

RCTs of infliximab (Jarnerot et al and Sands et al) and ciclosporin (D'Haens et al and Lichtiger et al), information on current UK clinical practice (UK IBD audit 2006) and expert clinical opinion were used to develop the model structure. The primary and secondary endpoints used in these clinical trials such as colectomy rate, remission rate etc were used to derive probable outcomes in the current analysis.

6.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The model structure reflects all essential features of the condition that are relevant to the decision problem. This has been verified by panel of UK gastroenterologists listed in appendix 9.4.

6.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

In the base case, two separate cycle lengths denoted as short term outcomes (0-3 months) and medium term outcomes (4-12 months) were used. These cycle lengths were selected to incorporate the existing clinical trial evidence. Two clinical trials each of infliximab and ciclosporin reported short term primary outcome (colectomy rate) and one clinical trial each of both drugs reported medium term outcome up to a period of one year.
These cycle lengths also reflect the nature of the decision problem. The short term outcomes address the primary goal of treatment which is to avoid immediate colectomy following an acute exacerbation whereas the medium term outcomes address the efficacy of these treatments in maintaining these outcomes over a one year time period. The medium term outcomes (9 months) addressed in this analysis may not be sufficient to capture all the relevant pathology and symptoms of the disease. Therefore, a long term follow-up analysis up to 10 years was conducted by extrapolating the trial evidence.

6.2.6.7 Was a half-cycle correction used in the model? If not, why not?

A half cycle correction has been used except during the first cycle (short term outcomes) in which it is assumed that all outcomes occur at the beginning of the assessment period. The clinical evidence suggests that the majority of colectomies during 0-3 months occurred during the first 30 days. Therefore, the half cycle correction was not applied to the first cycle

6.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Costs and outcomes were extrapolated beyond the trial period as part of the sensitivity analyses. In the absence of any data from clinical trials on long term follow-up, the colectomy rate from the medium term follow-up (4-12 months) was assumed to remain constant in subsequent years. Additional analysis assuming a full treatment effect (no colectomies) and no treatment effect (100% colectomies) beyond the first year also were conducted. Patients in surgical remission were assumed to maintain remission for the entire extrapolated timeframe.

b) Non-model-based economic evaluations

6.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

Not applicable as the economic evaluation is model based.

6.2.6.10 Provide details of the clinical trial, including the rationale for its selection.

Not applicable as the economic evaluation is model based.

6.2.6.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not applicable as the economic evaluation is model based.

6.2.6.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

Not applicable as the economic evaluation is model based.

6.2.6.13 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

Not applicable as the economic evaluation is model based.

6.2.7 Clinical evidence

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

6.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

The baseline risk of disease progression was estimated using the placebo arms of infliximab and ciclosporin clinical trials. In the current analysis this treatment strategy is addressed as 'standard care.' Patients entering clinical trials of both infliximab and ciclosporin were UC patients hospitalised with an acute flare of the disease. These patients were then randomised to receive active treatment or placebo. A meta-analysis of the placebo arms of the trials was conducted to derive a composite outcomes estimate for the standard care treatment arm. For details of the evidence synthesis methods, please refer to Appendix 9.6.
As stated above, the standard care treatment arm derived from the placebo arms of the clinical trials represents the baseline disease progression in the current analysis.

6.2.7.2 How were the relative risks of disease progression estimated?

The relative risk of disease progression on different treatment alternatives was determined by an indirect comparison between the clinical trials. For infliximab the efficacy estimates were derived from Jarnerot and Sands studies whereas for ciclosporin they were derived from D'Haens and Lichtiger. Please refer to the clinical section for the rationale regarding the selection of these clinical trials.
During evidence synthesis, the efficacy estimates from infliximab and ciclosporin trials were combined using meta-analysis techniques to derive a composite efficacy estimates for each treatment. These were then used in the current analysis using indirect comparison techniques to estimate the relative risk of disease progression under each treatment alternative. For details of the evidence synthesis methods, please refer to Appendix 9.6.

6.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Intermediate outcomes of colectomy and post-surgery complications were used to derive the final outcome of symptom free remission. The treatment pathway identified from the clinical trials and verified by clinical experts is described in section 6.2.1.

This treatment pathway suggested that the final outcome of interest (symptom free remission) could be achieved using a medical treatment such as infliximab or ciclosporin or interventional procedures such as colectomy. Non-responders to medical treatments would also undergo colectomy and achieve remission. Following colectomy, a proportion of patients suffer from post surgery complications.

However, these patients would receive treatment for their complications and achieve remission. Therefore, all patients hospitalised with an acute exacerbation of UC, upon treatment would achieve remission by the end of the first year.

The relationship between the intermediate outcome of colectomy and final outcome of symptom free remission was estimated using clinical trial data and expert opinion. The Jarnerot and D'Haens studies provided information on long term disease severity (clinical and/or endoscopic remission) of responders. Both studies indicated that a significant proportion of patients achieve and maintain remission. However, the severity and the resultant quality of life of patients not achieving or not maintaining remission was not reported. Further, clinical opinion suggests that patients losing endoscopic remission may not experience symptoms that affect their health related quality of life. Therefore, the current analysis assumes that all responders not experiencing another acute exacerbation were optimally maintained on immunomodulators and oral steroids and remain in symptom free remission. This assumption which was used in all the three medical treatment alternatives may adversely affect infliximab which has been shown to have a mucosal healing effect in the colon (Rutgeerts, 2005).

6.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

The health effects associated with the technology were included in the economic evaluations. A detailed description of the health effects is presented in section 6.2.8.

The adverse effects of medical treatments were excluded from the model.
Standard care : There was no information available on the side effects of continued IV steroid treatment followed by oral steroid and immunomodulator treatment in UC patients. However, the literature suggested a significant side effect burden for patients on long term corticosteroid treatment.
Infliximab : Information on the side effects of maintenance treatment with infliximab was available from infliximab clinical trials in moderate to severe patients (ACT I & II). However, it was unclear whether patients receiving just the induction dose would suffer side effects to the same extent as patients on scheduled maintenance treatment. The long term studies of infliximab maintenance treatment have also highlighted the non-significant side effect profile of infliximab. The current analysis assumed that side effects due to the induction dose of infliximab would not be significant and were therefore excluded.
Ciclosporin : Long term outcome studies of ciclosporin have highlighted significant side effect profile for the drug. A significant proportion of UC patients on IV and oral ciclosporin

suffer from side effects. However, there was no information available on the quality of life impact of these side effects. Therefore, rather than assigning an arbitrary decrement in utility, we selected to exclude the impact of ciclosporin side effects.
This assumption leads to a significantly conservative quality of life benefit for infliximab as both ciclosporin and standard care are associated with a number of side effects in a significant proportion of patients.

6.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Expert opinion sought during an advisory panel was used to develop the treatment pathway and validate model assumptions. The participants of this advisory panel were UK clinical experts in inflammatory bowel disease. They represented several geographic areas and practice settings (academic institutions vs general hospitals) across England and Wales. The feedback thus obtained therefore can be considered as a reasonable representation of current clinical practice of UC patients across the country. The UK gastroenterologists and health economic experts involved in the development of this model are listed in appendix 9.4. Apart from resource use of patients during and following their hospitalisation, no other parameter was estimated using expert opinion.

6.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

The assumptions made regarding the clinical evidence are mentioned in the relevant sections of this document. All the assumptions used to develop model framework and derive estimates of model parameters were based on recommendations of a clinical experts as mentioned previously. These experts represent current UK thought leaders in gastroenterology with a wealth of experience in clinical setting. Therefore, in absence of any conclusive evidence, their interpretation of the current practice was deemed reasonable.

6.2.8 Measurement and valuation of health effects

6.2.8.1 Which health effects were measured and how was this undertaken? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

The positive health effect measured was patients' health related quality of life associated with their improvement in disease severity. The baseline disease severity and change in disease severity associated with the treatment effect was estimated using disease severity indexes such as Harvey Bradshaw index. Patients hospitalised with an acute exacerbation were classified as *active UC* patients whereas treatment responders were classified as achieving *medical remission*. The health related quality of life associated with these health states was estimated using utilities for these health states. Similar utilities also were estimated for post-surgery health states of *surgical remission* and *surgical complications* as described below in section 6.2.8.2.
Negative health effects primarily comprised of adverse events associated with treatments and complications associated with surgery. Valuation of health effects associated with side effects of treatments was not undertaken for the reasons cited in section 6.2.7.4. The impact of complications associated with surgery was estimated as described in section 6.2.8.2 below.

6.2.8.2 Which health effects were valued? If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?

Health states along with their values used in the model are listed in table 6.2.8.2.

Table 6.2.8.2: Utility estimates associated with health states

	Arseneau (TTO)		HODaR (EQ-5D)	
	mean	SD	mean	SD
Remission	0.79	0.24	**0.88**	**0.14**
Active UC	0.32	0.31	**0.42**	**0.32**
Surgical remission	0.63	0.30	**0.60**	**0.38**
Surgical complications	0.49	0.32	-	-

Pre-surgery health states and post-surgery remission: The base case utilities were derived from the HODaR study and have been highlighted in table 6.2.8.2. This set of utilities were obtained from a UC patient survey carried out in Cardiff Hospital (HODaR study) using the EQ-5D. The details of the study including the design and population are presented in Appendix 9.13.

Utilities associated with pre-surgery health states also were available from ACT I and Arseneau study whereas utility for post-surgery complications was available from Arseneau study alone. However, HODaR study captured the utilities of UC patients admitted to the Cardiff hospital with an acute exacerbation using EQ-5D at the time of admission and following discharge. Therefore, they were deemed more appropriate for the purpose of this decision problem. HODaR utility estimation method also fitted the NICE reference case more appropriately compared to other estimates. In contrast, the ACT I trial population was comprised predominantly of moderate to severe UC patients in an outpatients setting and were non-UK residents whereas Arseneau study estimated utilities using TTO method. Therefore, utilities derived from ACT I were not used in this analysis and Arseneau study utilities were used in sensitivity analysis but were not used in base case.

Separate sets of utilities were available for IPAA and illeostomy, both from HODaR study and Arseneau paper. The Arseneau study estimated IPAA to result in a higher utility compared to illeostomy whereas HODaR study estimated health gains of illeostomy to be higher than IPAA. Due to this contrasting evidence, an average of the two utilities was used as utility for post-surgery remission.

Post-surgery complications: The utility associated with post-surgery complications was not available in HODaR study. The current analysis focussed only on post surgery complications immediately following surgery wherein patients were still in hospital recovering from their initial UC exacerbation. Therefore, we assumed the post-surgery complications utility to be equivalent to the utility of an active UC patient (0.42).

6.2.8.3 Were health effects measured and valued in a manner that was consistent with NICE's reference case? If not, which approach was used?

As explained above, the health effects associated with all the health states except 'post-surgery complications' were captured using EQ-5D and valued using UK population valuations which was consistent with NICE's reference case. Our literature search did not identify any utility estimates derived from the EQ-5D for patients with post-surgery complications. Therefore, we have assumed a utility for these patients equivalent to that for a patient with active UC.

6.2.8.4 Were any health effects excluded from the analysis? If so, why were they excluded?

No health effects were excluded from the analysis.

6.2.8.5 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health effects were expressed using QALYs.

6.2.9 Resource identification, measurement and valuation

6.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

Drug Costs
The cost of all drugs used in the analysis was calculated based on the average doses used in the clinical trials and was costed based on pack sizes in the BNF (September 2007). Table 6.2.9.1 outlines the drug costs used in the model.

Table 6.2.9.1: Drug costs used in the model

Cost of medications	Cost /day	Price	Packsize	Strength	Dose
Infliximab (5mg/kg) - Per infusion cost	£1,322.86	£419.62			
Ciclosporin (IV)	£8.80	£9.17	5mL	50mg/mL	4 mg/kg daily
Ciclosporin (Oral)	£2.23	£27.83	30 capsules	50mg	2 mg/kg daily
Azathioprine (Oral)	£0.51	£11.80	56 tablets	50mg	1-3 mg/kg daily
Corticosteroids (IV) - Hydrocortisone	£4.48	£4.48	5	100mg/mL	400 mg/day
Corticosteroids (Oral) - Prednisolone	£0.62	£14.51	56 tablets	25mg	60 mg/day

Infliximab acquisition and administration costs:

The cost associated with infliximab infusions is usually broken down into two components: the cost of the drug itself and the cost of administration. Table 6.2.9.1 gives a detailed drug acquisition cost for infliximab. To calculate the cost of drug acquisition, an average body weight of 80 kg was used. The average patient weight in infliximab clinical trials (ACT I & II) was 72 kg and that observed in HODaR database was 73 kg. Therefore, an 80 kg patient weight was deemed appropriate for purpose of this analysis. None of the clinical trials identified in our systematic review for this submission (Jarnerot, Sands, D'Haens and Lichtiger) reported the baseline weight of patients hospitalised with an acute exacerbation. Expert clinical opinion suggested that eligible patients have a significantly lower weight compared to UC patients in an outpatient setting. Therefore, the base case weight of 80kg is a highly conservative assumption. The uncertainty around this estimate was explored using 60 kg and 70 kg baseline weights in sensitivity analyses.

For drug administration, we used the cost of a "Consultant led face to face adult follow-up" attendance data in medical gastroenterology, i.e. £94, which was considered as an aggregate incorporating all tests, assessments and staffing costs associated with the infusion (NHS reference costs 2006-07). This administration cost has already been deemed appropriate in a previous NICE appraisal (TAG 134). In the current analysis it was assumed that the first infliximab infusion would not incur any additional administration cost as the patient was already hospitalised. Therefore, the

administration cost of 2 additional infusions (£188) was spread over the entire induction dose resulting in a mean administration cost of £62.66 per infusion.

Cost of concomitant medications

The use of concomitant medications in the treatment pathway was derived from clinical expert opinion. There was significant variation in the study baseline populations in terms of their concomitant medication use. The study sample sizes were too small to make any generalisation about the concomitant medication use of UC patients with an acute exacerbation. Therefore, a standard treatment pathway based on current UK clinical practice was developed and used in the analysis.

According to this treatment pathway

- All patients received initial treatment comprising of 72 hours of IV steroids
- Non-responders were offered a choice of treatment between infliximab + standard care, ciclosporin + standard care, standard care alone or surgery
- Standard care comprised of continued IV steroids
- These treatments were continued for a further next seven days after which patients were discharged and moved to an outpatient setting
- Patients on IV steroid treatment during hospital stay (i.e all patients except those who underwent surgery), were switched to oral steroid + immunomodulator treatment following discharge from hospital. This step was referred as 'bridging to immunomodulator' therapy.

The concomitant medication use in the model is displayed below.

Table 6.2.9.2: Concomitant medication use*

		First cycle cost (0-3 Months)				Ongoing Costs (per 3 month cycle)		
Concomitant medications	Cost /day	Placebo	Infliximab	Ciclosporin	Surgery	Medical Remission	Surgical Remission	Surgical Complications
Infliximab (Cost/infusion)	£1,741.14	0	3	0	0	0	0	0
Ciclosporin (IV)	£11.74	0	0	10	0	0	0	0
Ciclosporin (Oral)	£2.97	0	0	80	0	0	0	0
Corticosteroids (IV) - Hydrocortisone	£4.48	10	10	10	3	0	0	0
Corticosteroids (Oral) - Prednisolone	£0.62	80	80	80	0	90	0	0
Azathioprine (Oral)	£0.67	80	80	80	0	90	0	0
Subtotal		£148.49	£5,371.91	£503.35	£13.44	£116.65	£0.00	£0.00

The numbers in table denote number of days of treatment

*Resource use estimated by panel of UK gastroenterologists

Table 6.2.9.3: Estimates health care resource use*

		First cycle cost (0-3 Months)				Ongoing Costs (per 3 month cycle)		
Healthcare Use	Unit Costs	Placebo	Infliximab	Ciclosporin	Surgery	Medical Remission	Surgical Remission	Surgical Complications
Consultant visit	£92.44	2	2	2	3	1	1	0
Hospital episode cost /day	£272.68	10	10	10	10	0	0	10
Surgical procedure	£4,190.08	0	0	0	2	0	0	0
Diagnostic endoscopy (Hospitalised)	£1,511.52	1	1	1	1	0	0	1
Diagnostic endoscopy (Daycase)	£488.11	2	2	2	2	1	1	0
Subtotal		£5,399.39	£5,399.39	£5,399.39	£13,871.98	£580.55	£580.55	£4,238.30

*Resource use estimated by panel of UK gastroenterologists

Table 6.2.9.4: Total costs

	First cycle cost (0-3 Months)				Ongoing Costs (per 3 month cycle)		
Healthcare Use	Placebo	Infliximab	Ciclosporin	Surgery	Medical Remission	Surgical Remission	Surgical Complications
Cost of resource use	£5,399.39	£5,399.39	£5,399.39	£13,871.98	£580.55	£580.55	£4,238.30
Cost of concomitant medication	£148.49	£5,371.91	£503.35	£13.44	£116.65	£0.00	£0.00
Total costs	£5,547.88	£10,771.30	£5,902.74	£13,885.42	£697.20	£580.55	£4,238.30

Health care resources
The estimated health care resource use per cycle is listed in the table 6.2.9.3 above. The resources used by patients in each health state were estimated by a panel of four gastroenterologists highlighted in Appendix 9.4. Each clinician estimated the resource use independently and values used in the economic model were averages of individual estimates.

Consultant visits
The number of consultant visits was derived based on the treatment pathway. It was assumed that responders were to visit a consultant on day 30 and day 90 following hospitalisation. Patients achieving remission (medical or surgical) were assumed to have one consultant visit every 3 months in the follow-up period. Patients suffering from surgical complications were assumed to have no additional consultant visits during the period they were hospitalised for their complications.

Hospital episodes
All patients were assumed to have 10 days of hospitalisation during initial treatment period. This included first 3 days of IV steroid treatment and 7 days of recovery period following initiation of comparator treatments. Patients achieving and maintaining remission were assumed not to have any subsequent hospitalisation. Patients suffering post-surgery complications were assumed to have 10 days of hospital stay in addition to their stay due to their surgical procedure.

Surgical procedures
The primary surgical procedure included colectomy. As described in clinical section the surgical procedures primarily comprise of IPAA and illeostomy. The cost of each procedure was calculated based on expert opinion of UK surgeons.

1. Clinical expert opinion suggested that all patients undergoing colectomy for UC would first undergo an illeostomy. An illeostomy involves two separate surgical procedures in a period of approximately 3 months and therefore the total cost an illeostomy was estimated to be twice as much as a 'complex procedure in gastroenterology'.
2. The expert clinical opinion also suggested that a small proportion of illeostomy patients would undergo a third procedure called IPAA approximately 3 - 6 months after the illeostomy. This therefore, would incur additional resource use equivalent to a third surgery in these patients.

Although both procedures were carried out in current UK clinical practice, the exact proportions of each were unavailable. Therefore, it was assumed that all surgical procedures carried out were illeostomies. This assumption reduces the mean cost of a surgical procedures used in the current analysis and therefore adversely affect medical treatments compared to surgery.

Diagnostic procedures
Endoscopy carried out in two separate settings was used in the analysis.
Inpatient endoscopy: Based on the treatment pathway, it was assumed that all patients hospitalised with an acute exacerbation would initially undergo endoscopy to confirm presence and severity of UC. Patients suffering from post-surgery complications who also were hospitalised were assumed to have an additional endoscopy to confirm the type and extent of their complication.

Outpatient endoscopy (Daycase): Responders to medical or surgical treatment were assumed to have two additional day case endoscopies at day 30 and day 90 to confirm their remission status. Following the initial treatment period (0-3 months), all patients were assumed to have a diagnostic endoscopy once every 3 months.

The cost of resource use along with the cost of concomitant medication was used to estimate the cost of treatment for each comparator for the initial treatment period, first cycle and the subsequent cycles. This has been displayed in table 6.2.9.4.

6.2.9.2 How were the resources measured?

Please refer to section 6.2.9.1

6.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

The resource use was estimated using a panel of UK gastroenterologists and surgeons who also derived the treatment pathway. In contrast, the baseline and relative risks of disease progression were obtained from the clinical trials of infliximab and ciclosporin. The trials did not include complete resource use information and there was significant variation between the trial protocols especially around resource use of responders. The trials also were conducted outside of UK and represented the clinical practice in the respective countries. The clinical expert opinion suggested that the clinical practice in UK differed from that used in the trial protocols. Therefore, trial protocols were not used to derive the resource use estimates.

6.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)?

Yes, the resources used to treat UC were included for all relevant treatment periods.

Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

All assumptions along with their justification has been included in section 6.2.9.1.

6.2.9.5 What source(s) of information were used to value the resources?

The sources of resource use information and values used in the model are listed below.
Table 6.2.9.3: Sources of resources used in the model

Item		Mean	FCE	Lower limit	Upper limit	Length of stay	Source of information
Consultation (face 2 face follow-up visit)							
Consultant	Medical gastroenetrology	£94.0	410797	£73.0	£119.0		(TCLFUSFF) NSRC 06-07 NHS trusts & PCTs combined
Non consultant	Medical gastroenetrology	£71.0	23424	£45.0	£74.0		
Consultant	Surgical gastroenetrology	£89.0	38349	£81.0	£104.0		
Non consultant	Surgical gastroenetrology	£53.0	190	£53.0	£55.0		
Consultant visit		**£92.4**		**£72.3**	**£115.5**		
Hospitalisation							
Elective	IBD with major CC	£1,635.0	671	£639.0	£2,280.0	5	(TEI) NSRC 06-07 NHS trusts & PCTs combined
	IBD with intermidiate CC	£1,217.0	344	£478.0	£1,765.0	4	
	IBD without CC	£1,032.0	2090	£569.0	£1,566.0	3	
Nonelective	IBD with major CC	£1,305.0	19468	£883.0	£1,962.0	5	(TNEI) NSRC 06-07 NHS trusts & PCTs combined
	IBD with intermidiate CC	£899.0	10321	£617.0	£1,305.0	3	
	IBD without CC	£907.0	28741	£568.0	£1,289.0	3	

Hospital episode cost /day		**£272.7**		**£176.3**	**£398.4**	**3.8**	
Surgery							
Elective	Complex procedures for IBD	£5,235.0	1025	£3,942.0	£6,990.0	10	(TEI) NSRC 06-07 NHS trusts & PCTs combined
	Major procedures for IBD	£3,560.0	1790	£1,347.0	£4,755.0	7	
Nonelective	Complex procedures for IBD	£4,897.0	421	£2,799.0	£7,119.0	12	(TNEI) NSRC 06-07 NHS trusts & PCTs combined
	Major procedures for IBD	£4,034.0	1543	£1,775.0	£5,373.0	11	
Surgical procedure		**£4,190.1**		**£2,169.7**	**£5,642.2**	**10**	
Diagnostic procedures							
Elective	Endoscopy with cc	£1,490.0	1039	£722.0	£2,003.0	3	(TEI) NSRC 06-07 NHS trusts & PCTs combined
	Endoscopy without cc	£1,129.0	3712	£719.0	£1,428.0	2	
Nonelective	Endoscopy with cc	£2,034.0	2783	£1,331.0	£3,338.0	7	(TNEI) NSRC 06-07 NHS trusts & PCTs combined
	Endoscopy without cc	£1,509.0	4680	£1,027.0	£2,253.0	4	
Diagnostic endoscopy (Hospitalised)		**£1,511.5**		**£976.7**	**£2,228.2**	**4**	
Daycases	Endoscopy with cc	£489.0	6261	£367.0	£668.0		
	Endoscopy without cc	£488.0	52344	£361.0	£675.0		
Diagnostic endoscopy (Daycase)		**£488.1**		**£361.6**	**£674.3**		

6.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1?

The cost of a vial of infliximab is £419.62 excluding VAT. Infliximab is dosed by patient weight, so the number of vials required to treat a patient varies accordingly. For a patient with average weight of 80kg, the cost per infusion is estimated to be £1,741.14 including the cost of administration of £94.

6.2.9.7 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Yes, the resources were measured and valued in a manner consistent with the reference case.

6.2.9.8 Were resource values indexed to the current price year?

Majority of cost information was indexed to 2007. The resource costs were indexed to 2006-07 and the price of medication were indexed to 2007.

6.2.9.9 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

The assumptions used in the resource estimation and its justification have been provided in section 6.2.9.1.

6.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case? The timeframe for the base case analysis was one year. Therefore, no discounting of costs and health benefits was carried out in the base case. In the extrapolated analysis costs and outcomes were discounted at 3.5% as per the NICE reference case.

6.2.11 Sensitivity analysis

Sensitivity analysis should be used to deal with sources of main uncertainty other than that related to the precision of the parameter estimates.
For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.2.11.1 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

One-way sensitivity analysis
The variables subjected to univariate sensitivity analysis and its rationale is described below.

- Treatment effect: Base case analysis was performed for a period of one year. There was very little evidence for the long term outcomes (beyond one year) of infliximab and its comparators. Therefore, univariate sensitivity analysis was performed by assuming
    - Continued treatment effect: The rate of colectomy observed in the medium term follow-up was assumed to continue at a constant rate beyond the first year
    - Maximum treatment effect: All responders were assumed to continue in remission with no colectomy after the first year
    - Minimum treatment effect: All patients were assumed to undergo colectomy within the first cycle after the first year
- Patient weight: The base case analysis used a conservative estimate of 80 kg for the patient. Lower patient weights of 60 kg and 70 kg were used in the sensitivity analysis.
- Set of utility estimates: In the univariate analysis, utilities estimated in the Arseneau study were used instead of the HODaR study estimates
- Infliximab administration cost: The base case analysis used an administration cost of £94 per infusion. Based on a previous NICE guidance (TAG 134), this estimate falls within the acceptable range (£65.02-£124). Therefore, the administration cost was varied between this range in the univariate sensitivity analysis.
- Hospitalisation period: The base case assumed a hospitalisation period of 7 days following initiation of comparator treatments and a hospitalisation period of 10 days following post-surgery complications. Since, these estimates were based on expert opinion they were varied between 4-10 days and 7-13 days respectively during the sensitivity analysis.
- Infliximab infusions: The base case analysis assumed all patients receive full induction dose of infliximab including non-responders. This however was a very conservative assumption. The clinical trial evidence suggested majority of treatment failures occurred within the first 30 days following treatment (Jarnerot, 2005) and would not have received the 3rd infusion of infliximab. Therefore, univariate sensitivity analyses were performed with following two assumptions.
    - Treatment failures within first 30 days: Non-responders only receive first two infusions of infliximab.
    - Treatment failures within first 10 days: Non-responders only receive the first infusion of infliximab.

Probabilistic sensitivity analyses (PSA)
During PSA, the probabilities of primary outcome (colectomy), secondary outcome (post-surgery complications), utility estimates and unit costs were varied as described below.

- Outcome probabilities: The probability of the primary outcome (colectomy) for each of the treatment alternatives was derived from the indirect comparison of clinical

trials of infliximab and ciclosporin. A probabilistic sensitivity analysis (PSA) was performed using the estimates of variability from the indirect comparison.
The probability of post-surgical complications was derived from the UK IBD audit. However, the audit did not report the uncertainty around these estimates. Therefore, the probability of post-surgical complications was subjected to PSA using beta distribution.

- Unit costs: Unit costs were obtained from the published sources and the range reported around these estimates was used in PSA.
- Utilities: Two separate utilities sets were derived from two separate studies. The utility set from HODaR study was used in the base case and subjected to PSA. The set from Arseneau study was used in the one-way sensitivity analysis.

The parameters used in the sensitivity analysis along with their distributions and rationale are displayed in Table 6.2.11.1.

Table 6.2.11.1 Parameters subjected to PSA

Parameter	**Parameter values[1]**	**Distribution for PSA**	**Rationale**
Outcome probabilities	As derived from the evidence synthesis methods.	Beta distribution. Parameters (◎ and ◎) were set by using standard deviation around point estimates. E.g. n = (mean X (1 – mean)/SD^2) – 1 r = mean X n Parameters α = r ; β = n - r	This use of the beta distribution for utility estimates is a standard approach for PSA. The current estimates were derived from published studies and hence beta distribution was used.
Costs	Displayed in Table 6.2.9.3	Normal distribution. Probability, mean and std. deviation were obtained from the published cost estimates.	This use of the normal distribution for fixed cost estimates is a standard approach for PSA. The current estimates were derived from NHS published costs and hence Normal distribution was used.
Utilities	Displayed in Table 6.2.8.2	Beta distribution. Parameters (◎ and ◎) were set by using standard deviation around point estimates. E.g. n = (mean X (1 – mean)/SD^2) – 1 r = mean X n Parameters α = r ; β = n - r	This use of the beta distribution for utility estimates is a standard approach for PSA. The current estimates were derived from published studies and hence beta distribution was used.

6.2.11.2 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Probabilistic sensitivity analysis was undertaken. The details of the variables subjected to sensitivity along with the distributions and their sources are listed above in section 6.2.11.1.

6.2.11.3 Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?

The uncertainty associated with the model structure has not been investigated. Our literature search did not reveal any other CE study in this patient population. The clinical expert panel endorsed the treatment pathway used in this model which also was in line with the treatment protocols used in the clinical trials. Therefore, we did not succeed in our attempt to identify and hence address any structural uncertainty in the current analysis.

6.2.12 Statistical analysis

6.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

Separate rates for primary outcome of interest were captured from the clinical trials for the short term and medium term. The rates obtained from multiple clinical trials were then subjected to indirect comparison using advanced evidence synthesis techniques as described in Appendix 9.6. This resulted in combined transition probabilities for different treatment alternatives under considerations.

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

The clinical trial evidence suggested that the probabilities for the outcome of interest varied significantly for short term and medium term outcomes. These have been included in the current analysis.

6.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model. Following measures were adopted to validate the model.

- Model structure: The model structure was developed in consultation with clinicians and was validated by a panel of UK gastroenterologists listed in appendix 9.4.
- The model framework and content was also reviewed by external consultants who validated the accuracy of the model.
- Predictive validity: The patient flow through the entire model time frame was compared with the trial data to ensure that the model predicted patient flow similar to that observed in the trials. Numbers in the long term follow-up part of the model could not be matched as two of the four studies did not report long term follow-up data. However, the estimates were compared to ensure that they are as expected and in the direction of the observed evidence from clinical studies.

6.3 Results

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

- costs, QALYs and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a statement as to whether the results are based on a probabilistic sensitivity analysis
- cost-effectiveness acceptability curves
- scatter plots on cost-effectiveness quadrants.

6.3.1 Base-case analysis

6.3.1.1 What were the results of the base-case analysis?

The costs and benefits associated with each treatment and the resultant incremental analysis are displayed in the table 6.3.3.1 below.

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

Table 6.3.3.2 displays incremental cost effectiveness ratios of infliximab compared to the alternative treatments

Treatment comparisons	Incremental costs	Incremental QALYs	ICER
Infliximab vs Standard care	£1,341	0.12	£11,589
Infliximab vs Ciclosporin	£1,729	0.09	£18,425
Infliximab vs Surgery	£2,824	0.21	£13,407

6.3.2 Subgroup analysis

6.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

No sub-group analysis was conducted.

6.3.3 Sensitivity analyses

6.3.3.1 What were the main findings of the sensitivity analyses?

Results of the one-way sensitivity analysis are displayed below in table 6.3.3.1.1

Table 6.3.3.1.1 One-way sensitivity analysis

Parameter	Base case estimate	Sensitivity estimate	Results (Cost per QALY)*		
			IFX vs SC BC† - £11,589	IFX vs Ciclo BC† - £18,425	IFX vs Surgery BC† - £13,407
Patient weight	80 Kg	60 kg	£512	£5,759	£7,169
		70 kg (with vial sharing)	£6,050	£12,092	£10,287
Utility estimates	HODaR	Arseneau	£17,078	£27,128	£20,552
Long term treatment effect‡	1 year	Constant Tx effect	£35,739	£34,104	£18,765
		Maximum Tx effect	£997	£1,429	£1,471
		Minimum Tx effect	£56,319	£64,486	£65,290
Infliximab administration cost	£94.00	£65.02	£11,088	£17,808	£13,132
		£124	£12,107	£19,065	£13,692
Hospital stay following initiation of therapy	7 days	4 days	£11,589	£18,425	£9,523
		10 days	£11,589	£18,425	£17,291
Hospital stay following post-surgery complications	10 days	7 days	£12,046	£18,881	£13,919
		13 days	£11,132	£17,970	£12,895

*All results except 'Long term treatment effect' assume time horizon of 1 year as in the base case.
‡Sensitivity analysis assumes a time horizon of 10 years.
BC†-Base case ICER

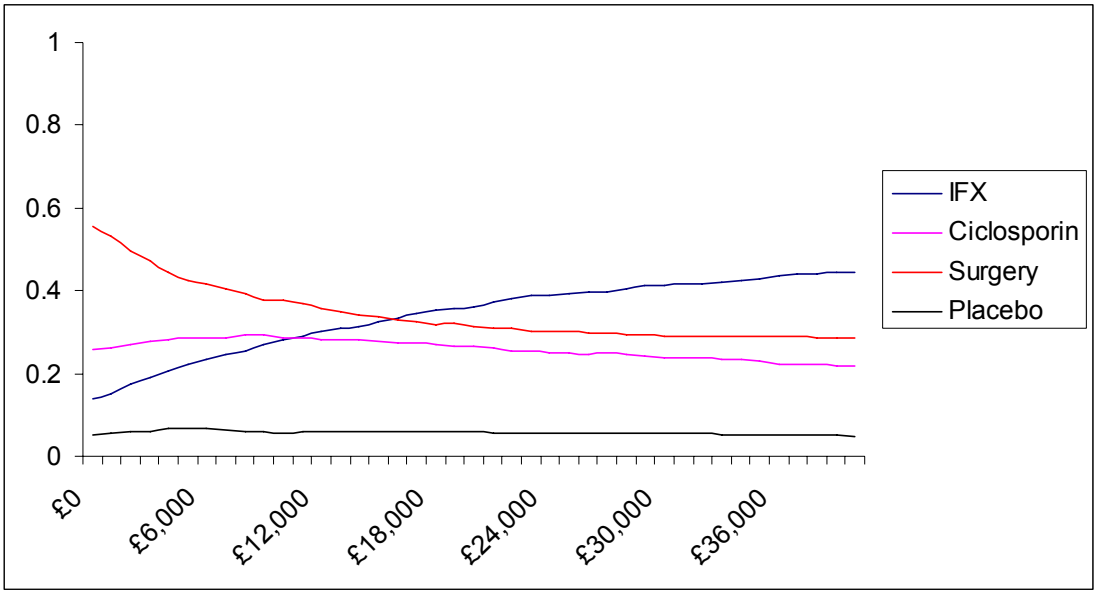
The results of the cost effectiveness analysis indicated patient weight to be one of the most important parameters affecting ICERs. The average patient weight in HODaR database for UC patients 6 months following discharge was 73 kg. Therefore, we used 80 kg patient weight in our base case analysis. However, the feedback received from clinicians suggested that patients hospitalised with an acute exacerbation tend to weigh significantly lesser than moderate to severe UC patients in an outpatient setting. The above results indicate that with a significant proportion of patients weighing less than 70 kg the cost effectiveness of infliximab can be further improved.

Another important parameter affecting ICERs was long term treatment effect. The sensitivity analysis demonstrated that even with a constant treatment effect the ICERs were marginally above the acceptable threshold. It is important to note that this extrapolation is based on a very small sample size in placebo (n=19), infliximab (n=17) and ciclosporin (n=11) treatment arms and therefore the results are subjected to a high degree of uncertainty. The long term follow-up (up to 2 years) to the Jarnerot study also demonstrated that patients avoiding colectomy and achieving remission were likely to maintain it for long term. Therefore, in the clinical practice the true ICERs for long term follow-up were likely to fall somewhere between constant Tx effect estimates and maximum Tx effect estimates from the sensitivity analysis.

The administration cost of infliximab used in the current analysis was £94. Previous NICE appraisals have used administration costs ranging from £65.02-£124 (TAG 134). Cost variation in this range resulted in ICERs that were well within the acceptable threshold. The other important parameter affecting ICERs was the hospitalisation period following initiation of therapy. We used a mean hospital stay of 7 days based on the clinical trial information, UK IBD audit data and clinical expert opinion. The sensitivity analysis suggested that even with a change of 50% in the estimated hospital stay, infliximab remains cost effective compared to the alternatives.
Other parameters such as utility estimates and the complications rate had a much smaller impact on resulting ICERs.

The results of the PSA suggested infliximab to be cost effective with a willingness to pay as low as £16,000.

Figure 6.3.1: Cost effectiveness acceptability curve



6.3.4 Interpretation of economic evidence

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

As explained in section 6.1.1, our literature search failed to identify any published economic evaluation of infliximab in UC. Therefore, the current results cannot be compared with the published literature.

6.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

This economic evaluation is specific to UC patients hospitalised with an acute exacerbation. This patient group is a sub-population of infliximab's licensed population comprising of moderate to severe UC patients. Therefore, this economic evaluation is only applicable to the patient group described in the decision problem.

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

Strengths

1. Baseline disease progression as well as treatment efficacy was determined RCT evidence.
2. Utility and cost estimates in accordance with NICE's reference case and uncertainty around them addressed using multiple sets of estimates derived from literature and conducting a PSA.
3. All assumptions were developed in consultation with a panel of UK gastroenterologists.
4. Where data was not available, all assumptions used were conservative and adversely affect infliximab's case against competitors.

Weaknesses

1. Small sample sizes in RCTs on which the analysis is based.
2. Lack of formal measures of variance and likely distributions of certain model parameters such as post-surgery complications to inform probabilistic sensitivity analysis
3. Unavailability of resource use estimates for UC patients and therefore estimates used in the model are based on expert opinion.

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

1. Incorporate long term outcomes of infliximab beyond the clinical trial period

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document 'Guide to the methods of technology appraisal'.

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

The estimated annual budget impact is based on following information and assumptions:
Identifying eligible patients

- Estimated prevalence of UC is 150 per 100,000 and estimated incidence per year is 15 per 100,000 in UK population (Ref)
- Approximately 15% of eligible patients would suffer from severe attack sometime during the course of their UC (Edwards, 1963; Stenson, 1995)
- Assuming a disease course of 10 years prior to colectomy and atleast 2 incidences of UC attack during this time, proportion of patients suffering from a UC exacerbation per year is 3% (Jess, 2007)
- 2% of these patients are eligible for and are offered infliximab treatment (UK IBD audit 2006)

7.2 What number of patients were assumed to be eligible? How was this figure derived?

Estimated population of England and Wales – 53.7288 million (Mid 2006 estimate)
Current UC patient population – 80,593
Patients likely to suffer from acute attack during their lifetime – 12,089
Patients likely to suffer from acute attack per year – 2,418
Patients likely to receive infliximab - 48

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

- It was assumed that patients would experience on average 2 admissions for UC exacerbation during the course of their disease.
- Based on the current published estimates, it was assumed that only 2% of patients admitted for an exacerbation would receive infliximab and this percentage was assumed to remain constant even after this appraisal.

7.4 What assumption(s) were made about market share (where relevant)?

Of the patients eligible and offered treatment in addition to their IV steroids, 60% would be receive ciclosporin, 20% would receive infliximab and remaining 20% would receive other treatments (UK IBD audit).

7.5 What unit costs were assumed? How were these calculated?

The following table illustrates the cost calculations of infliximab.

Drug	Unit cost	Dose and dosing schedule	Cost
infliximab	£419.62	1 vial 100mg Dose: 5mg/kg 60kg patient assumed 3 vials=£1,258.9 per infusion + £64 cost of administration Total cost/infusion = £1,322.9 Induction dose at Week 0, 2 and 6	Annual cost treatment = £3,968.9

7.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

The recommended dose is 5mg/kg. Infliximab is administered at weeks 0, 2 and 6 and is infused over a 2 hour period in an outpatient unit. It is expected that patients will the first dose in an inpatient setting and the following two doses in the outpatient setting. There is an associated mean cost of administration of £64 per infusion. This administration cost has been included in the cost calculations above.

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

Based on the results of clinical trials it was assumed that infliximab use results in 44% fewer colectomies during the first 3 months. The estimates of resource savings has been investigated in the cost effectiveness analysis.

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

No other resource saving opportunities have been identified.

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9 Appendices

9.1 Appendix 1

A hyperlink to the Summary of Product Characteristics is provided below.

9.2 Appendix 2: search strategy for section 5

9.2.1 The specific databases searched and the service provider used.

MEDLINE (PubMed), EMBASE (Ovid), and the Cochrane Library were searched using a combination of free text and MeSH terms.

9.2.2 The date on which the search was conducted.

The searches were conducted on the 18th of February 2008.

9.2.3 The date span of the search.

Date restrictions were not entered in the search interfaces. However, since online portals to the MEDLINE, EMBASE and Cochrane Library databases may vary in respect of the date-range of evidence they contain, our search is best replicated by using the same interfaces we have used. Namely PubMed for MEDLINE, Ovid for EMBASE and the Cochrane Collaboration's own online search library.

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

No design or methodological filters were used in order to detect both RCTs and non RCTs. References of retrieved studies and relevant systematic reviews were checked for additional references; no other hand searching was undertaken.

Table 9.2.4.1 Search strategy for infliximab studies

Database	Date restrictions	Search string
Medline (PubMed) Date searched: February 2008	None applied	#1 "Colitis, ulcerative"[MeSH] OR ulcerative colitis #2 (severe OR acute) AND ("Colitis, ulcerative"[MeSH] OR ulcerative colitis) #3 "infliximab"[substance] OR infliximab OR remicade #4 "tumor necrosis factor-alpha"[MeSH] OR tumor necrosis factor alpha #5 TNF-alpha OR TNF alpha OR anti-TNF-alpha OR anti TNF OR anti TNF alpha OR TNFA #6 (#1 OR #2) #7 (#3 OR #4 OR #5) #8 (#6 AND #7) #9 Limit #8: human, all adult: 19+ years
EMBASE Date searched: February 2008	None applied	#1 ulcerative colitis.mp. #2 ulcerative colitis – map to subject heading and explode #3 infliximab or remicade.mp. #4 tumor necrosis factor alpha.mp. #5 tumor necrosis factor alpha – map to subject heading and explode #6 (TNF-alpha OR TNF alpha OR anti-TNF-alpha OR anti TNF

		OR anti TNF alpha OR TNFA).mp. #7 (#1 OR #2) #8 (#3 OR #4 OR #5 OR #6) #9 (#7 AND #8) Limits: human, adult <18 to 64 years> or aged <65+ years>
Cochrane Library (Issue 1, 2008)	None applied	#1 MeSH descriptor "colitis, ulcerative" – explode all trees #2 ulcerative colitis #3 infliximab or remicade #4 tumor necrosis factor alpha #5 MeSH descriptor "Tumor Necrosis Factor-alpha" - explode all trees #6 TNF-alpha OR TNF alpha OR anti-TNF-alpha OR anti TNF OR anti TNF alpha OR TNFA #7 (#1 OR #2) #8 (#3 OR #4 OR #5 OR #6) #9 (#7 AND #8)

Table 9.2.4.2 Search strategy for ciclosporin studies

Database	Date	Search string
MEDLINE (Pubmed)	No date restrictions	#1 "Colitis, ulcerative"[MeSH] OR ulcerative colitis #2 "cyclosporin"[substance] OR cyclosporine OR Neoral OR Sandimmune OR Gengraf #3 "randomized controlled trial"[publication type] OR "clinical trials"[MeSH] OR "randomized controlled trials"[MeSH] #4 clinical AND trial* #5 random* #6 (#3 OR #4 OR #5) #7 (#1 AND #2 AND #6)
EMBASE (Ovid)	No date restrictions	#1 cyclosporin - map to subject heading and explode #2 cyclosporin.mp #3 (1 OR 2) #4 colitis, ulcerative – map to subject heading and explode #5 ulcerative colitis.mp #6 (4 OR 5) #7 clinical trials - map to subject heading and explode #8 controlled clinical trials - map to subject heading and explode #9 randomized controlled trial - map to subject heading and explode #10 random$ #11 (#7 OR #8 OR #9 OR #10) #12 (#3 AND #6 AND #11)

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

The license holder, Centocor, was contacted by Schering-Plough with a request to search the company databases for any relevant ongoing trials. None were identified outside those revealed by our search of clinicaltrials.gov.

9.2.6 The inclusion and exclusion criteria.

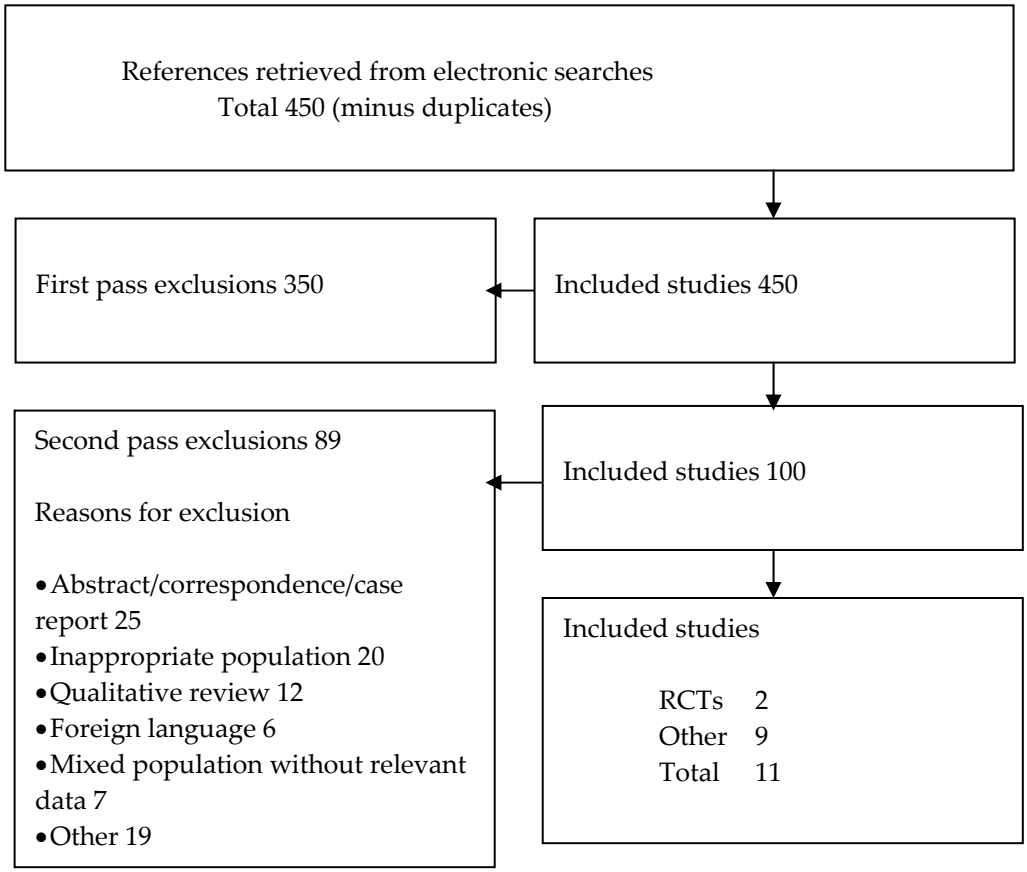
Criteria for inclusion in this assessment are presented in Table 9.2.6.1 below. Papers not matching all points as shown were excluded. Excluded papers are listed in the Appendix.

Table 9.2.6.1 Inclusion criteria

Population
o Al of the following ▪ Adult patients ▪ Acute severe UC refractory, intolerant or contraindicated to standard treatment (including corticosteroids, 6-mercaptopurine, azathioprine) ▪ Hospitalised
Intervention
o Infliximab Or o Ciclosporin
Comparator
o Standard clinical treatment options (including surgery), Ciclosporin, or placebo
Design and status
o At least one of: ▪ Systematic review ▪ RCTs (with appropriate comparator) ▪ Non RCTs (observational studies) o Published in full (single case reports, abstracts, letters, correspondence were excluded) o English language

Infliximab selection

Electronic searches and handsearching of reference lists identified 450 references that were downloaded into a local reference management programme (EndNote). The combined reference list was then queried using the terms 'severe', 'acute', and 'rescue', as well as being manually reviewed. Over 300 references were excluded on the basis of a clearly irrelevant title. One hundred and fifteen studies were reviewed in detail and 56 retrieved in full; 88 were excluded. The most common reason for exclusion was being an abstract, correspondence, or single case report. The second most frequent reason for exclusion was the use of an inappropriate patient population (e.g., mild or moderate disease, paediatric or steroid-dependent patients). The figure following provides an overview.



Ciclosporin selection

Three systematic reviews of ciclosporin for UC were identified (Pham 2006, Garcia-Lopez 2005, Shibolet 2005). One systematic review was in Spanish and was not retrieved (Garcia-Lopez 2005); the English abstract indicates that 31 studies were included, 22 (18 uncontrolled, 4 controlled) with intravenous cyclosporine, and 9 (all uncontrolled) using oral ciclosporin.

The review by Pham et al (2006) failed to provide sufficient information on the methods of searching or of inclusion or exclusion criteria applied but also reported four controlled trials; three fully published studies (D'Haens 2001, Lichtiger 1994, Van Assche 2003) and a fourth study available only as an abstract (Svanoni 1998). Pham et al (2006) also report an unspecified number of uncontrolled trials. Excluded studies and/or reasons for exclusion were not documented.

A Cochrane review was published in 2005 (Shibolet) and included two randomised controlled trials (D'Haens 2001, Lichtiger 1994). Five randomised controlled trials were excluded (Van Assche 2003, Svanoni 1998, Kornbluth 1994, Sandborn 1994, Van Assche 2002); two studies did not recruit patients with severe steroid refractory UC (Kornbluth 1994, Sandborn 1994), one study was only available as an abstract, was unblinded, and did not include a placebo arm (Svanoni 1998), and two studies tested two doses of cyclosporine again without placebo (Van Assche 2003, Van Assche 2002).

9.2.7 The data abstraction strategy

Data were abstracted by a single reviewer into a standardised data extraction sheets and used to populate the summary tables of all types of study which are presented in the Appendices.

9.2.8 List of excluded studies

Actis GC, Pellicano R, Pinna-Pintor M, Rizzetto M: Rescue with infliximab and surgical outcomes for refractory ulcerative colitis. J Am Coll Surg 2007, 205(4):e3-4.
Letter

Actis GC, Pellicano R, Pinna-Pintor M, Rizzetto M: Rescue with infliximab and surgical outcomes for refractory ulcerative colitis.[comment]. Journal of the American College of Surgeons 2007, 205(4):e3-4.
Comment

Ainsworth MA, Brynskov J: [Anti-TNF-alpha antibody treatment of patients with active ulcerative colitis]. Ugeskr Laeger 2007, 169(9):789-791.
Review (Danish)

Akobeng AK: Infliximab for induction and maintenance therapy for ulcerative colitis. J Pediatr Gastroenterol Nutr 2006, 42(5):589-590.
Comment

Armuzzi A, De Pascalis B, Lupascu A: Infliximab in the treatment of steroid-dependent ulcerative colitis. Eur Rev Med Pharmacol Sci 2004, 8:231-233.
Inappropriate patient population (steroid-dependent)

Armuzzi A, Lupascu A, De Pascalis B: Infliximab in the treatment of glucocorticoid-dependent ulcerative colitis: a 54-week randomized methylprednisolone-controlled tria. Gastroenterology 2004, 128(Suppl. 2):W1008.
Inappropriate patient population (steroid dependent); Abstract

Arseneau KO, Sultan S, Provenzale DT, Onken J, Bickston SJ, Foley E, Connors Jr AF, Cominelli F: Do Patient Preferences Influence Decisions on Treatment for Patients With Steroid-Refractory Ulcerative Colitis? Clinical Gastroenterology and Hepatology 2006, 4(9):1135-1142
Markov modelling

Baudet A, Rahmi G, Bretagne AL, Gloro R, Justum AM, Reimund JM: Severe ulcerative colitis: present medical treatment strategies. Expert Opin Pharmacother 2008, 9(3):447-457.
Review

Becker JM, Prushik SG, Stucchi AF: Infliximab for ulcerative colitis. N Engl J Med 2006, 354(13):1424-1426; author reply 1424-1426.
Letter

Bermejo F, Lopez-Sanroman A, Hinojosa J, Castro L, Jurado C, Gomez-Beldal AB: Infliximab induces clinical, endoscopic and histological responses in refractory ulcerative colitis. Rev Esp Enferm Dig 2004, 96(2):94-101.
Case report (only 1/8 patients had acute steroid-refractory disease)

Bocker U: Infliximab in ulcerative colitis. Scand J Gastroenterol 2006, 41(9):997-1000.
Review

Caprilli R, Viscido A, Latella G: Current management of severe ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol 2007, 4(2):92-101.
Review

Carbonnel F: [Management of severe or corticosteroid resistant ulcerative colitis]. Gastroenterol Clin Biol 2007, 31(4):398-403.
Review (French)

Carter MJ, Lobo AJ, Travis SP: Guidelines for the management of inflammatory bowel disease in adults. Gut 2004, 53 Suppl 5:V1-16.
Review

Castro Fernandez M, Garcia Diaz E, Romero M, Galan Jurado V, Rodriguez Alonso C: [Treatment of steroid-refractory ulcerative colitis with infliximab]. Gastroenterol Hepatol 2003, 26(1):54-55.
Spanish

Castro Fernandez M, Garcia Romero D, Sanchez Munoz D, Grande L, Larraona JL: Severe ulcerative colitis and toxic megacolon resolved with infliximab therapy [5]. Revista Espanola de Enfermedades Digestivas 2007, 99(7):427-428.

Spanish; letter

Caviglia R, Ribolsi M, Rizzi M, Emerenziani S, Annunziata ML, Cicala M: Maintenance of remission with infliximab in inflammatory bowel disease: Efficacy and safety long-term follow-up. World Journal of Gastroenterology 2007, 13(39):5238-5244.
Mixed population + mild/moderate disease

Chey, WY. (2001). Infliximab for patients with refractory ulcerative colitis. Inflamm Bowel Dis. 7 Suppl 1: S30-3
Mixed population (hospitalised and non-hospitalised)

Chey WY, Shah A: Infliximab for ulcerative colitis. J Clin Gastroenterol 2005, 39(10):920; author reply 920.
Letter

Cottone M, Mocciaro F, Modesto I: Infliximab and ulcerative colitis. Expert Opin Biol Ther 2006, 6(4):401-408.
Review

D'Haens G: Infliximab for ulcerative colitis: finally some answers. Gastroenterology 2005, 128(7):2161-2164.
Letter

Diez M, Sanchez E, Garcia Lopez S, Arroyo MT, Gomollon F: [Infliximab therapy in ulcerative colitis: initial experience in two referral centers]. Gastroenterol Hepatol 2007, 30(8):449-453.
Spanish

Eidelwein A, Cuffari C, Abadom V, Oliva-Hemker M: Infliximab efficacy in pediatric ulcerative colitis. Inflamm Bowel Dis 2005, 11:213-218.
Inappropriate patient population (paediatric)

Evans RC, Clarke L, Heath P, Stephens S, Morris AI, Rhodes JM: Treatment of ulcerative colitis with an engineered humna anti-TNF antibody CDP571. Ailment Pharmacol Ther 1997, 11:1031-1035.
Inappropriate patient population (mild/moderate disease only)

Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, Bala M, Johanns J, Olson A, Hanauer SB: The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. The American journal of gastroenterology 2007, 102(4):794-802.
Inappropriate patient popuation (sub acute)

Fleisher M, Rubin S, Levine A: Infliximab in the treatment of steroid-naïve ulcerative colitis. Am J Gastroenterol 2001, 96(Suppl.):S291-292.
Inappropriate patient population (steroid-naive)

Flor MJ, Cisneros JM: Acute respiratory failure in a patient treated with infliximab. Enfermedades Infecciosas y Microbiologia Clinica 2005, 23(8):503-504.
Spanish; case report

Frenz M, Simmons J, Travis S, Jewell D: Treatment and re-treatment of severe ulcerative colitis with infliximab: a case study. Inflamm Bowel Dis Monitor 2002, 3:119-120.
Case study

Gavalas E, Kountouras J, Stergiopoulos C, Zavos C, Gisakis D, Nikolaidis N, Giouleme O, Chatzopoulos D, Kapetanakis N: Efficacy and safety of infliximab in steroid-dependent ulcerative colitis patients. Hepatogastroenterology 2007, 54(76):1074-1079.
Inappropriate patient population (steroid dependent)

Godart B, Beau P, Benchellal Z, Bumsel F, Metman E: Ulcerative enteritis associated with ulcerative rectocolitis: Setting in remission after infliximab treatment. Gastroenterologie Clinique et Biologique 2007, 31(1):88-90.
Letter

Gornet JM, Couve S, Hassani Z, Delchier JC, Marteau P, Cosnes J, Bouhnik Y, Dupas JL, Modigliani R, Taillard F et al: Infliximab for refractory ulcerative colitis or indeterminate colitis: an open-label multicentre study. Alimentary pharmacology & therapeutics 2003, 18(2):175-181.
Mixed population

Hanauer SB: Infliximab or cyclosporine for severe ulcerative colitis. Gastroenterology 2005, 129(4):1358-1359; author reply 1359.

Letter

Hassan C, Zullo A, De Francesco V, Campo SM, Morini S, Panella C, Ierardi E: Tumor necrosis factor alpha in ulcerative colitis and diverticular disease associated colitis. Endocr Metab Immune Disord Drug Targets 2007, 7(3):187-194.
Review

Ierardi E, Della Valle N, Nacchiero MC, De Francesco V, Stoppino G, Panella C: Infliximab single administration followed by acute liver injury [2]. Inflammatory Bowel Diseases 2006, 12(11):1089-1090.
Letter

Ierardi E, Della Valle N, Nacchiero MC, De Francesco V, Stoppino G, Panella C: Onset of liver damage after a single administration of infliximab in a patient with refractory ulcerative colitis. Clinical Drug Investigation 2006, 26(11):673-676.
Case report (liver injury)

Jakobovits SL, Travis SP: Management of acute severe colitis. Br Med Bull 2006, 75-76:131-144.
Review

Jimenez JM: Infliximab in the treatment of severe ulcerative colitis. Rev Esp Enferm Dig 2004, 96(2):89-93.
Comment/editorial

Juillerat P, Christen-Zach S, Troillet F-X, Gallot-Lavallee S, Pannizzon RG, Michetti P: Infliximab for the treatment of disseminated pyoderma gangrenosum associated with ulcerative colitis: Case report and literature review. Dermatology 2007, 215(3):245-251.
Pyoderma gangrenosum treatment

Kaser A, Mairinger T, Vogel W, Tilg H. Infliximab in severe steroid-refractory ulcerative colitis: a pilot study. Wien Klin Wochenschr 2001, 113:930-3
Inappropriate patient population: met all inclusion criteria except that doesn't confirm that patients were hospitalised for treatment

Kaur N, Mahl TC: Pneumocystis jiroveci (carinii) pneumonia after infliximab therapy: A review of 84 cases. Digestive Diseases and Sciences 2007, 52(6):1481-1484.
Pneumocystis associated with infliximab use

Knigge K: Severe, steroid-refractory ulcerative colitis: Infliximab to the rescue? Evidence-Based Gastroenterology 2005, 6(4):110-111.
Comment

Kountouras J, Zavos C, Chatzopoulos D: Anti-tumor necrosis factor therapy for ulcerative colitis. Gastroenterology 2005, 129(3):1138-1139.
Letter

Lees CW, Shand AG, Penman ID, Satsangi J, Arnott IDR: Role of infliximab in ulcerative colitis: further questions [3]. Inflammatory Bowel Diseases 2006, 12(4):335-337.
Letter

Lichtenstein GR: Is infliximab effective for induction of remission in patients with ulcerative colitis? Inflamm Bowel Dis 2001, 7(2):89-93.
Comment

Ljung T, Karlen P, Schmidt D: Infliximab in inflammatory bowel disease: clinical outcome in a population based cohort from Stockholm County. Gut 2004, 53:849-853.
Mixed population

Lopez San Roman A, Van Domselaar M, Rivero M, Redondo C, Arribas R, Rey A: Complete remission of a primary rectal lymphoma on ulcerative colitis, after withdrawal of azathioprine and infliximab. Journal of Crohn's and Colitis 2008, 2(1):93-96.
Case report

Lupascu A, Armuzzi A, De Pascalis B, Carloni E, Lauritano EC, Pola P, Gasbarrini A: Sacroileitis and peripheral arthropathy associated with ulcerative colitis: Effect of infliximab on both articular and intestinal symptoms. Digestive and Liver Disease 2004, 36(6):423-425.

Case report

Mahadevan U, Terdiman JP, Aron J, Jacobsohn S, Turek P: Infliximab and semen quality in men with inflammatory bowel disease. Inflammatory bowel diseases 2005, 11(4):395-399.
Semen quality

Mamula P, Markowitz J, Brown K, Hurd L, Piccoli D, Baldassano R: Infliximab as a novel therapy for pediatric ulcerative colitis. J Pediatr Gastroenterol Nutr 2002, 34:307-311.
Inappropriate patient population (paediatric)

Mamula P, Markowitz J, Cohen L, von Allmen D, Baldassano R: Infliximab in pediatric ulcerative colitis: two-year follow-up. J Pediatr Gastroenterol Nutr 2004, 38:298-301.
Inappropriate patient population (paediatric)

Martin FDLML, Gisbert JP, Goiriz JFHR: Refractory and infected pyoderma gangrenosum in a patient with ulcerative colitis: Response to infliximab [5]. Inflammatory Bowel Diseases 2007, 13(4):509-510.
Letter

McGinnis J, Murray K: Infliximab for ulcerative colitis in children. J Pediatr Gastroenterol Nutr 2004, 39((Suppl. 1)):S282.
Inappropriate patient population (paediatric)

Mealy NE, Bayes M: Infliximab. Drugs of the Future 2005, 30(8):845-846.
To CHECK

Mocciaro F, Orlando A, Scimeca D, Cottone M: [Infliximab in moderate to severe steroid-dependent or steroid-refractory ulcerative colitis]. Recenti Prog Med 2007, 98(11):560-564.
Italian

Nos P, Hinojosa J: [Cyclosporine in ulcerative colitis flares]. Gastroenterol Hepatol 2005, 28(10):629-631.
Not infliximab, Spanish

Ochsenkuhn T, Sackmann M, Goke B: Infliximab for acute, not steroid-refractory ulcerative colitis: a randomized pilot study. Eur J Gastroenterol Hepatol 2004, 16(11):1167-1171.
Discusses treatment in patients contraindicated to conventional therapy but isn't stipulated as an inclusion criterion recruits steroid naïve (not steroid contraindicated)

Oliva-Hemker M, Roper S, Cuffari C, Leibowitz I: Infliximab therapy for pediatric ulcerative colitis. Gastroenterology 2002, 122:A616
Inappropriate patient population (paediatric); abstract

Papadakis KA, Treyzon L, Abreu MT, Fleshner PR, Targan SR, Vasiliauskas EA: Infliximab in the treatment of medically refractory indeterminate colitis. Aliment Pharmacol Ther 2003, 18(7):741-747.
Not Ulcerative Colitis

Pearce CB, Lawrance IC: Careful patient selection may improve response rates to infliximab in inflammatory bowel disease. J Gastroenterol Hepatol 2007, 22(10):1671-1677.
Mixed population (UC + IBD unclassified)

Peyrin-Biroulet L, Laclotte C, Roblin X, Bigard MA: Adalimumab induction therapy for ulcerative colitis with intolerance or lost response to infliximab: an open-label study. World J Gastroenterol 2007, 13(16):2328-2332.
Not infliximab

Prescott K, Costner M, Cohen S, Kazi S: Tumor necrosis factor-alpha inhibitor associated ulcerative colitis. Am J Med Sci 2007, 333(3):137-139.
Inappropriate patient population; not infliximab

Probert CS, Hearing SD, Schreiber S, Kuhbacher T, Ghosh S, Arnott ID, Forbes A: Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. Gut 2003, 52(7):998-1002.
Inappropriate patient population (patients with severe disease were excluded)

Quispel R, H.B. VDW, M. P, M.E. S, B. O: Fatal aseptic meningoencephalitis following infliximab treatment for inflammatory bowel disease. Gut 2006, 55(7):1056
Letter

Rizzello F, Gionchetti P, Venturi A, Campieri M: Review article: medical treatment of severe ulcerative colitis. Aliment Pharmacol Ther 2003, 17 Suppl 2:7-10.
Review

Rossetti S, Actis GC, Fadda M, Rizzetto M, Palmo A: The use of the anti-tumour necrosis factor monoclonal antibody--infliximab--to treat ulcerative colitis: implications and trends beyond the available data. Dig Liver Dis 2004, 36(6):426-431.
Review; checked for references

Ruiz P, San Salvador P, Ortiz de Zarate J, Cabezudo P, Marce L, Polo F, Blanco S, Orive V: [Infliximab as treatment for a severe outbreak of ulcerative colitis]. Gastroenterol Hepatol 2004, 27(7):430-431.
Spanish

Russell GH, Katz AJ: Infliximab is effective in acute but not chronic childhood ulcerative colitis. J Pediatr Gastroenterol Nutr 2004, 39(2):166-170.
Inappropriate patient population (paediatric)

Rutgeerts P, Feagan B, Olson A: A randomized placebo-controlled trial of infliximab therapy for active ulcerative colitis: Act I trial. Gastroenterology 2005, 128((Suppl. 2)):68.
Inappropriate patient population (ACT 1 trial); abstract

Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR et al: Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005, 353(23):2462-2476.
Inappropriate patient population (ACT 2)

Sandborn W, Feagan B, Olson A: A randomized placebo-controlled trial of infliximab therapy for active ulcerative colitis: Act I trial results through week 54. Am J Gastroenterol 2005, 100((Suppl)):S313.
Inappropriate patient population (ACT I); abstract

Sandborn W, Rachmilewitz D, Hanauer S: Infliximab induction and maintenance therpay for ulcerative colitis: the Act 2 trial. Gastroenterology 2005, 128((Suppl. 2)):688.
Inappropriate patient population (ACT 2); abstract

Sands BE, Kaplan GG: The role of TNFalpha in ulcerative colitis. J Clin Pharmacol 2007, 47(8):930-941.
Review

Schluender SJ, Ippoliti A, Dubinsky M, Vasiliauskas EA, Papadakis KA, Mei L, Targan SR: Does infliximab influence surgical morbidity of ileal pouch-anal anastomosis in patients with ulcerative colitis? Diseases of the Colon and Rectum 2007, 50(11):1747-1753.
Outpatient treatment only

Seiderer J, Goke B, Ochsenkuhn T: Safety aspects of infliximab in inflammatory bowel disease patients: A retrospective cohort study in 100 patients of a German University Hospital. Digestion 2004, 70(1):3-9.
Mixed population

Selvasekar CR, Cima RR, Larson DW, Dozois EJ, Harrington JR, Harmsen WS, Loftus EV, Jr., Sandborn WJ, Wolff BG, Pemberton JH: Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. J Am Coll Surg 2007, 204(5):956-962; discussion 962-953.
Mixed population and no relevant subgroup data presented

Serrano M, Schmidt-Sommerfeld E, Kilbaugh T, Brown R, Udall J, Mannick E: Use of infliximab in pediatric patients with inflammatory bowel disease. Ann Pharmacother 2001, 35(823-8).
Inappropriate patient population (paediatric)

Siegel CA, Bensen SP, Ely P: Should rare complications of treatment influence decision-making in ulcerative colitis? [1]. Inflammatory Bowel Diseases 2007, 13(2):242.
Letter

Sriram P, Reddy K, Rao G, Santosh D, Reddy D: Infliximab in the treatment of ulcerative colitis with toxic megacolon. Indian J Gastroenterol 2004, 23:22-23.
Case report

Su C, Salzberg B, Lewis J: Efficacy of anti-tumor necrosis factor therapy in patients with ulcerative colitis. Am J Gastroenterol 2002, 97:2577-2584.
Mixed population

Subramanian V, Pollok RCG, Kang J-Y, Kumar D: Systematic review of postoperative complications in patients with inflammatory bowel disease treated with immunomodulators. British Journal of Surgery 2006, 93(7):793-799.
Only Crohn's data for infliximab

Tan V, Bartlett M, Hosking P, Gibson PR: Annular purpura and ulcerative colitis: Response to infliximab. Digestive and Liver Disease 2007, 39(5):488-489.
Case report

Thukral C, Cheifetz A, Peppercorn MA: Anti-tumour necrosis factor therapy for ulcerative colitis: evidence to date. Drugs 2006, 66(16):2059-2065.
Review

Tissot B, Visee S, Pilette C, Prophette B, Puechal X: Lymphocytic meningitis with infliximab for ulcerative colitis [3]. Gastroenterologie Clinique et Biologique 2006, 30(12):1420-1422.
Letter

Truelove SC, Jewell DP: Intensive intravenous regimen for severe attacks of ulcerative colitis. Lancet 1974, 1(7866):1067-1070.
Not infliximab

Vespasiani Gentilucci U, Caviglia R, Picardi A, Carotti S, Ribolsi M, Galati G, Petitti T, Afeltra A, Cicala M: Infliximab reverses growth hormone resistance associated with inflammatory bowel disease. Alimentary pharmacology & therapeutics 2005, 21(9):1063-1071.
Growth hormone study

Viscido A, Habib FI, Kohn A, Papi C, Marcheggiano A, Pimpo MT, Vernia P, Cadau G, Caprilli R: Infliximab in refractory pouchitis complicated by fistulae following ileo-anal pouch for ulcerative colitis. Alimentary Pharmacology and Therapeutics 2003, 17(10):1263-1271.
Refractory pouchitis

Viscido A, Kohn A, Papi C, Caprilli R: Management of refractory fistulizing pouchitis with infliximab. European Review for Medical and Pharmacological Sciences 2004, 8(5):239-246.
Refractory pouchitis

9.3 Appendix 3: search strategy for section 6

The following information should be provided.

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

The search criteria were set deliberately wide as the preliminary search did not reveal relevant literature. The search terms used were 'Ulcerative colitis', 'Inflammatory bowel disease', 'Cost' and 'Economics' in combination with each other as described in section 9.3.4. No study met the inclusion criteria of full comparative economic evaluation. The databases searched are listed below.

Database	Time Span	Search strategy
Medline (PubMed)	1950 to date	Table 9.3.4.1
Medline (R) In Process	2000 to date	Table 9.3.4.2
EMBASE		Table 9.3.4.3
HTA	- to date	N/A
NHS EED	- to date	N/A

9.3.2 The date on which the search was conducted.

The initial search was conducted on 12th March 2007 and was repeated on 8th May 2007.

9.3.3 The date span of the search.

As outlined in section 9.3.1.

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

Table 9.3.4.1: Medline (PubMed) citations database Search Strategy

No.	Search term	Restrictions	Results
1	Ulcerative colitis	Unrestricted	21,652
2	Acute disease	Economics	26
3	2 and 3	Unrestricted	0
4	Inflammatory bowel disease or ulcerative colitis	Unrestricted	43,475
5	"Cost and cost analysis"	Unrestricted	4,808
6	1 and 5	Unrestricted	1
7	4 and 5	Unrestricted	1
8	Of 6 and 7 fitting the inclusion criteria	0	

Table 9.3.4.2: Medline In-Process and other non-indexed citations database Search Strategy

No.	Search term	Restrictions	Results
1	Ulcerative colitis	Unrestricted	21,653
2	Acute disease	Economics	26
3	2 and 3	Unrestricted	0
4	Inflammatory bowel disease or ulcerative colitis	Unrestricted	43,475
5	"Cost and cost analysis"	Unrestricted	4,808
6	1 and 5	Unrestricted	1
7	4 and 5	Unrestricted	1
8	Of 6 and 7 fitting the inclusion criteria	0	

Table 9.3.4.3: EMBASE citations database Search Strategy

No.	Search term	Restrictions	Results
1	Ulcerative colitis	Unrestricted	15,865
2	Acute disease	Economics	0
3	2 and 3	Unrestricted	0
4	Inflammatory bowel disease or ulcerative colitis	Unrestricted	65,000
5	"Cost and cost analysis"	Unrestricted	2,465
6	1 and 5	Unrestricted	2
7	4 and 5	Unrestricted	4
8	Of 6 and 7 fitting the inclusion criteria	0	

A broad search using the term "colitis" was conducted in NHS EED and HTA database. The search term resulted in 41 hits in NHS EED and 12 hits in HTA database. However, none of the hits met the inclusion criteria of full economic evaluation related to the decision problem.

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

No additional searches were conducted.

9.4 Appendix 4: List of UK experts consulted during this submission

Following is the list of UK gastroenterologists and health economists who supported development of this submission and provided their expert opinion as required. Of the name below, those who provided specific comments on the resource use are highlighted. Others provided general feedback on the disease, treatment pathway and place of comparators in current clinical setting.

Dr. Naila Arebi
St Marks Hospital, Northwick Park
Harrow Middlesex HA1 3UJ

Dr. James Lindsay
The Royal London Hospital, Whitechapel
London E1 1BB

Dr. Tim Orchard
St Mary's hospital, Pread Street,
Paddington, London W2 1NY

Dr. Simon Everett

Dr. Ian Arnott
Western General Hospital,
Crewe Road South, Edinburgh, EH4 2XU

Dr. Alan Lobo
Royal Hallamshire Hopsital,
Glossop Road, Sheffiled
South Yorks S10 2JF

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Frimley Park Hospital,
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Surrey GU16

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Dr. Stuart Bloom
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Prof. Owen Epstein
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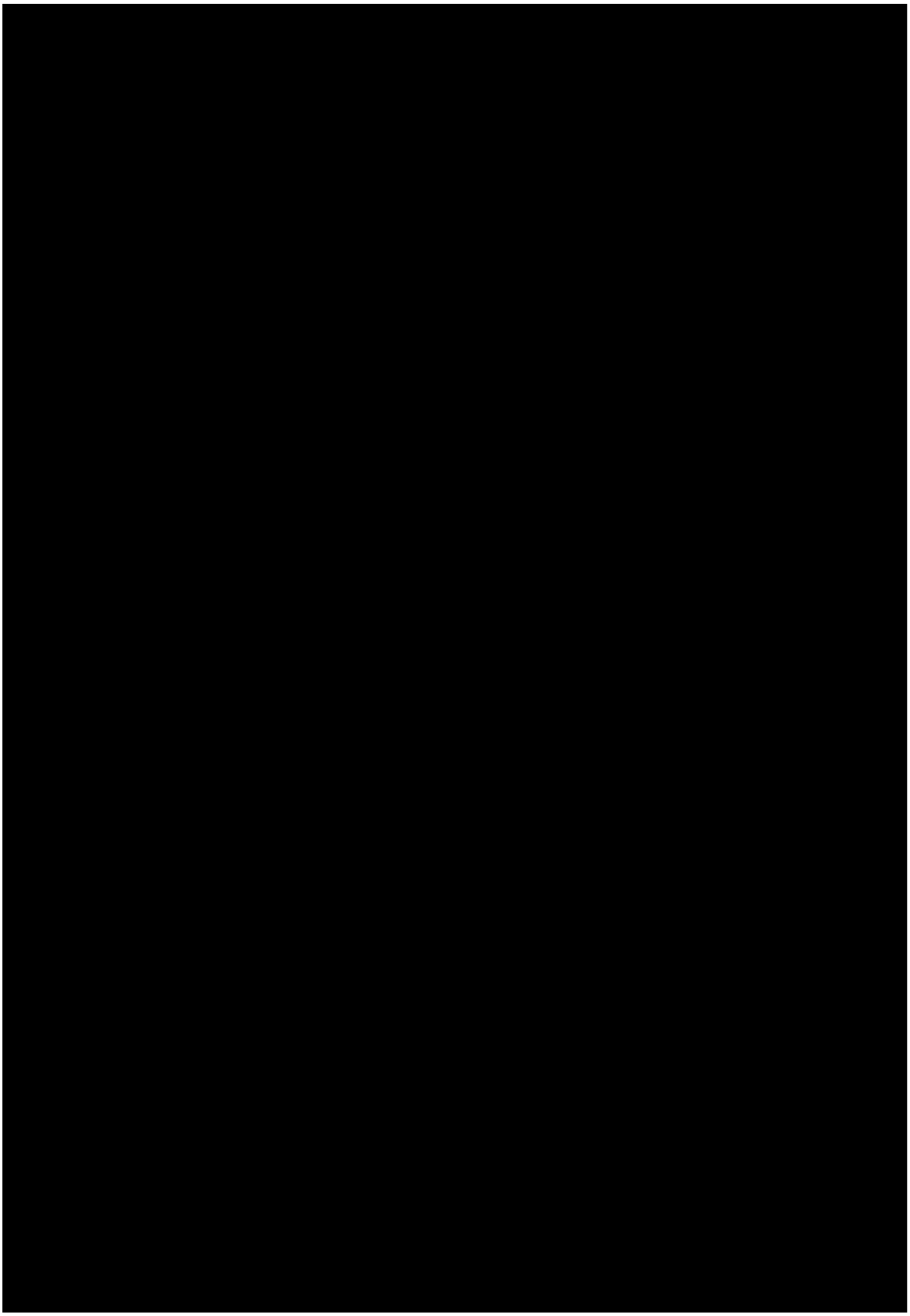
9.5 Appendix 5: Interpretation of infliximab's licence



9.6 Appendix: Indirect comparison methodology

Table 1. Study Data: Cumulative Probability of Colectomy at 3 and 12 months

Study	Placebo or Steroids	Infliximab	Ciclosporin
Colectomy at 3 months			
Järnerot 2005	14/21 (67%)	7/24 (29%)	-
Sands 2001	3/3 (100%)	0/3 (0%)	-
Lichtiger 1994	4/9 (44%)	-	3/11 (27%)
D'Haens 2001	3/15 (20%)	-	3/14 (21%)
Colectomy at 12 months			
Järnerot 2005	15/21 (71%)	10/24 (42%)	-
D'Haens 2001	6/15 (40%)	-	6/14 (36%)

The cost-effectiveness modelling was based on the estimated probability of colectomy for each treatment between 0 and 3 months and between 3 and 12 months (table 1). All the trials included placebo as common comparator. Jarnerot 2005 and D'Haens 2001 reported the cumulative number of colectomies at both 3 and 12 months, Lichtiger 1994 and Sands 2001 only reported results at 3 months.

As there were no trials directly comparing all relevant comparators, a network meta-analysis was conducted to allow the relevant comparators to be compared indirectly assuming that we can compare relative treatment effects, on a log-odds scale, across trials. For instance, treatments A & B can be compared based on trials comparing A & C and B & C, if we are able to assume that:

$$dAB = dAC - dBC$$

where dAB, dAC, and dBC are the differences in effects between treatments A & B, A & C, and B & C, respectively.
Independent estimates for the effects of treatment were made for the 0-3 and 3-12 month periods. The treatment effect estimated for the 3-12 month period is based on the probability of have a colectomy for those patients still at risk following the first three month period. The cumulative data reported in the trial was restructured to show the incremental results as illustrated in table 2 to facilitate the analysis.

Table 2: Analysis Data Set

Study	Treatment	Timepoint (months)	Number of Colectomies	Subjects at Risk
Jarnerot 2005	Placebo	3	14	21
	Infliximab	3	7	24
Sands 2001	Placebo	3	3	3
	Infliximab	3	0	3
Lichtiger 1994	Placebo	3	4	9
	Ciclosporin	3	3	11
D'Haens 2001	Placebo	3	3	15
	Ciclosporin	3	3	14
Jarnerot 2005	Placebo	12	1	7
	Infliximab	12	3	17
D'Haens 2001	Placebo	12	3	12
	Ciclosporin	12	3	11

A Bayesian hierarchical model was used to synthesise the relative treatment effects observed within the trials. The MTC model used Markov Chain Monte Carlo Methods (MCMC) and was based on those detailed in Lu et al 2007 [1].

Treatment Effect Model

The treatment effect model has a linear regression structure with the log odds ratio, $\log\left(\frac{p_i}{(1-p_i)}\right)$, for a trial arm i from study s at time point t having initially received treatment k being estimated as the sum of a study specific 'baseline' term $\mu_{s,t}$ and a treatment effect $\beta_{k,t}$:

$$\log\left(\frac{p_i}{(1-p_i)}\right) = \mu_{s,t} + \beta_{k,t}$$

Where $\beta_{1,\cdot}$=0 for placebo treatment and $\beta_{k,t}$ represents the log odds ratio for treatment k compared to placebo.

Likelihood for binary data

The observed number of colectomies r_i from n_i subjects at risk included in the model using a binomial likelihood where the probability of response is p_i from the previous equation.

$$r_i \sim Bin(F(t)_i, n_i)$$

Priors

The prior for the study specific baseline was $\mu_{s,\cdot} \sim N(0,10^6)$. The use of a vague prior for the study baseline ensures that the estimates of treatment effect are informed by the relative treatment effects within trials and not by the difference in the absolute response rates between trials. The treatment effect was modelled as a fixed effect with a prior $\beta_{k,\cdot} \sim N(0,10^6)$ and $\beta_{1,\cdot} = 0$ (representing placebo)

Implementation

The analysis was conducted using WinBUGS 1.4 (Medical Research Council Biostatistics Unit, Cambridge, UK). The WinBUGS code is included in the Appendix.

Results

The predicted log-Odds ratios from the analysis are shown in table 3. The confidence intervals are particularly wide for the 3-12 month time period as there were relatively little data available for this period, only 7 subjects were at risk in the Janerot 2005 placebo arm.

Table 3: Log-Odds Ratios of Colectomy compared to Placebo

Treatment	Timepoint	Mean	SD	2.5% CI	97.5% CI
Infliximab	0-3 Months	-2.07	0.66	-3.40	-0.82
Infliximab	3-12 Months	0.65	1.55	-2.03	4.01
Ciclosporin	0-3 Months	-0.33	0.69	-1.70	1.01
Ciclosporin	3-12 Months	0.12	1.02	-1.92	2.16

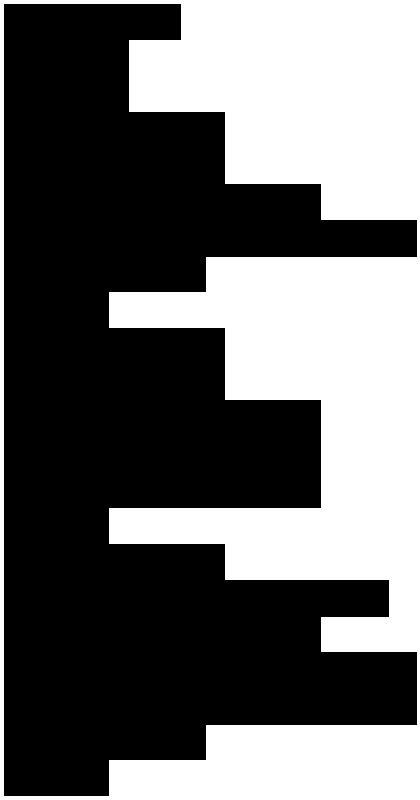
The predicted probabilites are shown in table 4. The placebo arm of the Janerot 2005 study was used to provide the baseline log-odds as this study included the technology of interest and reported at both 3 and 12 months. Using this study for the baseline allows the predicted probabilities from the analysis to be directly compared to the study.

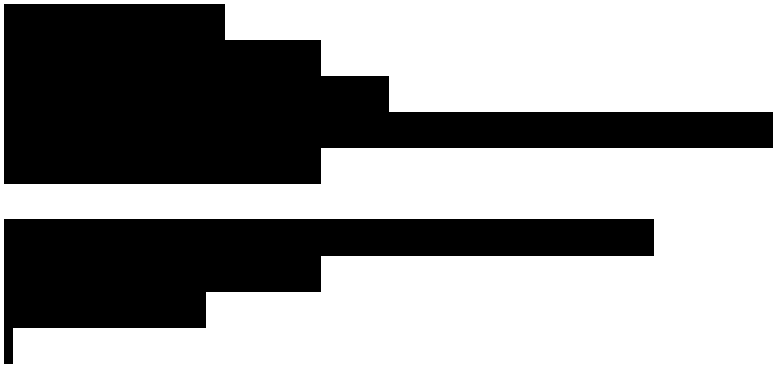
Table 4: Predicted Probabilities of Colectomy

Treatment	Timepoint	Mean	SD	2.5% CI	97.5% CI
Placebo	0-3 Months	0.67	0.10	0.46	0.85
Placebo	3-12 Months	0.14	0.12	0.00	0.47
Infliximab	0-3 Months	0.23	0.13	0.05	0.56
Infliximab	3-12 Months	0.27	0.27	0.00	0.92
Ciclosporin	0-3 Months	0.58	0.18	0.22	0.88
Ciclosporin	3-12 Months	0.18	0.19	0.00	0.70

The predicted posterior distribution was used in the final model to ensure that the correlations between the predicted probabilities for each treatment were captured.

[1] G. Lu, A. E. Ades, A. J. Sutton, N. J. Cooper, A. H. Briggs, and D. M. Caldwell. Meta-analysis of mixed treatment comparisons at multiple follow-up times. Stat Med, 26(20):3681–3699, Sep 2007.





9.7 Appendix 7: Details of considered systematic reviews

Objective	Search strategy	Inclusion criteria and included trials	Data synthesis and results	Quality/validity assessment
Lawson et al. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2006, 3:CD005112				
Objective: To evaluate the efficacy of infliximab for the induction of remission in ulcerative colitis and associated adverse events	MEDLINE (1966 to 2005) EMBASE (1984 to 2005) Cochrane Central Register of Controlled Trials (Issue 3, 2004) Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group Specialised Trial Register No language restrictions (#1 ulcerative colitis, #2 ulcerative colitis [MeSH], #3 colitis, #4 colitis [MeSH], #5 inflammatory bowel disease. #6 inflammatory bowel disease [MeSH], #7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6), #8 anti tumour necrosis factor OR anti tumor necrosis factor, #9 tumour necrosis factor alpha OR tumor necrosis factor alpha, #10 tumour necrosis factor antibod* OR tumor necrosis factor antibod*, #11 anti tumour necrosis factor antibod* OR anti tumor necrosis factor antibod*, #12	Population: patients with ulcerative colitis (any age) Intervention: infliximab Comparator: placebo or steroids Design: RCTs only 5 RCTs compared infliximab with placebo[1-4] 2 RCTs compared infliximab with steroids [5 6]	Review Manager 4.2 (Cochrane Collaboration) was used for data analysis. ITT principles were applied, missing values were assumed to denote a poor outcome. Dichotomous variables: Relative risk (RR) and 95% confidence intervals based on a fixed effects model and number needed to treat Continuous variables; weighted mean difference (WMD) and 95% confidence intervals Heterogeneity was assessed by inspection of graphical data and by calculating the chi squared statistic for heterogeneity. The I^2 was also calculated. Publication bias and subgroup analyses were not assessed due to too few trials being available. Sensitivity analyses were conducted based on random v fixed effect models.	Oxford scale[7] Cochrane criteria [8]

anti TNF OR anti TNF alpha, #13 TNF antibod* OR TNF alpha antibod*, #14 anti TNF antibod* OR anti TNF alpha antibod*, #15 infliximab OT monoclonal antibody cA2 OR Remicade, #16 CDP571, #17 etanercept, #18 adalimumab, #19 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18, #20 random*, #21 clinical trial, #22 clinical trial [MeSH], #23 blind OR placebo, #24 research OR design, #25 controlled clinical trial [MeSH], #26 randomised controlled trial OR randomized controlled clinical trial [MeSH], #27 random allocation [MeSH], #28 clinical protocol [MeSH], #29 placebo [MeSH], #30 double blind method [MeSH], #31 single blind method [MeSH], #32 research design [MeSH], #33 (#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32), #34 (#7 AND #19 AND #33)

Infliximab versus placebo

Clinical remission (8 weeks) based on 2 studies RR 3.22 (2.18-4.76), NNT=5 with significant heterogeneity I^2=71.6%. Using a random effects model did not make a significant difference to results or when a subgroup analysis was performed on patients receiving 5mg/kg.

Endoscopic remission/mucosal healing (8 weeks) based on 2 studies RR 1.88 (1.54-2.28), NNT=4, no significant heterogeneity.

Clinical response based on 2 studies RR 1.99 (1.65-2.41), NNT=4. Chi-squared test for heterogeneity not significant but I^2=44.7%. Applying random effects model made no significant difference

Treatment success based on 1 study RR 4.0 (0.28-57.98) no statistically significant difference

Colectomy based on 1 study RR 0.44 (0.22-0.87), a significant reduction

Quality of life based on 1 study WMD 11.0 (11.84-33.84) no significant difference

Infliximab versus prednisolone

Clinical remission based on 1 study RR 0.7 (0.28-1.77), no significant difference

Endoscopic remission based on 1 study RR 0.88 (0.31-2.44) no significant difference

			Treatment success based one 1 study RR 0.97 (0.61-1.55) Infliximab versus methylprednisolone Clinical remission based on 1 study – all patients achieved remission in both groups	
Gisbert JP, Gonzalez-Lama Y, Mate J: Systematic review: Infliximab therapy in ulcerative colitis. Ailment Pharmacol Ther 2007, 25:19-37				
Objective: review the efficacy and safety of infliximab for ulcerative colitis compared with placebo or steroids	Cochrane Library Issue 4, 2005 MEDLINE EMBASE CINAHL ISI Web of Knowledge (to January 2006) (Infliximab OR anti-tumor necrosis factor OR tumor necrosis factor OR tumor necrosis factor antibody) AND ulcerative colitis No language restrictions Manual search of abstracts from American Digestive Disease Week (UEGW) and United European Gastroenterology Week (UEGW) 2000 - 2005	Population: patients with ulcerative colitis (any age) Intervention: infliximab Comparator: placebo or steroids Design: for meta-analysis studies had to be randomised and include placebo or steroids as a control Studies were also required to have clear information on patient numbers and data reported separately for each therapy (unclear if a condition for RCTs	Mean percentage of response/remission was calculated and expressed as weighted mean (and corresponding 95% CI). Homogeneity was assessed using a test based on the chi squared test, due to low power of this test a minimum cut-off of P=0.1 was established as a threshold for significant heterogeneity. The I^2 statistic was also calculated. Meta-analysis was performed combining odds ratios of individual studies using a fixed effects model (Peto method) when heterogeneity was not significant, or a random effects model (DerSimonian and Laird) when results were heterogeneous. Significance and 95% CI along with number needed to treat (NNT) were calculated. The OR for the occurrence of adverse events and number needed to harm (NNH) was also calculated. Review Manager 4.2.8 developed by the Cochrane Collaboration was used.	Oxford scale[7] Quality scoring undertaken independently by two reviewers with disagreement resolved by consensus

or all studies)		
34 studies included; 5 RCTs compared infliximab with placebo[1-4]; 2 RCTs compared infliximab with steroids[5 6]		A priori subgroup analyses in the systematic review were planned for the age of patients (children or adult), indication (coricorefratory or corticodependent), dose, and number of infusions after remission. For meta-analysis sensitivity analyses were planned for control group (placebo or steroids), dose, and Oxford quality score. Weighted mean short-term response (partial or complete) and remission (complete response only) with infliximab was 68% (95% CI 65-71%) and 40% (95% CI 36-44%) respectively. Weighted mean long term response and remission was 53% (95% CI 49-56) and 39% (95% CI 35-42) Infliximb versus placebo (RCTs only): Short term response: 65% (61-69%) with infliximab v 33% (27-38%) with placebo; OR 3.6 (2.67-4.95), p<0.001, with no statistically significant heterogeneity. NNT 3 (3-4). Short term remission: 33% (29-37) with infliximab v 10% (6.4-14) with placebo; OR 4.56 (1.98-10.5), p<0.001, significant heterogeneity p=0.09 and I^2=66%. NNT 4 (3-6). Long term response: 53% (49-58) with infliximab v 24% (19-29%) with placebo; OR

			3.4 (2.52-4.59), p<0.001,with no statistically significant heterogeneity. NNT 3 (3-4) Long term remission: 33% (29-37%) with infliximab v 14% (9-18%) with placebo; OR 2.72 (1.92-3.83), p<0.001, with no statistically significant heterogeneity. NNT 5 (4-7) Adverse events 83% (80-86%) with infliximab v 75% (70-81%) with placebo; OR 1.52 (1.03-2.24), p=0.04, borderline heterogeneity p=0.12 and I^2=48%. NNH 14 (5-25) Sensitivity analyses results not extracted	
Rahimi et al Meta-analysis technique confirms the effectiveness of anti-TNF-alpha in the management of active ulcerative colitis when administered in combination with corticosteroids. Med Sci Monit 2007, 13(7):PI13-18				
Objective: to determine whether infliximab induces clinical reponse and remission in patients with ulcerative colitis	PubMed EMBASE 1966 to Sept 2006 ulcerative colitis, infliximab, anti tumor necrosis factor(s) Retrieved articles reviewed independently by 3 reviewers, data extraction also done by 3 reviewers. Disagreement resolved by consensus	Population: patients with ulcerative colitis (any age) Intervention: infliximab Comparator: placebo Design: RCTs only 5 studies included[1-4]	Data were extracted into 2x2 tables and was pooled and weighted. The odds ratio with 95% confidence intervals was calculated using a random effects model (using DerSimonian-Laird methods). The Breslow-Day test was used to test for heterogeneity. Four trials provided data for clinical response with infliximab versus placebo. Clinical remission with infliximab was 33% (175/522) and 12% (33/270) with placebo OR 3.24 (95% CI 1.6 – 6.57); p=0.0011	None applied

Breslow-Day test for heterogeneity p=0.0991

Three trials provided data for clinical response with infliximab versus placebo. Clinical response with infliximab was 66% (324/492) and 33% (81/247) with placebo

OR 3.93 (95% CI 2.84 – 5.45); p=0.0001

Breslow-Day test for heterogeneity p=0.4267

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1. Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlen P, Granno C, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology*. 2005/06/09 ed, 2005:1805-11.
2. Probert CS, Hearing SD, Schreiber S, Kuhbacher T, Ghosh S, Arnott ID, et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut*. 2003/06/13 ed, 2003:998-1002.
3. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005/12/13 ed, 2005:2462-76.
4. Sands BE, Tremaine WJ, Sandborn WJ, Rutgeerts PJ, Hanauer SB, Mayer L, et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. *Inflammatory bowel diseases*, 2001:83-8.
5. Ochsenkuhn T, Sackmann M, Goke B. Infliximab for acute, not steroid-refractory ulcerative colitis: a randomized pilot study. *Eur J Gastroenterol Hepatol*. 2004/10/19 ed, 2004:1167-71.
6. Armuzzi A, De Pascalis B, Lupascu A. Infliximab in the treatment of steroid-dependent ulcerative colitis. *Eur Rev Med Pharmacol Sci*, 2004:231-3.
7. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17(1):1-12.
8. Higgins JPT, Green S. 6. Assessment of study quality. *Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]*. Chichester, UK: John Wiley & Sons, Ltd, 2006.

9.8 Appendix 8: Details of included RCTs

Methods	Participants	Statistics	Outcomes
Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlen P, Granno C, Vilien M, Strom M, Danielsson A, Verbaan H et al: Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005, 128:1805-1811			
Design: R, DB, parallel group trial of infliximab or placebo in acute severe or moderately severe UC unresponsive to conventional treatment Duration: 3 months Location: 9 Swedish and 1 Danish centre (covering 7 hospital regions) Sponsorship: Swedish Federation of County Councils, Orebro County Research Foundation, Schering-Plough AB Sweden, Orebo University Hospital, Medical Research Council of Southeast Sweden, Foundation of Medical Science Region 3, Denmark (Grant 2-47-19-02), and participating hospitals. Randomisation and blinding: A local randomisation list was placed in one pharmacy per region. Randomisation was performed in blocks of 4 and known only by the statistician. Patients to be treated were reported to the pharmacy with their birth date, name, and weight, for correct dosing. Preparation of the solution for infusion was performed in pharmacy and delivered to the ward to blind the investigator Dosage: All patients received infliximab in addition to a standard betamethasone treatment. Day 0, IIVT with betamethasone 4mg IV twice daily. No rectal treatment was given. Once randomised to placebo/infliximab, a dose as close as possible to 5mg/kg was given as a slow infusion Other medication: When switching to oral treatment, prednisolone 40mg daily was given with a reduction of 5mg/day per week. Maintenance with a meslamine-based drug was started or continued. Azathioprine 1.5-2mg/kg could be added at the investigator's discretion. Trimethoprim 160mg and sulfamethoxazole 800mg was prescribed daily for 8 weeks	Population: Only patients with a definite or strong suspicion of UC were screened for inclusion Inclusion criteria 18-75 yrs of age Diagnosis of certain/probable UC verified by clinical history, appearance on endoscopy, and exclusion of infectious causation At hospitalisation, a severe or moderately severe attack according to the SEO index A fulminant colitis index ≥8.0 on day 3 of IIVT or a SEO index on day 5, 6, or 7 compatible with a severe or moderately severe attack of UC not responding to corticosteroids Exclusion criteria <18 or >75 yrs of age Pregnancy or planned pregnancy within 12 months Breastfeeding unless it was stopped Known or probable Crohn's colitis, infectious colitis, ongoing infection (abscess, central line infection, febrile urinary tract infection, active tuberculosis or exposure to tuberculosis A pulmonary radiograph was to precede treatment; signs of past tuberculosis or a primary complex warranted prophylactic treatment was given PPD tests were not performed Multiple sclerosis, malignancy, heart failure or treated heart failure, earlier treatment with infliximab or another antibody, another disease according to the investigator's judgement, psychiatric disease, alcoholism, or anything else whereby the patient was judged incapable of completing the trial resulted in exclusion Baseline Demographics:	Groups: Forty-five patients were randomised: 24 to infliximab and 21 to placebo. Analyses were conducted on an intention-to-treat basis and included all 45 patients. Power: On the basis of published results, it was assumed that 35% in the infliximab group and 60% in the placebo group would have a colectomy. Seventy patients in each group would provide a statistical power of 80% and a significance level at 5%. It was planned that interim analysis would be performed and that the future of the study would be decided after 70 patients had been treated. The inclusion time was calculated as 1.5–2 years. Analysis: Categorical data were analyzed with the Fisher exact test (2-sided). The log-rank test, paired t test (2 sided), and logistic regression analysis were also used as appropriate. Because this was an interim analysis, to reduce the risk of false- positive findings and to keep the overall significance level at 5%, a statistically significant P value should be <.029 instead of .05.	Primary endpoint: Colectomy or death within 90 days after infusion Secondary endpoints: Clinical remission according to the Seo index Mucosal healing 1 and 3 months after infusion

as protection against opportunistic infection. Safety: States that all patients were monitored on a daily basis by the gastroenterologist and surgeon, and that decisions about continued medical treatment or emergency colectomy were made as required.	Imbalance between "male/female" and "earlier known UC/first attack of UC", males and pre-existing UC more frequent in the infliximab arm Placebo (n= 21) versus Infliximab (n = 24) Male/female 8/13 16/8 Age, y, mean (range) 36.2 (19–61) v 37.5 (20–60) Smokers 2 v 0 Earlier known UC/first attack of UC 12/9 v 21/3 Extent of UC, total/extensive/distal 10/8/3 v 9/9/6 Seo index, day 0, mean (SD) 218 (30) v 212 (30) Included on fulminant colitis/Seo index 13/8 v 15/9 Fulminant colitis index, mean (range) 13.1(8.1– 25.3) v 12.7 (8.1–22.5) Seo index, mean (range) 195 (158–230) v 196 (155–225) Endoscopy at inclusion, severe/moderately severe inflammation 6/15 v 9/15 Hb, g/L, median (range) 119 (71–157) v 130 (63–165) Thrombocytes, 109/L, median (range) 444 (252–1131) v 381 (154–763) Albumin, g/L, median (range) 32 (16–48) v 31 (15–48) CRP, mg/L, median (range) 44 (8–324) v 65 (5–296)	
Results – Primary Significantly more patients in the placebo group 14/21 (67%) than in the infliximab group 7/24 (29%) underwent a colectomy (P=0.17), OR 4.9 (95% CI 1.4 – 17) Median time to colectomy after infusion was 8 days (range, 2 – 22 days) in the infliximab group and 4 days (range, 1 – 13 days) in the placebo group The cumulative proportion of patients not operated on after 90 days was 71% with infliximab and 33% with placebo (p=0.0038; log-rank test) Patients with a positive fulminant colitis index had a colectomy more frequently with placebo (69%) than infliximab	Results – secondary Clinical remission (both groups combined) Day 0 – Seo index 215 (SD 30) Day 30 – Seo index 108 (SD 20) Day 90 – Seo index 108 (SD 36) Endoscopic appearance was similar in both groups. 1 month (although some patients refused a new colonoscopy at this time point) 9 patients with severe disease at inclusion 4 had mild inflammation, 3 were in remission, and 2 moderately severe inflammation. 13 patients with moderately severe inflammation 5 were in remission, 5 had mild inflammation, 3 had moderately severe inflammation	Adverse events Death: No deaths occurred Adverse events: General – infliximab Central venous line scepticemia (n=1) Arthralgia, knee (n=2) Upper respiratory infection (n=2) Pneumothorax when adopting central venous line (n=1) Discrete exanthema, probably trimetoprim/sulphonamide (n=1) Pruritus during infusion (n=1) Perspiration day 30 (n=1) Postoperative – infliximab Long-lasting bleeding from rectal stump (n=1)

(47%) – p=0.276 Patients with less severe disease by the Seo index had no colectomies with infliximab and 62% with placebo – p=0.009 Patients with severe endoscopy had a colectomy more frequently with placebo (67%) than infliximab (22%) – p=0.136. Patients with moderately severe endoscopy had a colectomy more frequently with placebo (67%) than infliximab (33%) – p=0.143. Logistic regression showed that endoscopic appearance was not a confounder OR 4.8 (1.3-17) Despite randomisation more male patients and more patients with a first attack had been randomised to the placebo group, multivariate logistic regression analysis still showed results in favour of infliximab OR 5.7 (1.4-2.2) and OR 3.6 (1.0-1.37) respectively.	3 months: 6/15 infliximab patients and 2/6 placebo patients were in complete clinical and endoscopic remission	Ileus 48 days after infusion, probably mushroom related (n=1) Nausea, vomiting, abnormal liver tests, pneumonia (n=1+ Reflux, oral candidiasis (n=1) General – placebo Exanthema, probably trimetoprim/sulfamethoxazole (n=2) Epigastralgia, reflux, abnormal liver tests 50 days after infusion, probably azathiorpone (n=1) Headache, 38.5C 14 days after infusion, negative lumbar puncture (n=1) Ptosis, right eyelid, 32 days after infusion (n=1) Dermal sensations during infusion (n=1) Arthralgia 90 days after infusion (n=1) Cardiac pacemaker 111 days after infusion (n=1) Postoperative – placebo Reoperation due to septic complication-referable to rectal stump? (n=3) High fever, CRP >200 5 days after surgery, rectum flushed, normalisation (n=1) Urinary tract infection, fever, antibiotics (n=1)	

Methods	Participants	Statistics	Outcomes
Sands BE, Tremaine WJ, Sandborn WJ, Rutgeerts PJ, Hanauer SB, Mayer L, et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. Inflamm Bowel Dis. 2001:83-8			
Design: R, DB, parallel group trial of infliximab or placebo in severe UC unresponsive to steroids. Duration: 12 weeks Location: 6 centers (5 in the US and 1 in Belguim) Sponsorship: Unrestricted educational grant from Centocor Inc and a National Institutes of Health Mentored Patient-Oriented Research Career Development Award Randomisation and blinding: Patients were randomly assigned to receive a single intravenous infusion of placebo or infliximab 5, 10, or 20mg/kg (no details of methods of	Population: Between 18 and 65 years old Active UC of at least 2 weeks duration that had been diagnosed and documented by standard clinical, endoscopic, and histological methods Had received at least 7 days of corticosteroid therapy (>40 to <60mg/day prednisone equivalent), of which at least 5 days included intravenous administration Cyclosporine was not permitted within 3 months of enrolment Other medications including 5-aminosalicylates, antibiotics, 6-mercaptopurine, azathioprine, or antidiarrheal drugs, were permitted provided	Groups: Enrollment was terminated prematurely; 3 patients were randomised to placebo, 3 patients to infliximab 5mg/kg, 3 patients to 10mg/kg, and 2 patients to 20mg/kg Power: The study was designed to recruit 60 patients; however, enrolment was terminated prematurely because of slow accrual (11 patients were recruited in total) Analysis: Formal statistical analysis of results was not performed	Primary endpoint: treatment failure at 2 weeks after infusion (failure defined as: failing to achieve a clinical response as defined by a modified Truelove and Witts score of <10 and a 5-point reduction from baseline, if a patient received a dosage of >60mg/day corticosteroids or cyclosporine A or other immunomodulators due to worsening condition, if a patient underwent a nonelective or elective colectomy, if the patient died as a result of UC)

randomisation). Infusion bottles of infliximab solution were prepared at each study site according to assigned dose. Identical placebo was supplied in 20mL vials containing 0.1% human serum albumin. Dosage: Infliximab was supplied in vials as a sterile, non-pyrogenic solution of 100mg infliximab in 20mL of 0.15 sodium chloride, 0.001 M sodium phosphate pH 7.2, and 0.01% polysorbate 80. An appropriate volume of infliximab or placebo was withdrawn from the vial, filtered through a low protein-binding 0.22-uM filter and diluted to a final volume of 500mL with normal saline. Study medication was infused through a low protein-binding 0.22-uM inline filter over 3 to 4 hours. Other medication: Patients were permitted to receive sulfasalazine, mesalazine, antibiotics, azathioprine, 6-mercaptopurine, or antidiarrheal drugs at stable doses Physicians were allowed to alter medications for the benefit of the patient; however, changes that met criteria for treatment failure (addition of cyclosporine or other immunomodulators within 2 weeks of study infusion, or an increase in corticosteroid dosage) were to be considered treatment failures even if the patient's clinical status improved Safety: Safety evaluations during the study period included measurements of vital signs, haematology and clinical laboratory measurements, and occurrence of adverse experiences. All patients considered treatment failures continued to be monitored for safety	doses remained stable during the 2-week evaluation period All patients had severe, active UC as defined by Truelove and Witts classification of UC, all patients had a score >10 All patients had an endoscopic classification of moderately active or severe UC using the Blackstone scoring system Exclusion criteria Patients were excluded if UC was so severe that endoscopy was contraindicated, or if they had toxic megacolon, perforation of the colon, or disease that did not extend beyond the rectum All patients were tested for enteric stool infection and clostridium difficile and excluded for infection Baseline Demographics: Placebo Infliximab 5 mg/kg 10 mg/kg 20 mg/kg All patients (n = 3) (n = 3) (n = 3) (n = 2) (n = 11) Age (years) Mean ± SD 40.3 ± 16.0 43.7 ± 17.0 35.0 ± 3.5 . 38.0 ± 12.6 Median 39 37 37 . 37 Range 25–57 31–63 31–37 20–41 20–63 Gender Male 2 (66.7%) 2 (66.7%) 2 (66.7%) 2 (100%) 10 (90.9%) Female 1 (33.3%) 1 (33.3%) 1 (33.3%) 0 (0%) 1 (9.1%) Disease duration (years) Mean ± SD 4.0 ± 4.9 14.6 ± 18.8 3.8 ± 3.6 . 6.6 ± 10.3 Median 1.3 5.7 2.3 . 2.3 Range 1–9.7 2–36.2 1.3–7.9 0.9–4.1 0.9–36.2 Modified Truelove and Witts assessment score Mean ± SD 16 ± 3 13 ± 1 11 ± 0. 13 ± 3 Median 16 13 11. 12 Range 14–19 12–14 11–11 11–11 11–19 Endoscopic classification Moderately active (Grade 3) 2 (66.7%) 1 (33.3%) 1 (33.3%) 1 (50%) 5 (45.5%) Severe (Grade 4) 1 (33.3%) 2 (66.7%) 2 (66.7%) 1 (50%) 6 (54.5%	because of the small number of patients participating in the study	Secondary endpoints: Comparison of the individual components of treatment failure, change from baseline for the modified Truelove and Witts score, physician's and patient's global response evaluation, ESR, CRP levels, sigmoidoscopic ratings, and histological disease activity scores

Results – Primary	Results – secondary	Adverse events
Number of patients considered a treatment success at 2 weeks Placebo 0/3 (0%) Infliximab 4/8 (50%) – 2 at mg/kg, 1 at 10mg and 20mg/kg Infliximab non-responders: 2 did not meet modified Truelove and Witts criteria for response (1 received 10mg/kg and the other 20mg/kg), 1 patient received an increased corticosteroid dose and subsequent cyclosporine (5mg/kg), and 1 patient underwent elective colectomy (10mg/kg). Placebo nonresponders: 3/3 of the placebo patients underwent colectomy by 2 week evaluation (1 elective, 2 nonelective). 5/8 infliximab patients demonstrated a >5 point decrease from baseline in modified Truelove and Witts scores at more than 1 evaluation visit. 1 patient (20mg/kg) had a modified Truelove and Witts score of $\leq$4 and endoscopic assessments of quiescent disease – meeting criteria for the entire 12 week study period 1 patient (20mg/kg) did not meet criteria for response at week 2 but did meet criteria for clinical remission at week 6 Improvement was observed in 5/6 patients treated with infliximab who underwent sigmoidoscopic evaluations beyond the screening period	Decreases in ESR and serum levels of CRP correlated with improvement in modified Truelove and Witts score for patients treated with infliximb. Substantial variation was observed in serum TNFa concentrations in all patients treated with infliximab. Circulating concentrations of IL-6 were substantially decreased in all but 2 infliximab patients (IL-6 remained at baseline). Il-6 increased in patients treated with placebo.	Death: No patients died during the study Adverse events: All patients reported at least 1 adverse event during the study period. Most were mild or moderate in intensity. The most frequently reported adverse events in infliximab-treated patients were pruritus, headache, urinary tract infection (each occurring in 2 patients) Four patients reported five serious adverse events that required prolonged hospitalisation; one patient treated with placebo had a colectomy performed within 9 days of infusion due to worsening symptoms, another placebo patient was hospitalised 2 weeks following colectomy with decreased stoma output and ileus, one patient treated with infliximab 10mg/kg developed cellulites related to a skin wound, one patient treated with infliximab 20mg/kg developed a renal calculus. All serious adverse events resolved with appropriate treatment. No other adverse events associated with infusion were reported and no patients discontinued the infusion of study medication due to adverse events. No clinically significant abnormalities were reported in routine blood chemistries, urinalysis, haematologic parameters, or vital signs

Methods	Participants	Statistics	Outcomes
D'Haens G, Hertervig E, Friis-Liby I, Blomquist L, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology 2001, 120:1323-1329			
Design: R, DB, single-centre prospective study Duration: up to 12 months Location: single center in Belguim	Population: Inclusion criteria 18-70 yrs of age hospitalised with a severe attack of UC clinical activity score $\geq$ 10	Groups: overall 30 sequential patients presenting at emergency at outpatient clinics were recruited. 15 patients were each randomised to either cyclosporine or methylprednisolone. One patient in the cyclosporine group	Primary endpoint: Improvement in clinical-activity score Response was defined as a score of <10 on days 7 and 8

Sponsorship: NR Randomisation and blinding: Randomisation took place at the central hospital pharmacy. All infusion bags were covered, did not carry any reference to contents and were given with a titration pump. An independent physician not taking part in the care of the patients was aware of the treatment assignments and monitored blood cyclosporine concentrations (monitored everyday or more frequently if necessary), any dose adjustments were directly ordered to the pharmacist. Blinding ended on day 8. Dosage: Patients assigned to receive cyclosporine (Sandimmun; Sandoz, Basel, Switzerland) were given a continuous infusion of 4 mg/kg body wt per day in a 250-mL 0.9% NaCl infusion bag. The dose was adjusted to achieve blood cyclosporine concentrations of between 250 and 450mg/mL. Patients assigned to receive glucocorticosteroids were given 40 mg methylprednisolone (50 mg prednisone equivalent; Solumedrol; Upjohn, Puurs, Belgium) per day, also in 250 mL 0.9% NaCl. Both were administered as a single IV infusion over 8 days Other medication: Azathioprine was continued if patients had been using it for more than 3 months. Oral glucocorticosteroids were allowed for up to 14 days unless there had been an improvement of symptoms, and were discontinued at inclusion. Rectal steroids including budesonide enemas were not permitted in the 4 weeks before inclusion. Oral sulfasalazine or other mesalamine formulations were kept stable. Mesalamine enemas were continued if they could be retained. Patients already taking antibiotics continued to receive them only if clinically indicated. During the study, antibiotics were only initiated in case of intercurrent infections. Antidiarrheal drugs were continued if judged necessary and safe, but were not initiated during the study; use of these drugs (loperamide, codeine) was accounted for in the clinical activity score.	Exclusion criteria Uncontrolled hypertension, real insufficiency with a serum creatinine level of >2mg/dL, increased concentration of liver enzymes (>2 times upper limit of normal), active infection Pregnancy Parasites or clostridium difficile or if stool cultures grew enteropathogens Azathioprine treatment for less than 3 months or if the dose had been changed in the 4 weeks prior to admission Improvement on glucocorticoids in up to 14 days treatment immediately prior to inclusion Baseline Demographics: Cyclosporine group (n=15) v Methylprednisolone group (n=15) Mean age, yr (range) 36.7 ± 2.8 (20–67) v 37.3 ± 3.9 (19–63) 0.8 Sex (M/F) 8/7 v 10/5 Mean duration of disease, yr (range) 6.7 ± 1.2 (<1–16) v 5.4 ± 1.3 (<1–20) 0.5 Extent of disease, no. of patients Left-sided/universal 2/13 v 2/13 Concomitant medication Oral corticosteroids (<2 wk) 2 v 4 Sulfasalazine/mesalamine 14 v 9 Azathioprine 1 v 2 Mean clinical activity index at inclusion 13.9 ± 0.6 (10–17) v 13.2 ± 0.9 (10–20) 0.9	was found to have c. difficile toxins in faeces and was withdrawn on day 2. Power: NR Analysis: Proportions were compared by means of chi-squared tests with Yates correction for continuity. Quantitative variables were compared with the 2-tailed Student t tests. All patients were assessed on an intent-to-treat basis. For calculations and comparisons of renal functions, the signed rank test was used. Spearman's rank correlation coefficient was used for correlations (scintigraphy vs. biopsy score).	with a drop in the score from day 1 to day 8 of at least 3 points and the possibility to discharge the patient Secondary endpoints: endoscopic and histologic response, urinary clearance, HMPAO white blood cell clearance

Antihypertensive drugs were continued or initiated as indicated

Safety: In case of alarm symptoms with high fever or sepsis, important transfusion requirements, or development of toxic megacolon, surgical advice and/or intervention was immediately requested.

Results - primary

Nine of 14 patients (64%) had a response to cyclosporine therapy compared with 8 of 15 (53%) to methylprednisolone (P = 0.4)

Mean dose of cyclosporine administered IV over the 8 days was 2.7 ± 0.6 (range, 1.8 –3.5) mg/kg body wt per day, which corresponded to 196.7 ± 18.1 (range, 91–263) mg/day; cyclosporine blood levels during IV treatment averaged 376 ± 22 (range, 212– 488) ng/mL; concentrations in responders were not significantly different from those in nonresponders (means, 361 ± 34 [212– 488] ng/mL vs. 385 ± 30 [311– 482] ng/mL) (P = 0.6).

Mean decline in the clinical activity score was 5.4 (range, -1 to 14) with cyclosporine and 4.4 (range, -1 to 9) with methylprednisolone for all patients who completed the trial and 7.7 (range, 3–14) vs. 6.1 (range, 4 –9) in the responders.

The mean time to response was 5.2 ± 0.9 days (range, 2– 8) in the cyclosporine group vs. 4.3 ± 0.7 days range, 2– 8) in the methylprednisolone group (P = 0.2).

After day 8, blinding ended and interpretation of response and/or failure may have been subject to investigator bias.

Non-responders

The patient with C. difficile infection was treated with metronidazole without improvement and underwent colectomy. Two of the 5 patients in whom cyclosporine treatment failed also underwent colectomy; the 3 other

Results - secondary

Long-term response and colectomy

At 6 months 8/9 (89%) patients and, at 12 months, 7/9 (78%) patients initially controlled with cyclosporine maintained their remission on azathioprine as single therapy. Of the patients successfully treated with glucocorticosteroids, 4/8 (50%) were still in remission at 6 months and 3/8 (37%) at 12 months, but in this subgroup only a minority (3/8) were taking azathioprine.

Four initial nonresponders were successfully treated with the combination glucocorticosteroids + cyclosporine (n= 4); 6 and 12 months later, 3 of those patients were still in remission on azathioprine alone. The colectomy rate at 1 year was 5 of 14 (36%) in the cyclosporine group (3 nonresponders shortly after the initial study phase and 2 responders who had a relapse 6 and 12 months after the start of study) vs. 6 of 15 (40%) in the methylprednisolone group (3 nonresponders immediately after the initial phase and 3 responders who had a relapse: 2 at 4 months and 1 at 6 months after inclusion).

The changes Amsterdam 4-grade scoring for endoscopic severity after 1 week of blinded treatment and 1 month of follow-up showed a distinct trend toward endoscopic improvement after 1 week, which became clearly significant after 1 month. The histologic disease activity score lagged even more behind the clinical improvement than the

Adverse events

Death: None reported

Adverse events:

No patient discontinued due to adverse events and no dose reductions due to adverse events were necessary. Seizures did not occur, decreases in serum magnesium levels were observed in 2 and in serum potassium levels in 4 cyclosporine treated patients.

Adverse events during the first 8 days of treatment
Cyclosporine/methylprednisolone
Hypertension (systolic >140, diastolic >90) 1/0
Superficial thrombophlebitis 1/1
Headache 2/1
Vomiting 1/0
Epigastric discomfort 0/1
Hypokalemia (<3.5 mEq/L) 4/0
Hypomagnesemia (<1.7 mg/dL) 2/0
Increased creatinine >10% 0/0
Paresthesia 0/1
Myalgia 2/1

Adverse events with cyclosporine beyond the first week of treatment included gingival hyperplasia (n=3), hypertension (n=1), tremor (n=1), hair loss (n=1), and headache (n=3), all resolved completely after treatment discontinuation.

patients not responding to cyclosporine were given combination therapy with IV cyclosporine + methylprednisolone, which was successful in only 1 of 3 patients. The 2 patients not responding to combination therapy were discharged, one on oral cyclosporine (despite only modest improvement) and the other on oral glucocorticoids. The 7 patients not responding to methylprednisolone therapy were all given combined treatment with cyclo- sporine, which led to a response in 3 of 7 patients; 3 of the 4 nonresponders in this combination group under- went colectomy; the fourth patient was discharged on oral glucocorticosteroids and improved slowly later. 10 patients received combination therapy with cyclosporine + methylprednisolone (3 after failure of cyclosporine alone and 7 after failure of methylpred- nisolone alone), with success in 4 of 7 patients.	endoscopy. Only after a full month of potent anti-inflammatory therapy did the (unblinded) pathologist describe a significant reduction in the number of inflammatory cells and the severity of epithelial damage. Scintigraphic evaluation and renal impairment data not abstracted		

Methods	Participants	Statistics	Outcomes
Van Assche G, D'Haens G, Noman M, et al. Randomised, double-blind comparision of 4mg/kg versus 2mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology 2003;125:1025-1031			
Design: R, DB, single-centre prospective study Aim: to investigate whether a high-dose IV cyclosporine induction regimen of 4 mg/kg was superior to a lower dose regimen of 2 mg/kg at alleviating signs and symptoms of acute severe colitis and at avoiding colectomy. To compare the toxicity profile associated with the 2 dosing strategies. Duration: 2 weeks Location: Leuven University Hospital between August 1996 and April 2002 Sponsorship: NR Randomisation and blinding: Randomisation was performed on patient inclusion at the central pharmacy of the hospital.	Population: Inclusion criteria Male and female patients between 18 and 70 years of age Severe UC as defined by a score of 10 or more in the Lichtiger clinical activity index Exclusion criteria Renal insufficiency with a serum creatinine of more than 2 mg/dL, elevation of liver enzymes or bilirubin (2 times upper limit of normal), serum cholesterol below 150 mg/dL, uncontrolled hypertension, active viral or bacterial infections Pregnancy Parasites or clostridium difficile or if stool cultures grew enteropathogens	Groups: 38 patients were randomised to 4 mg/kg daily and 35 patients to 2 mg/kg of cyclosporine daily Power: Sample size estimates showed that, with a sample size of 35 patients in each group, a 30% difference in the proportion of clinical responders could be demonstrated with 80% power (-error, 0.05), based on the assumption that 82% of patients would respond to 4 mg/kg6 and 50% to 2 mg/kg IV cyclosporine. Analysis: All patients were analyzed	Primary endpoint: The proportion of patients with a clinical response Clinical response was defined as a score of less than 10 at day 8 with a drop of 3 from baseline Secondary endpoints: colectomy rates, median change in clinical activity index, median time to response, incidence of hypertension, and mean increase in serum creatinine Endoscopy score

Blood levels monitored by an independent physician who was not involved in the care of the patients. Dose changes were directly communicated to the central pharmacy
for the next IV infusion bag to obtain blood levels between 250 and 350 ng/mL in the 4-mg/kg-dose group and between 150 and 250 ng/mL in the 2-mg/kg-dose group. All other physicians and the patients were blinded for treatment assignment. They were not blinded for serum creatinine levels or blood pressure measurements.

Dosage: Patients assigned to the high-dose group were started on a continuous 24-hour infusion of Sandimmune (cyclosporine-a; Novartis, Basel, Switzerland) at an initial dose of 4 mg/kg. Patients in the low-dose group started at a dose of 2 mg/kg IV. From day 1 through day 8, patients were treated with continuous cyclosporine infusions.

Other medication: IV corticosteroids were allowed if given prior to enrollment at a stable dose for at least 5 days without clinical response and were kept stable until day 8 of the trial. Patients on oral corticosteroids were eligible if they had been started at least 14 days from inclusion without clinical benefit. Oral corticosteroids were discontinued on day 1, and patients were converted to IV steroids. At day 8, patients' conversion to oral steroids was again performed, and steroids were tapered by 5 mg of prednisolone (or equivalent) per week. Azathioprine or 6-mercaptopurine was allowed if they had been started at least 3 months prior to inclusion and the dose had not been changed in the 4 weeks before admission. In those patients, doses were kept stable throughout the study. In all other patients, azathioprine 2.0 –2.5 mg/kg was initiated at day 8 and continued with regular monitoring for toxicity. Oral mesalamine or sulphasalazine was maintained at stable doses, and rectal mesalamine was also maintained at identical doses for the first 8 days, provided the patient was able to retain the enema. Patients receiving antibiotics at inclusion were continued on the antibiotics if judged clinically necessary, and, during the study, institution of antibiotics was only allowed

Baseline Demographics:
4 mg/kg v 2 mg/kg
N (male/female) 38 (21/17) v 35 (21/14)
Age (yr) 39 14 v 41 14
Concomitant steroids 55.2% (21) v 60.0% (22)
Concomitant azathioprine 21.0% (8) v 25.7% (9)
Active smokers 10.5% (4) v 11.4% (4)
Disease extension (% pancolitis) 42% v 48%
Median CAI at D0 13 (10–17) v 11 (10–16)
Mean CRP 64.1 60.1 v 54.1

on an intention-to-treat basis. For quantitative data, statistical analysis was performed using 1-way analysis of variance for multiple comparisons, followed by a 2-tailed, paired t test for parametric, or Wilcoxon Rank sum test for nonparametric observations. Statistical signifi- cance was accepted at a P value 0.05. Mulivariate analysis with stepwise logistic regression was performed to test for parameters influencing clinical response.

for intercurrent infections

Safety: Restorative proctocolectomy was performed at any time during the blinded or unblinded phase of the study when considered clinically necessary by treating physicians and surgeons.

Results – Primary	Results – secondary	Adverse events
Clinical response was reached by 32/38 (84%) in the 4-mg/kg group and by 30/35 (85%) in the 2-mg/kg dose group. One patient in the 4-mg/kg group had an anaphylactic reaction immediately after starting the first infusion and was withdrawn from the study. This patient was treated with oral cyclosporine and did well. The median change in CAI was 7 (95% CI, 5.7– 8.3) in the 4-mg/kg group and 6 (95% CI, 4.6 – 8.4) in the 2-mg/kg group. The median time to response was 4 days in both groups (4 mg/kg: range, 1–7 days; 95% CI, 3.4 – 4.6; 2 mg/kg: range, 1– 8 days; 95% CI, 3.2– 4.8). Short-term (14 days) colectomy rates were similar; 5/38 (13.1%) versus (3/35 (8.6%)	Mean change in c-reactive protein level at Day 8 as compared with baseline was similar in the 2 groups (4 mg/kg, 41.5 ± 56.9 mg/L; 2 mg/kg, 41.2 ± 54.9 mg/L). Endoscopy score was the same in both treatment groups (2, range 1-3) and did not change between day 1 and day 8 Active smoking, mean cylosporine dose, age, location of disease (left-sided vs. pancolitis), and concomitant steroid and azathioprine therapy were evaluated for their predicting value toward response. In multivariate analysis, only active smoking was inversely correlated with clinical response (OR, 0.06; 95% CI, 0.008 – 0.407) The mean daily doses administered to patients over 8 days were 1.82 ± 0.32 (2-mg/kg group) and 2.65 ± 0.47 mg/kg (4-mg/kg group), respectively (P<0.0001). The area under the curve for the doses during 8 days was 13.3 ± 1.1 (2 mg/kg) vs. 19.7 ± 1.2 mg/kg/day (4 mg/kg) (p<0.005). Mean cyclosporine blood levels throughout 8 days of treatment were 237 ± 33 ng/mL in the 2-mg/kg group and 332 ± 43 ng/mL in the 4-mg/kg group (P 0.0001).	Death: None reported Adverse events: 4 mg/kg 2 mg/kg Hypertension 9/38 3/35 * Increase serum creatinine (>10%) 7/38 6/35 Tremor/paresthesia 3/38 2/35 Fever 3/38 1/35 Diabetes mellitus 1/38 0/35 *(p<0.08) One patient in the 4-mg/kg group had an anaphylactic reaction immediately after starting the first infusion and was withdrawn from the study

Methods	Participants	Statistics	Outcomes
Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. New England Journal of Medicine 1994;330:1841-1845			
Design: R, DB, placebo controlled, prospective study followed by open-label period Duration: Location: Patients admitted to Mt. Sinai Hospital in New York or the University of Chicago Hospital between April 1991 to April 1992 or patients who were transferred to either institution after having no response to this therapy elsewhere Sponsorship: NR Randomisation and blinding: No details on methods of randomsation. One physician who was aware of the patients' treatment assignments monitored blood cyclosporine concentrations and adverse effects and made adjustments and also randomly adjusted the dosages of placebo. The patients assigned to the placebo group received an identical-appearing intravenous solution of cremaphor and alcohol. The patients were evaluated daily by a gastroenterologist who was aware of their treatment assignments and by at least one gastroenterologist who was not aware of their treatment assignments or the results of any laboratory studies. Dosage: The patients assigned to receive cyclosporine were given a dose of 4 mg/kg per day by continuous infusion for up to 14 days. The patients assigned to the placebo group received an identical-appearing intravenous solution of cremaphor and alcohol. The dose of cyclosporine never exceeded 4 mg per kilogram per day, but it was reduced if the serum creatinine concentration increased by 30 percent above base line, serum liver-enzyme values increased by 50 percent, or diastolic blood pressure consistently exceeded 90 mm Hg despite antihypertensive therapy	Population: Inclusion criteria No response to intravenous corticosteroid therapy (equivalent to a daily dose of 300 mg of hydrocortisone) after seven or more days A score of 10 or higher on a clinical-activity index Lockhart-Mummery and Morson criteria were used to establish the diagnosis of ulcerative colitis and to distinguish this form of colitis from Crohn's colitis A colonoscopy or barium enema showing the characteristic changes of ulcerative colitis extending at least to the splenic flexure Inactive disease - flexible sigmoidoscopy of the first 30 cm (or less) of the colon was performed to confirm that the disease was once again active. Exclusion criteria Bacterial or parasitic pathogens in stools, a positive test for Clostridium difficile toxin, septicemia, perforation of the bowel, megacolon, active fungal or viral infection, or uncontrolled hypertension, Treatment with mercaptopurine, azathioprine, or any investigational drug within the preceding two weeks. Elevated serum concentrations of hepatic enzymes (3x normal +), hyperbilirubinemia (2x normal +), renal dysfunction (serum creatinine concentrations more than 33% above the upper limit of normal), or a serum cholesterol concentration of less than 120 mg per deciliter (3.1 mmol per litre). Baseline Demographics: Mean age - yr (range) 34 (18-60) v 43 (20-65)	Groups: 20 patients were included; 11 patients were treated with cyclosporine and 9 patients were treated with placebo Power: the trial was terminated after 20 patients had been studied, when the physician who was aware of their treatment assignments noted a significant difference between the two group, confirmed by the study monitor and two independent reviewers. No power calculations reported. Analysis: Quantitative variables were compared with two-tailed Student's t-tests. Qualitative variables and differences between centers were compared with chi-square analysis with Yates' correction. All patients were assessed on an intention-to-treat basis	Primary endpoint: clinical-activity score A score of less than 10 on two consecutive days was considered to indicate a positive response to therapy. The score on the second of these two days was considered the final score Patients whose clinical-activity scores did not fall below 10 for 2 consecutive days after 14 days of treatment or whose condition worsened were considered to have no response to treatment Secondary endpoints: not defined

Other medication: All patients received 100 mg of hydrocortisone intravenously every eight hours + hydrocortisone enemas (100 mg in a total volume of 60 ml) nightly if the drug could be retained. Patients receiving mesalamine enemas before entry continued to receive them if the drug could be retained. Oral sulfasalazine, olsalazine, or mesalamine was continued in the same doses in patients already taking these medications. Patients who were already taking antibiotics continued to receive them if clinically indicated. The patients were treated with loperamide or codeine in an attempt to control diarrhea; the use of these drugs was accounted for in the clinical-activity score. Antihypertensive drugs were continued or initiated, as indicated, if the diastolic blood pressure consistently exceeded 90 mm Hg. Acetaminophen, H2-receptor antagonists, or aluminum-based antacids were given as needed. Three patients were receiving total parenteral nutrition when they entered the study, but it was not initiated in any patient during the study. Safety: Depending on the severity of their colitis as determined by the gastroenterologist and surgeon, they either underwent colectomy or were offered open-label cyclosporine therapy, administered by continuous intravenous infusion in a dose of 4 mg per kilogram per day for a maximum of 14 days (after they had withdrawn from the trial; the treatment code was not broken).	Sex M/F 4/7 v 5/4 Mean duration of disease – yr (range) 6 (<1-22) v 2 (<1-8) Mean duration of parenteral corticosteroid therapy before entry – days (range) 16 (3-30) v 17 (3-36) Mean clinical activity index (range) 13 (10-16) v 14 (12-17) Extent of disease – n (%) Universal 8 (73) v 8 (89) Left-sided 3 (27) v 1 (11) Concomitant medications before and during the trial – n (%) Sulfasalazine or analogue 5 (45) v 4 (44) Glucocorticoid or mesalamine enemas 4 (36) v 5 (56) Antibiotics 8 (73) v 6 (67) Transfusions – n (%) 7 (64) v 5 (56) Parenteral nutrition – n (%) 1 (9) v 2 (22)	

Results – Primary	Results	Adverse events
9/11 (82 percent) in the intravenous cyclosporine group had a response to therapy compared with 0/9 patients in the placebo group (P<0.001) Mean time to a response (second consecutive day on which the clinical-activity score was less than 10) was 7 days (range, 3 to 14)	Non-responders Of the two patients in the cyclosporine group who did not have a response, one had a grand mal seizure 12 hours after beginning therapy. The drug was stopped, and the patient underwent a colectomy. This patient had hypocholesterolemia and should have been excluded from the study, but she was counted as having no response to	Deaths: None reported Adverse events: 4/11 patients (36%) initially treated with cyclosporine had paresthesias compared with none of the patients in the placebo group. Hypertension, defined as a systolic blood pressure of more than 140 mm Hg or a diastolic blood pressure of more than 90 mm Hg for two consecutive days, was noted

Mean clinical-activity score in the cyclosporine group fell from 13 (range, 10 to 16) to 6 (range, 2 to 8), and the mean score in the placebo group fell from 14 (range, 12 to 17) to 13 (range, 11 to 18).

At the end of the study the mean decline in the clinical-activity score in the cyclosporine group was significantly greater than that in the placebo group (P<0.001).

One patient in the cyclosporine group who had a response to therapy elected to undergo colectomy.
All 14 patients with a response, except the 1 who chose to undergo colectomy, were treated with oral cyclosporine and discharged from the hospital 48 hours later.

cyclosporine therapy according to the intention-to-treat criterion. The condition of the second patient rapidly deteriorated after eight days of cyclosporine therapy, and a colectomy was performed.

No patient in the placebo group had a decline in the clinical-activity score to below 10 on two consecutive days. 4/9 patients (44 percent) underwent colectomy. One underwent colectomy on day 3 because of toxic megacolon. Another underwent colectomy after clinical deterioration in her condition was noted; this patient later died of gram-negative sepsis with superimposed cytomegalovirus infection. Two patients had surgery for refractory symptoms. The condition of the other five patients (56 percent) was stable, and they were therefore given open-label intravenous cyclosporine after the study period.

During this period of open-label cyclosporine therapy, the evaluating physicians remained unaware of the patients' initial treatment assignments and no other treatment was introduced. The condition of all five patients who had received placebo earlier improved, with a decrease in their mean clinical-activity score from 11 (range, 11 to 13) to 7 (range, 2 to 9). The mean time to a response in this subgroup was 7 days (range, 4 to 8).

Among the 11 patients who initially received cyclosporine, the mean blood concentration was 482 ng per milliliter (range, 339 to 653) in the 9 who had a response to therapy and 484 ng per milliliter in 1 who had no response (the other patient who had no response received cyclosporine for only 12 hours).

in 4/11 (36%) patients in the cyclosporine group, two of whom required treatment. Hypertension developed in one patient in the placebo group (11 percent). One patient in each group reported nausea and vomiting.

None of the patients had nephrotoxicity or hepatotoxicity.

One patient treated with cyclosporine had a grand mal seizure after the initiation of therapy but had no more seizures after cyclosporine was discontinued.

Headaches occurred as the only side effect in two of the patients who received cyclosporine after receiving placebo.

	In the five patients who received cyclosporine after receiving placebo, the mean blood cyclosporine concentration was 524 ng per milliliter (range, 375 to 620). There was no correlation between blood concentrations and the rapidity of response. The dosage was decreased in five patients because of elevated blood cyclosporine concentrations	

9.9 Appendix 9: Details of included non-RCTs

Methods	Participants	Statistics	Outcomes
Actis, G. C., M. Bruno, et al. (2002). Infliximab for treatment of steroid-refractory ulcerative colitis. Digest Liver Dis 34: 631-4			
Design: Uncontrolled open study of consecutive patients admitted to a referral clinic for severely active UC refractory to sequential medical treatments **Duration**: 9 months **Location**: Italy **Sponsorship**: NA **Dosage**: Infliximab intravenous infusion 5mg/kg prepared following the manufacturer's instructions. 5, 2 and 1 patients received 1, 2, and 3 injections respectively **Other medication/treatment**: six patients had received maximum dose parenteral steroids for at least 7 days. Two patients treated in a day hospital , one had not responded to a daily oral dose of 50mg prednisolone for 15 days and the other had relapsed after azathioprine dose reduction **Safety**: NA	**Population**: Six patients were treated whilst in hospital for persistently active disease after a course of at 7 days of parenteral steroids at the maximum dose. 2 patients were treated in a day hospital unit; one had not responded to a daily oral dose of 50mg prednisone for the previous 15 days (and had required cyclosporine to control a steroid-refractory attack in 1997), the other patient had relapsed following a dose reduction in azathioprine treatment (100mg to 50mg/day). The patients in the study scored at least 10 prior to treatment on the Clinical Activity Index **Baseline Demographics**: Sex: 4 males and 4 females Age: 20 to 60 years Disease duration: 3 months to 13 years Haemoglobin 9.3±0.99 g/dl Erythrosedimentation rate 45+9 hr Albumin 2.99+0.7 g/dl C-reactive protein 54+22 mg/l	**Groups**: 8 patients were recruited **Power**: NA **Analysis**: NA	Initial response (an initial response to infliximab was expected to manifest as a decrease in stooling and faecal blood, yielding a 50% reduction or more in the Clinical Activity Index) Maintenance of response

Results	Results	Adverse events	
Initial Response 4/8 (50%) did not show an initial response to infliximab and were referred for immediate colectomy (2 had universal colitis and 2 had left-sided involvement) 4/8 (50%) responded with a reduction in CAI score of 50% (2 had universal disease, one had sub-total colitis, and in the other the left colon only was affected. A parallel biochemical response was also achieved with a decrease in the level of acute phase reactants, particularly CRP	Maintenance of response The four patients responding to treatment were followed up for 1 to 7 months. One patient has had one injection, one has had three, and the remaining two patients have had two injections. The former two have maintained clinical remission and are steroid-free; of the other two, one relapsed needing elective colectomy at week 5 after the first injection, the other showed a >50% reduction in haemaglobin needing transfusions at day 56 in the absence of clinical haematochezia, an overt clinical relapse was noted at 6 months and the patient received a second injection which was followed by a slow improvement. All four responders (with the exception of the patient submitted to colectomy) received AZA at a daily dose of 2mg/kg.	No acute or chronic untoward reactions associated with infliximab were recorded in the patients studied.	
Methods	**Participants**	**Statistics**	**Outcomes**
Chey, W. Y., A. Hussain, et al. (2001). Infliximab for refractory ulcerative colitis. Am J Gastroenterol. 96: 2373-81			
Design: Uncontrolled open study **Duration**: NA **Sponsorship**: NA **Randomisation and blinding**: pathologist blinded to treatment for histological	**Population**: 8 patients that had failed maximal medicinal therapy and were scheduled for surgical total colectomy were included. All patients had tried 5-aminosalicylates, in doses up to 4g/day and were currently on maintenance therapy; all had tried parenteral steroids, and had not responded, and most were on 6-mercaptopurine. In three patients 6-	**Groups**: 8 patients were included; 2 patients are presented separately as case studies, results for the remaining 6 patients are summarised as a group **Power**: NA	Responses were determined by three parameters; clinical/subjective improvement, appearance on repeat endoscopy, and histological grade scoring of endoscopic biopsies. Scoring was done using a simple

scoring **Dosage**: patients received infliximab 5mg/kg diluted with 250ml of isotonic saline and infused intravenously over 2 hours **Other medication/treatment**: patients continued any medications they were already taking; post-treatment all patients maintained on aminosalicyclic acid, 6-mercantopurine, and a tapering dose of prednisone **Safety**: vital signs were monitored during infusion; patients observed for 1 hour as out-patients (though it says all patients had been admitted to hospital) or followed up in hospital for 2 to 4 days after infusion	mercaptopurinewas previously used but had to be discontinued due to side-effects. **Baseline Demographics**: Age 59.9 years (range 19-79) Median duration of ulcerative colitis 10.8 years (range 1-30) 5-aminosalicylates 8/8 patients 6-mercaptopurine 5/8 patients oral steroids 6/8 patients (also described as failing parenteral steroids?) pANCA positive 7/8 patients ASC positive 1/8 patients Baseline mean histological score 7.4 $\pm$ 0.7 (95% CI 6.8-8.0, range 6-8)	**Analysis**: Pre- and 1 week post-infliximab scores were analysed by a paired t test, and the nonparametric Wilcoxon signed rank test	rating scale by a pathologist blind to the details of ulcerative colitis treatment Repeat colonoscopy or flexible sigmoidoscopy was performed approximately 1 week after infusion whenever possible to assess response visually and histologically. Clinical response measured using Disease activity index (Lichtinger) which evaluated the patient's degree of diarrhoea, hematochezia, abdominal pain and tenderness, fecal incontinence, and general well-being
Results	**Results**	**Adverse events**	
By both the paired t test and Wilcoxon signed rank test, there was a statistically significant difference between the disease activity index scores of the 8 patients pre- and post- infliximab infusion ($p<0.01$ and $p=0.004$ respectively) 1 week post infusion histological grading	No relapses reported	**Death**: None reported **Adverse events:** infusion rate did not require adjustment due to infusion related adverse events. All patients were discharged from hospital or out-patient unit (again, says all patients were admitted earlier on) without complications. Patients were seen for follow-up but reported no delayed complications or adverse effects (up to 5 months after	

scores showed a statistically significant improvement p=0.0004 and p=0.0078. Assessments were repeated at 4 and 8-16 weeks and also showed statistically significant improvement from baseline (1 patient lost to follow-up) Pre-biopsy mean score 7.4 Post-biopsy (1 week) mean score 3.6 Follow-up biopsy (4 weeks) mean score 2.6 Long-term biopsy (8-16 weeks) mean score 2.3 There was no statistically significant difference between means from week 1, week 4 and 8-16 weeks		infusion for 1 patient)	
Methods	**Participants**	**Statistics**	**Outcomes**
Kohn A, et al (2002). Anti-tumour necrosis factor alpha (infliximab) in the treatment of severe ulcerative colitis: result of an open study on 13 patients. Dig Liver Dis. 34 :626-30 relates to Kohn, A., C. Prantera, et al. (2004). Infliximab in the treatment of severe ulcerative colitis: a follow-up study. Eur Rev Med Pharmacol Sci. 8: 235-7			
Design: uncontrolled open study **Aim:** To evaluate the efficacy and safety of infliximab in the treatment of severe ulcerative colitis refractory to conventional therapy (methyl-prednisolone 60mg daily for 7+ days) **Duration**: March 2000 to April 2001 (median patient follow-up 10.1 months)	**Population**: 13 patients with severe UC refractory to methyl prednisolone 60mg/day for at least 7 days. The diagnosis of UC was established by endoscopic and histological criteria. Severity of disease was established using Truelove and Witts classification. Abdominal x-rays were obtained to establish extent of colitis and ascertain possible megacolon or perforation. A flexible protosigmoidoscopy was performed to evaluate	**Groups**: 13 patients were included **Analysis**: No details	Clinical response defined as CAI ≤10 on two consecutive days Patients whose condition worsened or whose CAI score failed to fall below 10 for 2 consecutive days within 7 days of infliximab treatment were defined as

Location: 2 hospitals in Italy **Sponsorship**: No details **Dosage**: A single infusion of 5mg/kg, patients were able to received further infusions at the treating clinician's discretion **Other medication/treatment**: all concomitant medications were continued if clinically indicated **Safety**: patients whose condition worsened or whose CAI score failed to fall below 10 for 2 consecutive days within 7 days of infliximab treatment underwent colectomy	disease activity. All patients were tested for enteric stool pathogens and clostridium difficile and had chest x-rays to rule out respiratory infections. All patients presented endoscopic features of severe disease at basal proctosigmoidoscopy **Baseline Demographics**: Mean age – yrs (range) 37 (12-62) Sex – M/F 8/5 Mean duration of disese – yrs (range) 4 (1-11) Mean duration of parenteral corticosteroid therapy before infliximab – days (range) 13 (6-21) Mean CAI before infliximab (range) 13 (6-21) Extent of disease Universal 11 (85%) Left-sided 2 (15%) Serum immune marker: pANCA 6/11 (54%) Concomitant medications before and after infliximab Sulfasalazine or Mesalamine 11 (85%) Glucocorticoid or Mesalamine enemas 8 (62%) Antibiotics 2 (15%) Azathioprine/6MP 6 (46%) Transfusions 2 (15%) Parenteral nutrition 2 (15%)		nonresponders and underwent colectomy Serum levels of C-reactive protein at baseline and at 7 days in nonresponders

Results	Results	Adverse events	
10/13 (77%) had a clinical response to therapy on 2 consecutive days; 9/13 showed a dramatic clinical improvement after 48-72 hours and 1 patient had a clinical response after 6 days 2/13 (15%) underwent colectomy within 3 days due to clinical deterioration (another patient with no evidence of clinical response after 7 days refused surgery and was lost to follow-up 1 patient relapsed at 5 months, the other 9 maintained clinical remission throughout the follow-up period	Mean CAI score in responders fell from 14 (range 11-19) to 5.4 (3-10) after 3 days, to 3.5 (1-6) after 7 days Mean follow-up was 10.1 months and all 10 responders were able to discontinue corticosteroid therapy. 7/10 continued on azathioprine or 6-MP alone or in combination with sulfasalazine or 5-acetylsalicylate acid. 2 patients discontinued immune modifiers due to intolerance and were kept on sulfasalazine and local treatment with steroids, 1 patient was maintained on sulfasalazine and local treatment with 5-acetylsalicylate acid. 2/3 nonresponders were tested for pANCA and were positive compared with 4/10 responders. Serum levels of CRP correlated with clinical course	**Death**: None reported **Adverse events:** 1/13 (8%) developed a rash that was controlled by slowing the infusion rate	
Methods	**Participants**	**Statistics**	**Outcomes**
Kohn, A., M. Daperno, et al. (2007). Infliximab in severe ulcerative colitis: short-term results of different infusion regimens and long-term follow-up. Aliment Pharmacol Ther. 26: 747-56			
Design: Retrospective analysis of medical records (n=46) and prospective data collection (n=37) from 2003 onwards using a shared clinical form **Aim:** To evaluate short- and long-term effectiveness and safety of infliximab in	**Population**: 83 patients with acute severe or moderately severe UC were recruited. All patients were candidates for colectomy due to resistance to intensive intravenous glucocoticoid treatment more at least 7 days. Patients were recruited according to severe	**Groups**: 83 patients were included. To investigate if patients with severe disease, as originally defined by Truelove and Witts by all five criteria, may show a different response, two	**Primary endpoint:** survival free from colectomy or death, within 2 months from the first infliximab infusion. **Secondary endpoints:** clinical remission at 1 month

severe refractory ulcerative colitis **Duration and follow-up**: From May 2000 to January 2006. Patients were followed up after the first infusion by serial clinical evaluation. Clinical activity was evaluated using CAI. If there was no recent contact (<2 months), the patient was evaluated by telephone interview **Location**: 10 gastroenterology units in Italy **Sponsorship**: NA **Dosage**: A single intravenous infusion of infliximab 5mg/kg, patients were able to receive a further one or two infusions based on individual physician's preferences (and not on clinical response) **Other medication/treatment**: All concomitant medications were continued if clinically indicated **Safety**: Patients whose condition worsened or failed to respond to treatment underwent colectomy. To perform colectomy was a joint medical-surgical decision.	flare-up as defined by Truelove and Witts and modified by Chapman – six or more bloody motions per day and at least one of the following; fevere (mean evening >37.5C or >37.8C for 2 days out of 4), tachycardia (>90 per minute), anaemia (decrease in haemoglobin levels greater than 75%), erythrocyte sedimentation rate >30mm/h. Clinical activity was measured by the Lichtinger Clinical Activity score (CAI) for acute UC. All patients had a score of ≥12 calculated prior to the first infliximab dose. All patients had UC diagnosis established by commonly accepted clinical, endoscopic, and histological criteria. Abdominal x-ray films were obtained to exclude toxic megacolon or performation and to establish the approximate extent of colitis. A flexible proctosigmoidoscopy was usually performed to evaluate disease activity at hospital admission, based on usual policy at different centres. Endoscopic severity was considered as both presence and absence of deep colonic ulcer based on Carbonnel criteria and overall observers' global evaluation. All patients were tested for enteric stool pathogens and clostridium difficile toxin. A chest radiograph was performed in all patients	subgroups were formed; 66 patients fulfilled all five criteria for severity (group S1) and 17 fullfilled all but one or two criteria (group S2) **Analysis**: Carried out using MEDCALC (9.0) Descriptive statistics were used to summarise data; frequencies and median with interquartile ranges for categorical and continuous variables, respectively, as appropriate. Univariate analysis was carried out to explore differences between groups: chi-squared, Fisher's exact test and Mann-Whitney test for categorical and continuous variables, as appropriate. Stepwise logistic regression was used to test the independent association of different clinical characteristics to the outcome variables, i.e. early or	after first infliximab infusion and during long-term follow-up Time to clinical relapse defined as the need for a new steroid course and/or infliximab or surgery A CAI score of <10 on two consecutive days was considered a clinical response; clinical remission was defined as a CAI score of 4 or less. Colectomy performed within 2 months from the first infusion of inflixmab was defined as early colectomy, any colectomy performed during the follow-up period was considered late colectomy. Serum levels of C-reactive protein were evaluated before, 3 and 7 days after infliximab infusion or before clectomy in patients who

	and intradermal test with PPD, together with accurate personal history evaluation was carried out since 2001 for excluding ongoing or past tuberculosis. **Baseline Demographics** (statistically significant P values are highlighted in bold) All patients; subgroup S1; subgroup S2 Male/female 49/34; 38/28; 11/6 (p=0.798) Age (years), median (IQR) 36 (27-50); 26 (26 – 51); 37 (35 – 46) (p=0.502) Disease duration, months median (IQR) 37 (12-72); 28 (12 – 72); 50 (37 – 82) (p=0.055) First year of disease, n (%) 18 (22); 16 (24); 2 (12) (p=0.339) Disease extent, n (%) Total colitis 56 (67); 42 (64); 14 (82) Left sided colitis 23 (28); 20 (30); 3 (18) Distal colitis 4 (5); 4 (6); 0 (p=0.285) Smokers, n (%) 6 (7); 6 (9); 0 (p=0.44) Concomitant medications Aminosalicylates 47 (57); 38 (58); 9 (53) (p=0.788) Antibiotics 52 (63); 42 (64); 6 (35) (p=0.053) Azathioprine/6MP 20 (24); 14 (21); 6 (35) (p=0.535) Cyclosporin 9 (11); 9 (14); 0 (p=0.192) Parenteral nutrition, n (%) 27 (32); 22 (33); 5 (29) (p=0.986) Blood transfused patients, n (%) 15 (18); 14 (21);	delayed colectomy and clinical relapse (set as dependent variables). Survival analyses (for 60-day colectomy, late colectomy and clinical relapse) was carried out using Cox proportional-hazards regression. P-values <0.05 were considered statistically significant; wherever appropriate, 95% CI were also reported.	failed to respond.

	1 (6) (p=0.266) Hb g/dL, median (IQR) 10.6 (8.9 – 12); 10.2 (8.7 – 11.4); 12.2 (11.4 – 12.9) **(p=<0.001)** CRP mg/dL, median (IQR) 45 (30 – 72); 48 (32 – 78); 30 (17 – 43) **(p=0.019)** CAI, median (IQR) 14 (12-15); 14 (13 – 16); 11 (11 – 13) **(p=<0.001)** Endoscopy, n (%) 79 (95%); 65 (98); 14 (82) **(p=0.026)** Severe/moderately severe 62/17; 50/15; 8/6 (p=0.236) Deep ulcers 47 (59); 30 (60); 8 (57) (p=0.918) Duration of IIVT before infliximab, days, median (IQR) 8 (6 – 13); 9 (6 – 13); 6 (1 – 12) (p=0.116) Dose of methylprednisolone or equivalent, mg/day, median (range) 60 (20 - 80); 60 (20 – 80); 60 (30 – 80) (p=0.489)		
Results - primary endpoint	**Results – secondary endpoint**	**Adverse events**	
84% (70/83) patients had avoided colectomy at 2 months 15% (12/83) patients were operated on in the absence of clinical response (2 patients within 4 days due to clinical deterioration) Median time to operation after infliximab infusion was 27 days (95% CI 8 – 53); four and seven patients underwent colectomy	61 patients (73%) reached clinical remission (CAI ≤4) at 1 month 27 patients (39%) relapsed after a median interval of 13.5 months (IQR 5 – 23). The relapse rate was not associated with any maintenance regimen. Of those who relapsed, 13 patients were treated successfully with oral/parenteral glucocorticoids, two patients received further infliximab infusions, and 12	**Death**: No UC death-related deaths were reported. One patient died of pulmonary abscess, 11 days after the first infliximab infusion. The patient was a 71 year old male with a 2 year history of UC, on mesalazine maintenance when he experienced a severe steroid-refractory relapse of UC which responded to infliximab after 12 days of steroid treatment. Two days after hospital discharge, on glucocortcoids, he developed pneumonia complicated by pulmonary abscess (Legionella pneumophila serogroup 1 was isolated from sputum samples). Despite treatment, the patient died of	

within 15 and 30 days respectively 26 patients received one infusion (9, 35% had subsequent colectomy) and 57 patients had >2 infusions (3, 5% had subsequent colectomy) p=0.001, OR 9.53 (2.31 – 39.26) 66 patients were included in subgroup S1 (12, 18% had a colectomy) and none of the 17 patients in subgroup S2 required colectomy p=0.114, OR 1.22 (1.09 – 1.37) No UC death-related deaths were reported No clinical characteristic was associated with 2 month colectomy rates, including basal bowel motions, CAI, endoscopic findings, CRP or ESR levels. The only variable significantly associated with the risk of colectomy was number of infliximab infusions (p=0.001). Cox proportional hazards regression confirmed that the number of infliximab infusions was the only significant predictor or short-term colectomy p=0.005, RR 5.764 (95% CI 1.54 – 21.62) Overall colectomy rate (early and delayed) was 29% (24/83)	patients required surgery. Cox-proportional hazards regression showed that no covariate was significantly associated with follow-up colectomy (p=0.693). Among patients who underwent surgery, 3 were receiving aminosalicylates, 8 immunosuppressants, and 1 re-treatment with infliximab. No analysis showed any effect of the initial number of infliximab infusions or other variable for remission free from colectomy and disease relapse during follow-up	septic shock 8 days later. **Adverse events:** Nine out of 83 patients (11%) reported severe adverse events (five infections and four infusion reactions). more Primary tuberculosis n=1 Pneumonia n=1 Herpes simplex virus infection with fever and headache n=1 Candida Albicans sepsis n=1 (probably not related to treatment) Infusion reactions (2nd infusion) n=1 Infusion reactions (3rd infusion) n=3 No newly diagnosed malignancies or dysplasia or postoperative complications were reported Postsurgical mortality in patients who underwent colectomy was 0% Short-term postsurgical morbidity was 33% (8/24) Infectious complications n=2 Early anastomotic leaks treated conservatively n=2 Pouch-related adverse events n=3 Non-fatal pulmonary embolism n=1

Methods	Participants	Statistics	Outcomes
Lees, C. W., D. Heys, et al. (2007). A retrospective analysis of the efficacy and safety of infliximab as rescue therapy in acute severe ulcerative colitis. Aliment Pharmacol Ther 26(3): 411-9			
Design: Retrospective cohort study of infliximab as a rescue therapy for patients with acute severe UC unresponsive to intravenous corticisteroids. Data were collected retrospectively by case note review on a standardized data collection form. **Duration**: May 2005 to November 2006 **Location**: 8 different hospitals across Scotland (two additional sites indicated they had patients treated with infliximab but failed to provide data or case notes) **Sponsorship**: Declaration of personal and funding interests by authors, no other information **Dosage**: Intavenous infliximab 5mg/kg (range 4.2 to 5.6mg/kg). The timing of administration was at the physician's discretion **Other medication/treatment**: After admission all patients were treated with high-dose intravenous corticosteroids,	**Population**: 39 patients were included. Patients were included if they satisfied the following criteria; • Hospitalisation for acute severe UC, satisfying Truelove and Witts criteria for severe colitis • Failure to respond to intravenous corticosteroids • Treatment with infliximab 5mg/kg as rescue therapy during the acute admission The diagnosis of UC adhered to Lennard-Jones criteria and the disease was classified according the Montreal classification **Baseline Demographics**: Sex, male/female 23/16 Median age at diagnosis 30.7 years (IQR 21.9 to 43.3) Median age at admission 31.7 years (IQR 24.1 to 45.6) Median duration of diagnosis at admission 123 days (IQR 0 to 885) First presentation at admission 14/39 (35.9%) Drugs on admission (prior diagnosis of UC) Oral 5-ASA 20/25 (80%) Azathioprine/MP 6/25 (24%) Oral prednisolone 14/25 (56%)	**Groups**: 39 patients were included **Analysis**: Descriptive data were displayed as median values with interquartile ranges. Predictors of response (clinical parameters: sex, age at diagnosis, smoking status, disease extent; laboratory parameters on admission and day 3 of intravenous corticosteroid therapy: stool frequency, C reactive protein, serum albumin) were analysed by univariate analysis, using chi-squared or Mann-Whitney U testing for categorical and continuous data respectively. P-value <0.05 was considered significant and odds ratios were given with 95% cofidence intervals and two-sided p-values.	**Primary outcome:** Colectomy Patients were defined as initial responders if they were discharged from hospital without having surgery during the acute admission. Late non-responders were defined as those having colectomy in the 90 days following infliximab treatment. Successful withdrawal of corticosteroid therapy at day 90 was also assessed

either hydrocortisone 100mg q.d.s or methylprednisolone 60mg/24 hours by continuous infusion **Safety**: Non-responders underwent urgent colectomy. Adverse events were assessed by case note review.	Disease extent (Montreal classification) Unknown 1/39 Proctitis 2/38 (5.3%) Left-sided colitis 18/38 (47.4%) Extensive colitis 18/38 (47.4%) Smoking status at admission Unknown 4/39 Current smoker 2/35 (5.7%) Ex-smoker 10/35 (28.6%) Never smoked 23/35 (65.7%)	A logistic regression model was used for multivariate analysis incorporating clinical and laboratory factors listed above (Minitab software 13.20). Sensitivity and specificity of predictive values were generated by reciver-operator characteristic curve (GraphPad Prism 4.0)	
Results	**Results**	**Adverse events**	
26/39 (66.6%) avoided urgent colectomy at the point of hospital discharge and were discharged as early responders. 13/39 (33.3%) of patients underwent colectomy, before hospital discharge (nonresponders) at a median of 5 days (range 1-8 days) after infliximab therapy. There were more urgent colectomies in patients with a first presentation of UC 7/15 (46.7%) than in those with an established diagnosis 6/24 (25%), p=0.16, OR 2.63 (CI 0.67-10.4) Patients treated with infliximab 5 days or less after admission were more likely to	At 90 days 17/24 (70.8%) had withdrawn corticosteroid therapy and 20/24 (83.3%) were established on azathioprine/MP immunosupression Successful withdrawal of steroids at day 90 was comparable in those treated single or multiple infusions (3/5 (60%) v 14/19 (73.7%), p=0.61) 10/26 (38.5%) responders had more than 1 infliximab infusion; 5 patients had 3 doses (0, 2, 6 weeks), 1 patient went on to an 8 weekly maintenance schedule, and one had a second infusion at 26 weeks. Both of the 2 patients requiring colectomy during median follow-up had received only one dose of infliximab	**Death**: There was one death in a 71 year old male, an ex-smoker with a past history of ischaemic heart disease (myocardial infarction 6 and 13 years ago), transient ischaemic attach and mild chronic obstructive pulmonary disease. He was diagnosed with left-sided UC 4 months prior to admission and treated with oral balsalazide. 9 days after admission (after 8 days of intravenous corticosteroid therapy), he was treated with infliximab. He responded and was discharged home 1 week after therapy on 40mg prednisolone, 1.8 mg/kg azathioprine and balsalazide. Two weeks later he presented with bronchopulmonary pneumonia, despite 2-3 days of ICU therapy he died from overwhelming septicaemia. **Adverse events:** *Postoperative:* Severe fungaemia n=1	

undergo urgent colectomy than those treated after 6 days or more, though the difference was not significantly different 5/9 (55.6%) v 7/29 (24.1%), p=0.11, OR 3.93 (CI 0.82 – 18.8) At 90 days no additional patients had undergone colectomy During a median follow-up of 203 days (IQR 135.5 – 328.5) 2 additional colectomies were reported Serum albumin was predictive of colectomy (P=0.05); a serum albumin of <30 g/L at admission or <34 g/L on day 3 of intravenous corticosteroid therapy were significantly more likely to undergo colectomy (p=0.05, OR 6.86 (CI 1.03-45.6) and p=0.02, OR 12 (1.28-112.7) respectively	5 further patients had a second infusion to treat clinical relapse (2, 10, 12, 26 and 39 weeks after the first infusion). The patient re-treated at 39 weeks had a delayed hypersensitivity reaction to the second infusion	Pelvic collection n=1 Uncomplicated urinary tract infection n=2 Severe psychological morbidity relating to stoma formation n=1 *Infectious:* Death from Pseudomonas pneumonia n=1 Varicella-zoster infection n=1 Cellulitis associated with intravenous cannula n=1 *Infusion reactions:* Acute infusion reaction n=1 Delayed hypersensitivity reaction n=1 *Others:* Self-limiting transaminitis n=1	
Methods	**Participants**	**Statistics**	**Outcomes**
Regueiro, M., J. Curtis, and S. Plevy, Infliximab for hospitalized patients with severe ulcerative colitis, in J Clin Gastroenterol. 2006. p. 476-81			
Design: Retrospective review using medical archives and inpatient pharmacy database **Duration**: Patients treated between 2000 and 2004 **Location**: University of Pittsburgh and	**Population**: 12 were treated with infliximab after discussion of other medical and surgical options. All subjects had a confirmed diagnosis of UC by clinical, endoscopic, and pathology reports. All patients were refractory to oral and intravenous corticosteroids, had intractable diarrhoea and bleeding despite prednisone treatment for at least 2 week prior to admission.	**Group**: 62 patients were admitted with severe UC; 19 responded to intravenous corticosteroids, 13 had a colectomy on admission, 4 had a change of diagnosis to Crohn's disease, 3 had Clostridium difficile, 2 were	Response to infliximab was defined as avoidance of colectomy by 6 months and cessation of corticosteroids DAI was measured at baseline and two weeks after infusion

Medical Center Presbyterian/Montefoire Hospital **Sponsorship**: Not reported **Dosage**: One or more doses of infliximab 5mg/kg administered as an intravenous infusion over 2 hours. An induction regimen (2 and 6 weeks) followed by a maintenance regimen (every 8 weeks after induction) was intended for patients who responded initially **Other medication/treatment**: **Safety**: Adverse events not reported	UC was defined by superficial inflammation of the mucosa that was continuous from the rectum extending proximally but without small bowel involvement. Extent of colitis was classified as left-sided (distal to the splenic flexure) or pancolonic (proximal to the splenic flexure). Disease activity was defined using the Disease Activity Index (DAI) which accounts for stool frequency, rectal bleeding, and physician rating (mild disease correlates with a score of 1 to 3, moderate disease with a score of 4 to 6, and severe disease with a score of 7 to 9). For the purposes of this study, remission was defined as a score of 0. **Baseline Demographics**: Sex, male/female 8 (67%)/4 (33%) Age, median (range, y) 36 (19 to 78) Disease Activity Index 9 Disease activity Severe 12 (100%) Moderate 0 (0%) Mild 0 (0%) Duration of UC 5.5 mo (1 mo to 4 yrs) Extent of UC Left sided 1 (8%) Pancolitis 11 (92%) Medications at admission 5-aminosalicyclic acid 10 (83%)	treated and responded to cyclosporine, and 9 enrolled in a research trial. **Analysis**: Data extracted from physical, colonoscopy, and pathology reports, operative notes, discharge summary, outpatient clinic notes and inpatient pharmacy records. Information was made available through a de-identification software programme. Patient data collected included age, sex, duration of UC, extent of UC, prior corticosteroid use, concomitant medication at admission, medication started during hospital stay, dose and frequency of infliximab, response, colectomy, time from first infliximab infusion to colectomy. Changes in DAI were	

	Corticosteroids 12 (100%) Azathiorpine or 6-mercaptopurine 0 (0%) Antibiotics 1 (8%) Medications started in hospital IV corticosteroids 12 (100%) Infliximab 12 (100%) Azathiorpine or 6-mercaptopurine 4 (33%) Steroid refractory 12 (100%)	analysed using Wilcoxon signed-rank test and considered significant if P<0.05	
Results - Responders	**Results - Nonresponders**	**Adverse events**	
3/12 patients responded to infliximab (median DAI=1, range 0 to 3) and were able to avoid colectomy and discontinue corticosteroids (median follow up 26 mo, range 20 to 27 mo. DAI scores did not significantly decrease from a baseline level of 9 to 8 2 weeks after the first dose of infliximab. DAI scores began to improve 2 weeks after the first infusion (score of 5, 7 and 9) and continued to improve after the second dose. By 4 weeks, DAI had dropped to 2, 3, and 4 respectively. One patient had been treated with cyclosporine without response. All 3 responders had a re-staging colonoscopy within 1 year of hospitalisation and endoscopic response was found to correlate with clinical response (DAI 1, 0, and 3)	9/12 patients failed to respond and ultimately required colectomy; 2 patients did not respond during hospitalisation and the other 7 within 5 months of hospitalisation. DAI scores did not significantly decrease from a baseline level of 9 to 8 2 weeks after the first dose of infliximab. Median number of infliximab infusions in patients in nonresponders: 3 doses (range 1 to 4); 3 patients received 1 dose prior to colectomy (week 0), 2 patients 2 doses (0 and 2 weeks), 1 patient 3 doses (0, 2 and 6 weeks), and 3 patients 4 doses (0, 2, 6 and 14 weeks)	**Death**: Not reported **Adverse events:** Not reported	

9.10 Appendix 10: Details of safety from infliximab maintenance RCTs in UC

Safety from ACT I and ACT II trials

The ACT I and ACT II trials collected extensive safety information. A summary from these trials is given in this section, as it is the most detailed and representative source of evidence in the collection of relevant RCTs.

Safety from ACT I and ACT II

The proportion of patients experiencing any adverse event (AE) was similar in both placebo and patients receiving infliximab 5mg. There was a slight increase in the number of adverse events reported among Infliximab patients in ACT 1 compared to ACT 2 (Table 1) but this may be just a product of the increased length of the study rather than a cumulative effect of the medication as the placebo group showed a similarly increased number of AEs. There were more serious adverse events (SAEs) reported by patients receiving placebo than active treatment in both studies (Table 1). Of these the majority involved the gastrointestinal tract including worsening of UC (Table 2, Table 3), abdominal pain and nausea. A single patient in the ACT 2, 5mg infliximab study arm suffered a lupus-like reaction which was also considered a SAE. Neurological adverse events in the form of optic neuritis occurred in two patients receiving 5mg infliximab, one in each study. Other SAEs included infections such as upper respiratory tract infections, TB and pneumonia; basal cell carcinoma, prostatic adenocarcinoma and a colonic dysplasia. These were all low in incidence.
There was one death during the ACT 2 study in a patient receiving 5mg infliximab. It occurred in the post 30 week extension period when patients deemed to be benefiting from infliximab were continued on the treatment. The death was due to a complication of histoplasma pneumonia.

Table 1: Summary of main adverse events, ACT 1 and ACT 2

	ACT 1		ACT 2	
	Placebo n (%)	5mg Infliximab n (%)	Placebo n (%)	5mg Infliximab n (%)
Any Adverse Event	103 (85.1)	100 (87.6)	90 (73.2)	99 (81.8)
Serious Adverse Event	32 (26.4)	26 (21.5)	24 (19.5)	13 (10.7)
Infection	47 (38.8)	53 (43.8)	29 (23.6)	33 (27.3)
Serious Infection	5 (4.1)	3 (2.5)	1 (0.8)	2 (1.7)
Acute Infusion Reaction	13 (10.7)	12 (9.9)	10 (8.1)	14 (11.6)

Table 2: Adverse events occurring in >= 10% of either treatment group, ACT 1 and ACT 2

	ACT 1		ACT 2	
	Placebo n (%)	5mg Infliximab n (%)	Placebo n (%)	5mg Infliximab n (%)
Worsening of UC	40 (33.1)	23 (19.0)	20 (16.3)	11 (9.1)
Abdominal Pain	16 (13.2)	11 (9.1)	14 (11.4)	10 (8.3)
Nausea	14 (11.6)	14 (11.6)	9 (7.3)	6 (5.0)
Upp. Resp. Tract Infection	28 (23.1)	20 (16.5)	14 (11.4)	16 (13.2)
Pharyngitis	10 (8.3)	12 (9.9)	3 (2.4)	7 (5.8)
Pain	19 (15.7)	14 (11.6)	11 (8.9)	9 (7.4)
Rash	16 (13.2)	14 (11.6)	3 (2.4)	2 (1.7)
Arthralgia	18 (14.9)	21 (17.4)	6 (4.9)	16 (13.2)
Headache	27 (22.3)	22 (18.2)	18 (14.6)	19 (15.7)
Fever	10 (8.3)	14 (11.6)	12 (9.8)	13 (10.7)
Anaemia	12 (9.9)	4 (3.3)	13 (10.6)	6 (5.0)
Fatigue	11 (9.1)	14 (11.6)	6 (4.9)	6 (5.0)

Table 3: Number of subjects with 1 or more serious adverse events by WHOART system-organ class, ACT 1 and ACT 2

	ACT 1		ACT 2	
WHOART system-organ class of disorders	Placebo n (%)	5mg Infliximab n (%)	Placebo n (%)	5mg Infliximab n (%)
Gastro-intestinal disorders	18 (14.9)	17 (14.0)	19 (15.4)	11 (9.1)
Body general disorders	2 (1.7)	2 (1.7)	0 (0)	3 (2.5)
Musculo-skeletal disorders	1 (0.8)	2 (1.7)	0 (0)	1 (0.8)
Respiratory system disorders	2 (1.7)	1 (0.8)	0 (0)	0 (0)
Cardiovascular disorders	0 (0)	1 (0.8)	0 (0)	0 (0)
Central & peripheral nervous system disorders	1 (0.8)	1 (0.8)	0 (0)	0 (0)
Red blood cell disorders	2 (1.7)	1 (0.8)	2 (1.6)	1 (0.8)
Resistance disorders	4 (3.3)	0 (0)	2 (1.6)	2 (1.7)
Myo-, endo-, pericardial, coronary & valve disorders	0 (0)	0 (0)	1 (0.8)	0 (0)
Vascular (extracardiac) disorders	3 (2.5)	1 (0.8)	1 (0.8)	0 (0)
Ear and hearing disorders	0 (0)	0 (0)	0 (0)	1 (0.8)
Metabolic a disorders	3 (2.5)	0 (0)	0 (0)	0 (0)
Neoplasms	0 (0)	1 (0.8)	0 (0)	1 (0.8)
Skin and appendages disorders	2 (1.7)	1 (0.8)	0 (0)	0 (0)
Urinary system disorders	3 (2.5)	1 (0.8)	1 (0.8)	0 (0)
White cell and RES disorders	0 (0)	1 (0.8)	0 (0)	0 (0)
Blood disorders	1 (0.8)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	2 (1.7)	0 (0)	1 (0.8)	0 (0)
Reproductive disorders	3 (2.5)	0 (0)	0 (0)	0 (0)

Discontinuation of Treatment

Discontinuation of treatment was greater in the placebo arms of both studies than the treatment arms (Table 4). Discontinuation due to adverse events in the ACT 1 study was similar for placebo and 5mg infliximab groups (11 (9.1%) and 10 (8.3%) respectively) but in the ACT 2 study there were 12 (9.8%) adverse event related discontinuations in the placebo group compared with 2 (1.7%) in the 5mg infliximab group. Rates of infusion reactions (defined as any adverse event occurring within 2 hours of an infusion) were similar across the placebo and 5mg infliximab groups (Table 4). A possible delayed hypersensitivity reaction occurred in two patients receiving placebo and two patients receiving 5mg infliximab in ACT 1. In ACT 2, no patients receiving placebo or 5mg infliximab experienced possible delayed hypersensitivity reactions.

Table 4: Discontinuation of drug infusions, ACT 1 and ACT 2

	ACT 1		ACT 2	
	Placebo N/N (%)	5mg Infliximab n/N (%)	Placebo n/N (%)	5mg Infliximab n/N (%)
Discontinued Infusions	74/121 (61.2)	45/121 (37.2)	56/123 (45.5)	24/121 (19.8)
Discontinued due to Adverse Event	11 (9.1)	10 (8.3)	12/123 (9.8)	2/121 (1.7)
Discontinued due to Infusion Reaction	0 (0)	2 (1.7)	0 (0)	0 (0)

Positive tests for antinuclear antibodies and anti-double helix DNA antibodies was only seen in those subjects receiving infliximab, specifically 10.7% of subjects in ACT 1 and 4.9% in ACT 2. Subjects receiving infliximab also developed antibodies to the drug in a small number of cases, 7.8% ACT 1 and 9.5% in ACT 2; this may have lead to an elevated number of subjects experiencing infusion reactions (Table 5).

Table 5: Infusion reactions, by antibodies to infliximab result, ACT1 and ACT 2*

Infusion Reaction n/N (%)	**ACT 1** (at week 54)	**ACT 2** (at week 30)
Positive Test for Antibodies	5/14 (35.7%)	6/12 (50%)
Negative or Inconclusive Test for Antibodies	21/215 (9.8%)	17/176 (9.7%)

* Data includes 10mg infliximab groups

There were no serious infusion reactions or anaphylaxis in the groups of subjects testing positive for infliximab antibodies in either study, but during the ACT 1 study a single patient receiving 5mg infliximab testing positive for antibodies suffered a serious delayed hypersensitivity reaction.

Patients in the 5mg infliximab group had at least half the number of UC-related hospitalisations within the study period (Table 6). The numbers of colectomies and ostomies within the study period are similar, with slightly more occurring in the placebo group of both studies (Table 6).

Table 6: Hospitalisations, Colectomies and ostomies, ACT 1 and ACT 2, through week 54

	ACT 1		ACT 2	
	Placebo n (%)	5mg Infliximab n (%)	Placebo n (%)	5mg Infliximab n (%)
UC-related hospitalisations (mean +- SD)	[redacted]	[redacted]	[redacted]	[redacted]
Colectomy	[redacted]	[redacted]	[redacted]	[redacted]
Ostomy	[redacted]	[redacted]	[redacted]	[redacted]

Additional Studies of relevance

Probert et al recorded 2 SAEs that qualified as life threatening or severe, both in patients receiving placebo. All other SAEs were rated mild with no significant difference between groups. There were no significant infusion reactions observed (REF Probert 2003)

Long-Term Safety Profile

Presently the drug manufacturer Centocor® is conducting a study named RESULTS-UC (T62) to collect long-term safety information in UC infliximab patients who participated in ACT I or ACT II trials. The latest report from this study was distributed in October 2006 and was submitted to the EMEA. The study report concluded that no new safety trends emerged in this review, suggesting that the adverse events profile found in the main ACT I/II studies reflect the safety issues in subsequent years. However the follow-up in RESULTS-UC remains relatively short.

More generally speaking the benefit-risk profile of TNF-α blocking agents is positive and the safety findings to date are similar within the class (Desai and Furst, 2006). More than 5,706 patients have received infliximab in the setting of company sponsored clinical trials (Centocor dossier, on file). An estimated 843,151 patients have been exposed to infliximab since launch of the drug in 1998 (Centocor, data on file).

The Health Technology Assessment NHS R&D HTA Programme have published the longest overview of infliximab safety (Chen et al 2006) in the form of a meta-analysis of trials for all anti-TNF products. In addition to safety observations in short-term efficacy trials, Chen et al noted the following about long-term safety in anti-TNF treatments:

Malignancy and Lymphoma

Chen et al cite a number of sources which have concluded that the incidence of lymphoma in patients treated with anti-TNF products is significantly elevated relative to the general population. However the incidence of other malignancies in anti-TNF recipients was found to be similar to the background level.

Pulmonary Fibrosis

Chen et al cited data from the British Society of Rheumatologists Biologics Register (BSRBR) which suggested possible elevated mortality in the long term for TNF-treated patients who had pulmonary fibrosis at death, however they noted that pulmonary fibrosis patients were overrepresented in this group relative to the controls.

9.11 Appendix 11: Details of RCTs in which acute, refractory UC patients were a subgroup

Description	Relevant patients and treatment	Relevant results
Daperno et al: Outcome of a conservative approach in severe ulcerative colitis. Dig Liver Dis 2004, 36(1):21-28.		
Retrospective study of 149 episodes on 115 patients admitted at a single centre between June 1994 and June 2001 for severe UC. Diagnosis of UC was made using clinical, endoscopic, radaiological and histopathological criteria. Intravenous and topical corticosteroids and supporting treatment were administered, second-line strategies for non-responders included oral cyclosporin, infliximab, and surgery. 76% responded to first line corticosteroids, of whom 24 relapsed and 6 subsequently required colectomy.	36/115 were treated for severe UC refractory to intravenous corticosteroids whilst hospitalised Infliximab n=6 5mg/kg b.w. and repeated the following week if complete response was achieved Oral ciclosporin n=15 5mg/kg b.w./day with adjustment to maintain therapeutic range If remission was achieved, maintenance with azathioprine 2-2.5mg/kg b.w./day was instituted	4/6 (67%) had a good response to infliximab therapy 2/6 (33%) required colectomy 8/15 (53%) had a good response to oral ciclosporin 7/15 (47%) required colectomy All patients responding to second line treatment with oral ciclosporin or infliximab were started on azathioprine. 4 stopped the treatment after 2-3 years 1/8 cyclosprine responders required subsequent colectomy (for chronic active colectomy), median follow-up 5.3 months, range 12-60 0/4 infliximab responders required colectomy, median follow-up 17.7 months, range 13-19 No disease-related mortality was reported
Jakobovits et al. Infliximab for the treatment of ulcerative colitis: outcomes in Oxford from 2000 to 2006. Aliment Pharmacol Ther 2007, 25(9):1055-1060		
Retrospective uncontrolled study of patients admitted at a single centre January 2000 and July 2006. Steroid free remission defined as normal stool frequency and no rectal bleeding whilst not taking steroids. Sustained response defined as steroid free remission for greater than 3 months.	14/30 patients were treated for acute severe UC refractory to intravenous corticosteroids whilst hospitalised Infliximab was administered at a dose of 5mg/kg, follow-up infusions were provided on an 'as needed' basis	12/14 (85%) avoided colectomy during admission 6 patients underwent colectomy a median of 274 days after *first* infusion 8/14 (57%) ultimately underwent colectomy a median of 88 days after *last* infusion 2/14 (14%) achieved sustained steroid free remission

14/30 (47%) had their first infusion for severe UC as an in-patient, the remainder were treated as out-patients with moderate steroid-refractory or dependent disease.		
Ferrante et al: Predictors of early response to infliximab in patients with ulcerative colitis. Inflamm Bowel Dis 2007, 13(2):123-128		
Open prospective study of the first 100 patients admitted to a single centre. Patients had 1st IFX between January 2000 and February 2006. Diagnosis of UC was established using clinical, radiologic, endoscopic, and histologic examination. Clinical response was defined as complete if there was no diarrhoea and bleeding and partial if there was marked clinical improvement but persistent rectal blood loss. 42 patients had participated in ACT1 and majority of patients had moderate-severe disease and were not hospitalised for infliximab infusion.	5/100 patients were treated for acute severe UC refractory to intravenous corticosteroids whilst hospitalised. 1 patient had also already failed treatment with intravenous ciclosporin. Patients were treated with one or more infliximab infusions at 5 or 10mg/kg	3/5 (60%) showed a complete clinical response 4 weeks after the first infusion (including 1 patient who had also received intravenous ciclosporin) 1/5 (20%) improved significantly after a second infusion 1/5 (20%) required colectomy within 2 months of the first infliximab infusion

Appendix 9.12

(The entire report is 'Academic in Confidence')

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Final Report – UC Quality of Life Survey

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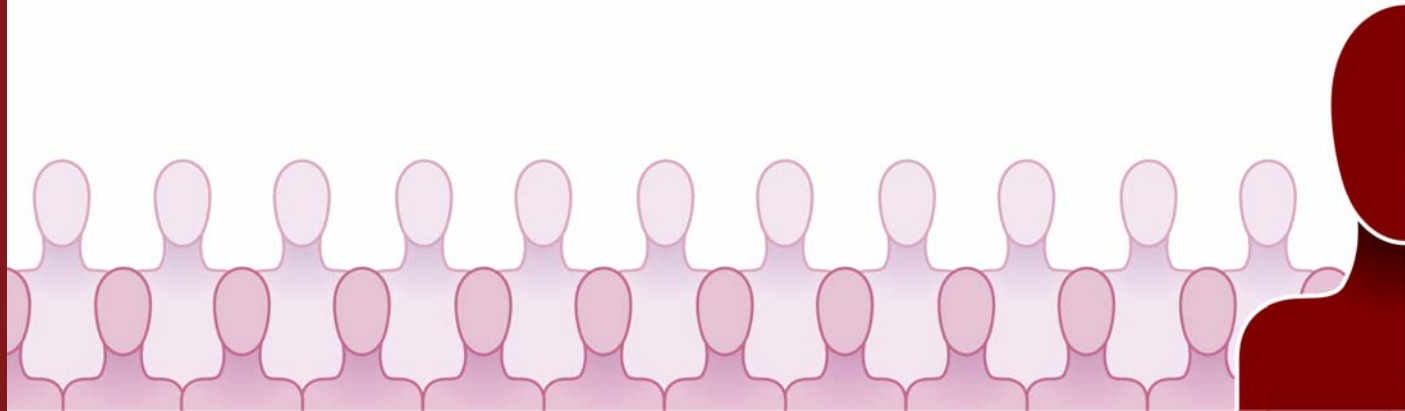
3. April 2007 — Date



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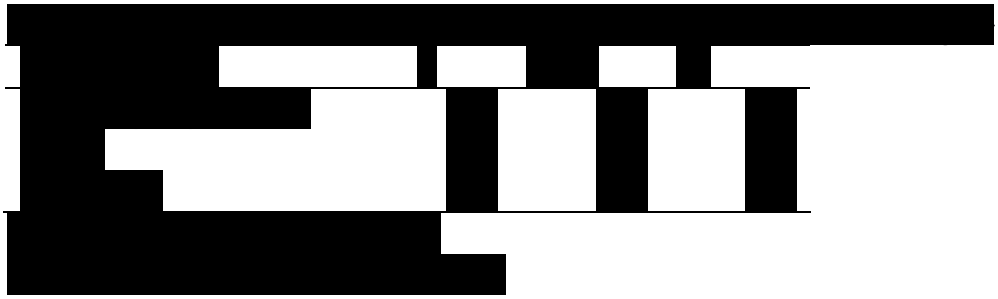

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