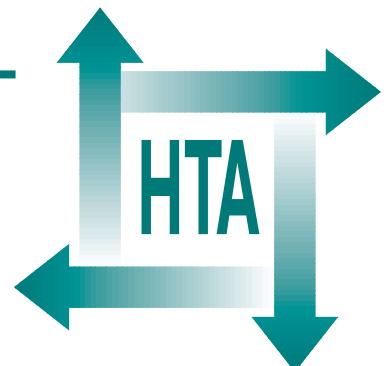# Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease

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Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease

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Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

ACCENT Crohn's disease clinical trial evaluating infliximab in a new long-term treatment regimen.

Crohn's Disease Activity Index (CDAI)
A composite index of overall activity of Crohn's disease as assessed by physicians. It was developed in the 1970s by a group of gastroenterologists as a tool to assess the response, or lack of response, of the disease to a given treatment regimen.[1]

The index consists of eight variables (two subjective) related to the disease, each being weighted according to their ability to predict disease activity. The number of loose stools is a major element of this score. The total score ranges from 0 to over 600 (it is not possible to define a definite numerical upper limit for the score as one variable is based on haematocrit and one on body weight measurement).

At the time the score was developed, various cut-off values were identified. These were based on the scores recorded for a group of 112 patients using the CDAI versus the physician's subjective overall evaluation of 'how the patient was doing'. A score of 150 or below was taken to represent inactive disease and scores above 450 very severe disease. It is not clear what change in the CDAI represents a minimum clinically important difference in disease activity. Since its development in the l970s, the CDAI has been used widely in clinical trials evaluating interventions in Crohn's disease.

Crohn's Disease Endoscopic Index of Severity Scale that assesses five segments of the intestine: rectum, sigmoid and left colon, transverse colon, right colon and ileum. The presence of nine different types of mucosal lesions is assessed for each segment. Using a 10-cm visual analogue scale, each segment is scored for the percentage of the segmental surfaces affected by the disease (0% indicates no involvement and 100% complete involvement). Each segment is also scored for the percentage of the segmental surface affected by ulcerations only.[2] Lower scores indicate endoscopic improvement.

Inflammatory Bowel Disease Questionnaire
This was developed in the late 1980s as a tool to measure quality of life in patients with inflammatory bowel disease.[3] The 32-item questionnaire is used to evaluate general activities of daily living, intestinal function (e.g. bowel habit and abdominal pain), social performance, personal interaction and emotional status. Responses are graded on a seven-point Likert scale: 1 = worst function to 7 = best function. Scores range from 32 to 224, with higher scores denoting better quality of life. Patients in remission usually score 170–190.[4]

Four-dimensional scores cluster items as bowel (e.g. loose stools and abdominal pain; ten questions); systemic (e.g. fatigue and altered sleep pattern, five questions); social (e.g. work attendance and need to cancel social events, five questions), and emotional (e.g. anger, depression and irritability, 12 questions). The questionnaire takes approximately 15–30 minutes to administer.[3,5]

Fistula An unnatural, narrow channel leading from the bowel to the skin or another tissue, such as the bladder, from which gastrointestinal secretions exude.

Perianal Disease Activity Index (PDAI)
This is a composite index of the severity of perianal disease as assessed by physicians. It was developed in 1995 because conventional

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Glossary *contd*

disease activity scores were not considered to reflect the severity of perianal disease. The index consists of five variables related to perianal disease activity. Each of these elements is graded on a five-point Likert scale. The total score ranges from 0 to 20. The index is based on symptoms, daily activities and functions that can be affected by perianal disease that are not already part of the standard CDAI. In the PDAI, a higher score represents more severe disease. The index has demonstrated good correlation with physician and patient global assessment for validity and reliability.[6]

List of abbreviations

Anti-ds DNA	antibodies to double-stranded DNA	ITT	intention-to-treat
CDAI	Crohn's Disease Activity Index	NCCDS	National Co-operative Crohn's Disease Study
CDEIS	Crohn's Disease Endoscopy Index of Severity	NNT	number needed to treat
CI	confidence interval	NR	not reported
CRP	C-reactive protein	OR	odds ratio
ECCDS	European Co-operative Crohn's Disease Study	PDAI	Perianal Disease Activity Index
EMEA	European Medicines Evaluation Agency	QALD	quality-adjusted life-day
		QALY	quality-adjusted life-year
FDA	[US] Food and Drug Administration	RA	rheumatoid arthritis
HACA	human antichimeric antibody	RCT	randomised controlled trial
IBDQ	Inflammatory Bowel Disease Questionnaire	SD	standard deviation
		TB	tuberculosis
IQR	interquartile range	TNF	tumour necrosis factor

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract of unknown aetiology. It can occur at any age, but most commonly presents in those aged 15–25 years. Approximately 31,000 people in England and 1800 in Wales are estimated to have the disease, with about 2650 new cases being diagnosed each year.

Patients with Crohn's disease suffer recurrent attacks with acute flares of the disease interspersed with periods of spontaneous remission. The disease can be complicated by the development of obstructions, perianal disease and fistulae (seen to develop in about one-third of patients).

Crohn's disease is currently neither medically nor surgically curable. Treatment is aimed at reducing symptoms and maintaining/improving quality of life while minimising toxicity. Corticosteroids and immunomodulators (chiefly azathioprine or 6-mercaptopurine) form the mainstay of treatment for active Crohn's disease. Treatment is less clear in fistulising Crohn's disease. When fistulae result from mechanical strictures, surgery will return patients to good health. Fistulae that develop in the absence of an obstruction respond poorly to drug therapy. Simple perianal fistulae show an excellent response to surgery. When medical treatment is required, azathioprine and 6-mercaptopurine are currently considered the most effective, although randomised controlled trial (RCT) data are limited. Overall, surgery will be required by 50–80% of patients with Crohn's disease at some stage. Main indications are strictures causing obstructive symptoms, failure to respond to medical therapy and complications, such as fistulae.

Infliximab is the first tumour necrosis factor inhibitor to be licensed for the treatment of Crohn's disease. Infliximab is indicated for use in adults with chronic active or fistulising Crohn's disease who have not responded to an adequate course of conventional treatment. The drug is given by intravenous infusion. Treatment can be repeated up to 14 weeks from the last infusion in patients where signs and symptoms of the disease recur. Re-administration after this time is not recommended because of the risk of delayed hypersensitivity.

Objectives

The objectives of the review were to address the following questions.

- How effective is infliximab as a second- or third-line treatment for severe active Crohn's disease in adults who have not responded to conventional treatment?
- How effective is infliximab at reducing the number of draining fistulae in adult patients with fistulising Crohn's disease who have not responded to conventional treatment?
- What is the frequency and severity of adverse effects associated with the use of infliximab?
- What adverse events are associated with repeated treatment with infliximab?
- How cost-effective is infliximab for the above indications compared with standard practice?

Methods

A systematic review of RCTs addressing the above questions was undertaken. The economic evaluation submitted by Schering-Plough Ltd was critiqued and the cost/quality-adjusted life-year (QALY) re-estimated by adjusting the assumptions.

Results

Number and quality of studies
Four RCTs were included in the review: three completed and one ongoing, with preliminary data available to 30 weeks. All trials appeared to be of good methodological quality but this could not be confirmed in the case of the ongoing study.

Clinical effectiveness
The use of infliximab in chronic active Crohn's disease resistant to conventional treatment was evaluated in three trials involving 754 patients. Only the two smaller trials ($n = 181$) had been completed. The larger ACCENT I trial ($n = 573$) has yet to be fully reported. A single dose of

infliximab was associated with significant treatment benefit at week 4 (number needed to treat (NNT) = 3 for response defined as a ≥ 70-point reduction in Crohn's Disease Activity Index), with approximately 30% of patients achieving remission of their symptoms at this time (NNT = 4). Benefit was, however, short-lived with the majority of patients relapsing beyond week 12. Data on repeated treatment were less clear. The evidence suggested that a positive treatment effect was seen, but current data were too limited to confirm this. The full results from the ACCENT I trial will address this.

Only one trial evaluated the use of infliximab in fistulising Crohn's disease. A three-dose treatment course resulted in complete healing of perianal/abdominal fistulae for more than 21 days in 46% of patients treated with infliximab versus 13% treated with placebo (NNT = 4). Again, treatment benefit was short-lived, with a median duration of 3 months. Data on repeated treatment are not currently available but will be provided by the ACCENT II trial.

Cost-effectiveness
Costs
For a 70 kg patient, the cost of one dose of infliximab, 5 mg/kg, is approximately £1800, with a three-dose course costing about £5400.

Cost/QALY
Using the Schering-Plough Ltd model, the cost/QALY in the treatment of chronic active Crohn's disease was calculated as £6700 with a single-dose treatment, £10,400 with episodic re-treatment and £84,400 with maintenance treatment. It is considered that these overestimate the benefits of infliximab owing to assumptions that the drug influences the natural history of the disease (see below).

In fistulising Crohn's disease, the cost/QALY values were high, £102,000–123,000 for initial treatment and £82,000–96,000 with the most favourable re-treatment assumptions on closure rates.

Sensitivity analyses
The chronic active model was highly sensitive to rate of 'flare' for episodic treatment. The flare rate chosen was 10%, which seemed reasonable based on clinical opinion. If more frequent flare was seen, then costs increased substantially: the incremental cost/QALY was £55,000 with a 50% likelihood of flare. The fistulising model was relatively insensitive to costs offset (owing to surgery averted), even when 100% offset was assumed.

Limitations of the assumptions made
In developing the model for chronic active Crohn's disease, the manufacturer made the implausible assumption that treatment with infliximab would alter the natural course of the disease. There were no observational data available but the RCT data suggest that patients return to their pre-treatment disease state with time.

Conclusion

Implications for practice
Infliximab is a specialised treatment requiring intravenous administration. Patients being considered for infliximab treatment need to be fully assessed by specialists experienced in the management of severe Crohn's disease. These patients will have disease that is not amenable to conventional medical and surgical management. Use of infliximab is, therefore, likely to be limited to a small group of patients, in whom benefits over existing treatment can be expected.

Recommendations for research
Considerable further research is required in this rapidly developing therapeutic field. In particular, research needs to clarify optimal dosage and dosage frequency for infliximab, the characteristics of poorly responding patients, and its optimal place in therapy amongst the other available treatment options, including surgery.

Chapter 1
Objectives and background

Objectives of the review

- To assess the evidence for the effectiveness of infliximab for the treatment of severe active Crohn's disease or fistulising Crohn's disease in adults who have not responded to a full and adequate course of therapy with conventional treatment.
- To assess the evidence on the cost and cost-effectiveness of infliximab for these indications.

Description of Crohn's disease

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract of unknown aetiology. Any part of the gastrointestinal tract can be affected but the terminal ileum (30–35%) or the ileocaecal region (40%) are most commonly involved. The disease is confined to the colon in about 20% of patients and to miscellaneous locations (e.g. the mouth or anorectum) in 5%.[7–10]

In Crohn's disease the lining of the gut is swollen and ulcerated with thickening of the wall of the intestine. The inflammation seen may spread through the wall to involve neighbouring structures. Local perforation of the wall can lead to localised or widespread infection or an opening in the skin (fistula) through which intestinal contents emerge.[8]

Crohn's disease must be differentiated from other inflammatory bowel diseases (especially ulcerative colitis). Diagnosis may be delayed for several years in patients with intermittent abdominal symptoms. An average interval of 35 months from the onset of symptoms to diagnosis was documented by the National Co-operative Crohn's Disease Study (NCCDS).[11]

Aetiology
The cause of Crohn's disease is unknown but is believed to involve genetic, environmental, infectious and immunological factors. Studies in animals suggest that chronic intestinal inflammation results from overly aggressive cellular immune responses to selected bacteria that are present normally in the lumen as a result of genetically determined defective immunoregulation (loss of tolerance) or abnormal function or healing of the mucosal barrier.[12]

Presentation
The clinical features of Crohn's disease are variable and are partly determined by the site of the disease. The majority of patients complain of diarrhoea (70–90%), abdominal pain (45–66%), weight loss (65–75%) and anal lesions (50–80%). Fever (30–40%) and rectal bleeding (45%) are also common.[7]

Ileal disease is often associated with obstructive symptoms (colic, vomiting). There may be symptoms of malabsorption. A long-term follow-up study has suggested that ileocolic location of the disease is associated with the highest morbidity, especially in terms of the need for surgery.[13]

Colonic disease is particularly associated with rectal bleeding, perianal disease and extraintestinal manifestations involving the skin or joints. Symptoms of anaemia are common. The rectum may be the only site of the disease, particularly in elderly patients.[14] Proctitis, however, often accompanies ileal disease. Very rarely, the disease affects only the mouth, stomach or duodenum.[7,13]

Complications
Crohn's disease can be complicated by the development of obstructions, fistulae and perianal disease. Strictures are most common in the small bowel but can also develop in the large bowel. They may be asymptomatic initially but will eventually cause obstructive symptoms.

Fistulae develop in about one-third of patients. These may be enterocutaneous (through the abdominal wall), enteroenteric (bowel-to-bowel), enterovisceral (bowel-to-tissue, e.g. bladder) or perianal (bowel-to-perineum). Enterocutaneous, enteroenteric and enterovisceral fistulae usually result from a mechanical stricture. Surgery will return these patients to good health.

Perianal disease comprises fissures, fistulae and abscesses. It is a frequent complication of colonic and ileocolic disease (documented in > 35% of patients in one American cohort).[13] The cause of perianal fistulae is not clear. A spontaneous

healing rate is seen but surgical management (draining of abscesses) or medical treatment is often required.

Other complications of Crohn's disease include acute dilatation, perforation and massive haemorrhage (particularly when the disease affects the colon), and carcinoma of the small bowel (< 5% at 10 years) or colon. Extraintestinal manifestations (e.g. articular disorders, dermatological lesions, ocular disorders or hepatic disorders) have been documented to develop in more than 15% of patients,[13] occurring predominantly in patients with colonic Crohn's disease.[7]

Prognosis
Most patients with Crohn's disease lead full and active lives and can be kept in reasonable health. Nevertheless, patients are at risk of recurrent attacks, with acute flares in the disease interspersed between periods of spontaneous remission. In any one year, 50% of patients will experience symptoms. These will be severe in about one-quarter of all patients.[7,8]

At least 50% of all patients with Crohn's disease require surgical treatment during the first 10 years of their disease; one in 12 will require two or more operations during this period. Surgery is usually performed for specific complications (such as internal obstructions, internal fistulae or toxic megacolon). Only a relatively small number of patients require operations for chronic illness or failure of medical therapy.[13] Following resection for ileal or ileocaecal disease, at least 50% of patients relapse within 10 years and about half require further surgery.[7,8]

Five years after the onset of the disease, 15–20% of patients are disabled by their disease.[8] However, Crohn's disease is no longer associated with significantly increased mortality due to improved surgical and medical management.

Determining disease activity
Defining disease activity in Crohn's disease is complicated by the heterogeneous patterns of disease location and complications. No single 'gold standard' indicator of clinical disease has been established. Composite indices of disease activity have been developed for use in clinical trials,[14] along with disease-specific instruments to measure quality-of-life factors. These include the Crohn's Disease Activity Index (CDAI), the Perianal Disease Activity Index (PDAI) and the Inflammatory Bowel Disease Questionnaire (IBDQ) (see the glossary for details).

Classification of Crohn's disease
Crohn's disease is not considered a single homogeneous clinical entity. Unfortunately, there is no generally accepted simple classification of Crohn's disease that distinguishes its principle varieties on the basis of essential differences in clinical behaviour and outcomes.[9]

Definitions of different severities of Crohn's disease
Infliximab is indicated for the treatment of severe active Crohn's disease or fistulising Crohn's disease unresponsive to conventional treatment. There are no standard definitions to identify these patients; hence in this study, the following working definitions were used.

- **Severe active Crohn's disease** Patients who have a CDAI score of > 450.[15]
- **Treatment-resistant** Patients with persisting symptoms (CDAI > 150) despite the introduction of medical treatment (e.g. corticosteroids or azathioprine).
- **Fistulising Crohn's disease** Patients with enterocutaneous, enteroenteric, enterovisceral or perianal fistulae.
- **Remission** Patients who are asymptomatic or without inflammatory sequelae[14] and with a CDAI of < 150.

Epidemiology (prevalence/incidence)
Crohn's disease occurs in all age groups but most commonly presents in those aged 15–25 years. Women are slightly more likely to be affected than men (see *Table 1*). No marked difference in incidence is apparent across the social classes.[7,16] The disease does, however, appear to be more common in whites than in blacks and Asians. In particular, there may be an increased incidence (three- to six-fold) among Ashkenazi Jews.[8]

TABLE 1 *Annual incidence of Crohn's disease per 100,000 population (as measured during 1991–1993). Adapted with permission from the British Society of Gastroenterology*[8]

	Age group (years)		
	15–44	45–64	65+
Men	6.0	3.2	2.9
Women	7.7	3.0	2.0

A clear familial aggregation has been documented. Approximately 15–20% of patients with Crohn's disease have one or more family members (usually first degree relatives) with either Crohn's disease or ulcerative colitis.[7]

Smokers are more likely to develop Crohn's disease than those who do not smoke (relative risk 3:4).[8,17] Other factors recognised as exacerbating Crohn's disease include intercurrent infections and non-steroidal anti-inflammatory drugs.[7,18]

There are no accurate data on the incidence and prevalence of Crohn's disease. The extent of the disease varies across the world, with the highest levels reported in western Europe and the USA. Incidence has been reported to have increased about five-fold throughout northern Europe since the 1950s (*Figure 1*).[19]

The prevalence of Crohn's disease in the western world is estimated to be 50–100/100,000 population with an incidence of 10/100,000/year. In the UK, prevalence is estimated to be 62.5/100,000 (31,095 people in England and 1836 in Wales), with about 3000 new cases diagnosed each year (approximately 2500 people in England and 150 in Wales).[8,20] There are no reliable data on the proportion of patients with different severities of the disease in England and Wales. Data on morbidity from the literature are given in *Table 2*.[8,21,22]

The lifetime clinical course of Crohn's disease was evaluated in a 24-year population-based inception cohort of patients with the disease in Olmstead County, USA. The cohort consisted of 174 patients with a median age at diagnosis of 28.1 years followed up for a median of 10 years. A Markov cohort analysis projected a future life expectancy of 46.4 years for a representative Crohn's disease patient aged 28.1 years at the time of diagnosis. The projected future clinical course consisted of 11.1 years (23.9%) in medical remission (no medications), 18.9 years (40.7%) in post-surgical remission (no medication), 12.7 years (27.4%) on an aminosalicylate or similar drug and 3.2 years (6.9%) on corticosteroids or immunosuppressants. Over time, the proportion of patients with mild disease (on aminosalicylates) rapidly increased but at any given time only a small proportion of patients required surgery or corticosteroid or immuno-suppressant treatment.[23] These data were used to derive utility scores by stage,[24] which were used in modelling the cost-effectiveness of interventions.

The anatomical location of the disease is known to be a major determinant of clinical care and complications. Ileocolic location is associated with the highest morbidity, particularly in terms of the need for surgery. A follow-up study of 615 patients diagnosed with Crohn's disease at the Cleveland Clinic between 1966 and 1969 reported that 91.5% of patients with ileocolic disease, 65.5% with disease of the small intestine and 58% with disease of the colon/anorectal regions required surgery over the mean follow-up period of > 13 years.[13]
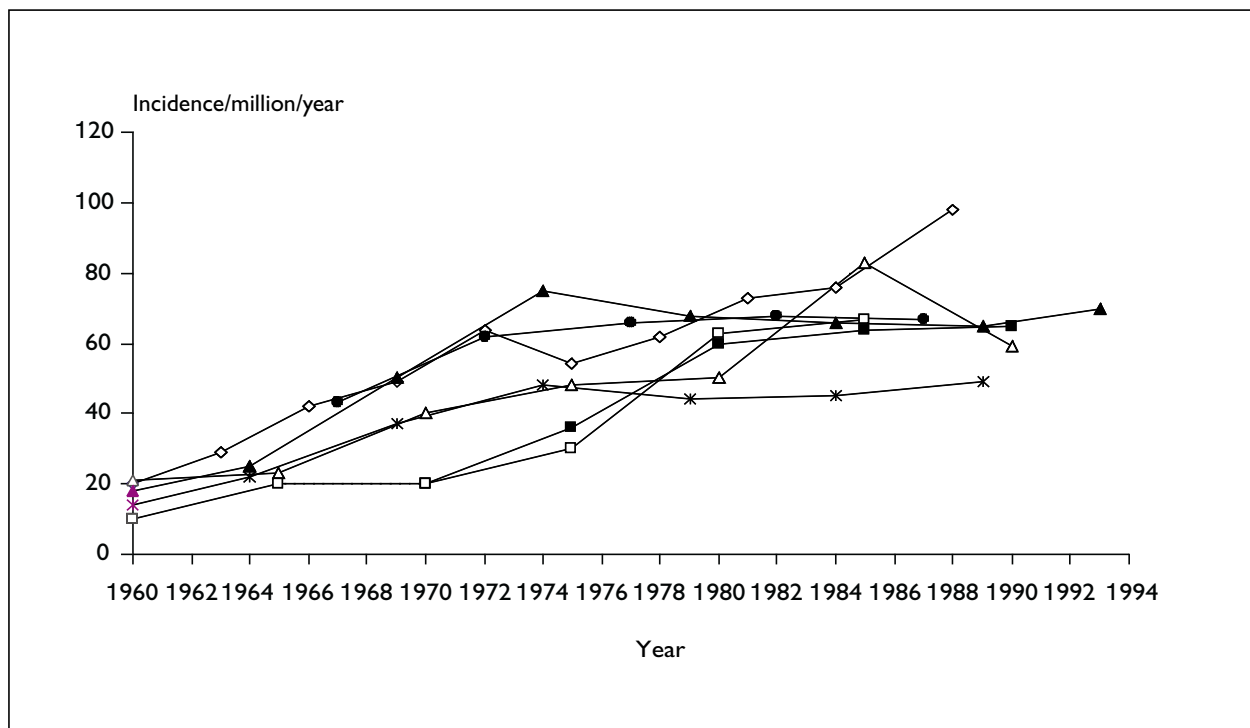

FIGURE 1 *Recent time trends in the incidence of Crohn's disease. ◇, Aberdeen, UK; ■, Blackpool, UK; △, Cardiff, UK; □, Derby, UK; ✳, Stockholm, Sweden; ●, Orebro, Sweden; ▲, Rochester, USA. Adapted from Logan, 1998[19] with permission from the BMJ Publishing Group and Professor RFA Logan*

TABLE 2 *Expected morbidity in any given year*

Stage of disease	Proportion of Crohn's disease patients			Estimated number of patients for average health authority of 500,000
	Munkholm *et al.*, 1987[21]	British Society of Gastroenterology, 1996[8]	Andersson *et al.*, 1998[22]	
Patients diagnosed with Crohn's disease	–	–	–	313
Remission	55%	< 50%	58–69%	156–216
Active disease		> 50%		
Mild–moderate	15%	–	19–29%	47–91
Moderate–severe	} 30%	–	10–12%	31–38
Severe symptoms		25%	1–4%	3–78
Fistulising disease	NR	NR	NR	–
Surgery	5% mean annual rate (35% required operation during year of diagnosis, 12% during first year, 8% during second year)	–	5.7%	16–18

Current service provision

Crohn's disease is managed in both primary and secondary care. General practitioners largely manage patients with quiescent or low-grade symptoms. Patients with extensive active disease, those who are steroid-dependent, being treated with immunosuppressants or requiring surgery are managed in secondary care.[8]

Crohn's disease is neither medically nor surgically curable. Treatment is, therefore, aimed at reducing symptoms to maintain/improve quality of life while minimising short- and long-term toxicity.[14] A number of therapeutic agents, which have been variably evaluated, are currently used. Unfortunately, differences in study design, patient populations, drug regimens and endpoints hamper the combining and comparison of data collected on these drug therapies in clinical trials.

Induction of remission (CDAI ≤ 150)
Active Crohn's disease
Aminosalicylates, corticosteroids, antibiotics and immunosuppressants have all been evaluated in the treatment of active Crohn's disease. The NCCDS[25] and the European Co-operative Crohn's Disease Study (ECCDS)[26] conducted in the late 1970s/early 1980s, provided key data on the efficacy of aminosalicylates and corticosteroids. Data on other treatments have been chiefly provided by later studies. Mesalazine and sulphasalazine are accepted as having only modest efficacy. In the NCCDS and ECCDS, 38% versus 26% and 50% versus 37% of patients achieved clinical remission with short-term

sulphasalazine treatment (16–18 weeks) compared with placebo.[25,26] Similar efficacy has been reported with mesalazine.[27,28] In particular, benefit with sulphasalazine has only been consistently demonstrated in patients with colitis and ileocolitis.[26]

Short-term (4–8 weeks) treatment with corticosteroids forms the mainstay of therapy in active Crohn's disease. In the NCCDS and ECCDS, 47% versus 26% and 83% versus 37% of patients treated with oral prednisolone and placebo, respectively, for 16–18 weeks achieved clinical remission. Budesonide in a controlled ileal release oral formulation has demonstrated similar efficacy to prednisone (remission rates of 51–69% over 8–10 weeks) in patients with active disease of the ileum, ileo-caecal region or ascending colon.[4,29] In severe active disease, hospital admission and intravenous administration of corticosteroids may be required.

Despite a good initial response, it is recognised that, of those who do respond to oral corticosteroids, a proportion will become treatment resistant and others, dependent on treatment, will relapse once the dose is reduced or treatment discontinued. In one cohort followed in the 1980s, 48% of patients had a complete response to corticosteroid treatment at 30 days, 32% had a partial response and 20% had no response. After 1 year, 56% of patients were resistant to (20%) or dependent on (36%) corticosteroids.[30]

Both azathioprine and 6-mercaptopurine are widely used in the management of active Crohn's

disease. A Cochrane review (last substantive update April 1998) combined the data from three randomised controlled trials (RCTs) of azathioprine and 6-mercaptopurine therapy in adult patients ($n = 425$) with active Crohn's disease.[31] Overall, the odds ratio (OR) of a response to azathioprine or 6-mercaptopurine therapy compared with placebo in these patients was 2.36 (95% confidence interval (CI), 1.57 to 3.53; number needed to treat (NNT) = 5). These immunosuppressants also demonstrated steroid-sparing effects (OR = 3.86, 95% CI, 2.14 to 6.96; NNT = 3). Conversely, the OR for a patient suffering an adverse event requiring withdrawal from treatment was 3.01 (95% CI, 1.30 to 6.96; NNT = 14).[31] In particular, treatment with these drugs was associated with the risk of bone marrow suppression and pancreatitis. Regular patient monitoring is, therefore, essential.

Trials have also been undertaken with once-weekly intramuscular methotrexate therapy. Such treatment has been demonstrated to induce clinical remission with total steroid withdrawal in 39% of patients dependent on steroids compared with 19% treated with placebo for 16 weeks.[32] The immunosuppressants cyclosporin, tacrolimus and mycophenolate mofetil have been evaluated in small groups of patients with Crohn's disease. Preliminary data suggest they may offer some benefit, although results have been conflicting.[33–35] Larger RCTs are now under way with tacrolimus.[35]

Other treatments that are used are oral antibiotics (chiefly metronidazole and/or ciprofloxacin) and enteral nutrition. RCTs with antibiotic therapy are scarce, with most reporting negative results.[4] Clinical opinion currently considers these drugs modestly effective in mild to moderately active Crohn's disease. Antibiotics have an obvious role where there is associated sepsis or bacterial overgrowth in the small intestine. The efficacy of enteral nutrition as a primary therapy of active Crohn's disease has been evaluated in a meta-analysis of eight trials in 413 patients. Enteral nutrition was found to be inferior to cortico-steroids (pooled OR = 0.35, 95% CI, 0.23 to 0.53). There is also some evidence that patients relapse more quickly if their active disease is treated with an elemental diet compared with patients treated with corticosteroids.[8]

Fistulising Crohn's disease
Enterocutaneous, enteroenteric and enterovisceral fistulae commonly result from a stricture and, therefore, require surgical management. Fistulae that develop in the absence of an obstruction respond poorly to drug therapy. Simple perianal fistulae (generally those with a single external opening) comprise the majority of fistulae observed in patients with Crohn's disease. These fistulae show an excellent response rate to surgery (fistulotomy), with healing rates of 70–100% and recurrence rates of < 20% documented in the literature.[36]

Complex fistulae (those with many openings, those that are high, those with internal openings above the dentate line, those with horseshoe tracts or those with high blind extensions) typically cannot be healed by surgery alone without significant resulting morbidity.

Of the drugs available, the aminosalicylates and corticosteroids have demonstrated no efficacy in the treatment of this complication. Anecdotal reports and uncontrolled trials suggest antibiotics can cause some fistulae to heal over the short term.[4,36] Currently, immunomodulatory agents are considered the most effective drugs for the management of fistulising Crohn's disease. Controlled clinical trial data are, however, limited. In the Cochrane review of azathioprine and 6-mercaptopurine, a response rate was reported of 55% with azathioprine or 6-mercaptopurine therapy versus 29% with placebo (OR = 4.58, 95% CI, 0.49 to 42.82; NNT = 4) favouring fistula healing. Larger trials are, however, required to evaluate whether a significant benefit is seen with treatment.[31] Trials are under way to evaluate the efficacy of tacrolimus in fistulising Crohn's disease after preliminary studies suggested potential benefit.[35,36]

Maintenance treatment
Data on the efficacy of drugs for the maintenance of remission in Crohn's disease are conflicting. The NCCDS and ECCDS failed to demonstrate statistically significant efficacy with sulphasalazine as a maintenance treatment following medically induced remission. Data for mesalazine are less clear. In two meta-analyses published in 1994, a reduction in the relapse rate of approximately 50% with mesalazine was reported, predominantly in patients with ileal and ileocolonic disease.[37,38] In a more recent meta-analysis, it was reported that mesalazine treatment significantly reduced the symptomatic relapse rate compared with placebo (NNT = 16). However, subgroup analysis suggested significant benefits were confined to patients following surgical remission (NNT = 7), with non-significant benefit apparent in patients following medical remission.[39] The use of con-ventional systemic corticosteroids in patients

with clinically quiescent Crohn's disease did not appear to reduce the risk of relapse over a 24-month period of follow-up (OR = 0.72, 95% CI, 0.30 to 1.35).[40]

Azathioprine and 6-mercaptopurine are the mainstays of maintenance therapy. In a pooled analysis, maintenance of remission with azathioprine was seen in 67% versus 52% of patients treated with placebo (OR = 2.16, 95% CI, 1.35 to 3.47; NNT = 7). A steroid-sparing effect was also noted (OR = 5.22, 95% CI, 1.06 to 25.63; NNT = 3 for quiescent disease). In this pooled analysis, the number needed to harm was calculated at 19 for withdrawals due to adverse events (OR = 4.36, 95% CI, 1.63 to 11.67).[41] Unfortunately, the trials to date have been of relatively short duration. The long-term efficacy of azathioprine as maintenance therapy is unclear. Currently, it is recommended that treatment be continued for 3–5 years.[31,42]

Surgical management

Some 50–80% of patients with Crohn's disease will require surgery at some stage. The main indications for surgery are strictures causing obstructive symptoms, failure to respond to medical therapy and complications, such as fistulae and perianal disease.[8]

Maintenance therapy after surgical resection has been seen to prolong remission of the disease since it is nearly inevitable that recurrence of Crohn's disease will occur.[7,14,43] Despite maintenance therapy, symptoms recur after surgery in about 35% of patients within 5 years and in about 73% of patients within 20 years.[44]

Anti-tumour necrosis factor and Crohn's disease

Human tumour necrosis factor (TNF) is a naturally occurring cytokine with multiple biological actions, including the mediation of inflammatory responses and modulation of the immune system. TNF-α is thought to play a central role in the immuno-pathology of Crohn's disease. Raised levels are seen in all types of cells, tissues and secretory fluids in patients with the disease.

Anti-TNF antibodies have been developed to block the effects of TNF-α. These antibodies bind to released TNF-α as well as to membrane-bound TNF-α.[45,46]

Technology under evaluation – infliximab

Infliximab (Remicade™, Schering-Plough Ltd, Welwyn Garden City, UK) is a chimeric human–murine monoclonal antibody that binds with high affinity to TNF-α, inhibiting its activity. Schering-Plough Ltd launched infliximab in the UK on 1 September 1999. Infliximab is indicated for use in adults (≥ 18 years) for the 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
- fistulising Crohn's disease in patients who have not responded despite a full and adequate course of therapy with conventional treatment.[47]

Infliximab is also licensed for use in rheumatoid arthritis (RA) in combination with methotrexate to reduce the signs and symptoms of the disease when the response to disease-modifying drugs, including methotrexate, has been inadequate.

Infliximab is a powder that requires reconstitution and dilution before administration. It is given as an intravenous infusion over at least 2 hours. In severe active Crohn's disease, the recommended dose is 5 mg/kg as a single infusion. In fistulising Crohn's disease, infliximab is given as an initial 5 mg/kg infusion over at least 2 hours, followed by additional 5 mg/kg infusions 2 and 6 weeks later.

For both indications, infliximab treatment can be re-administered within 14 weeks of the last infusion should the signs and symptoms of the disease recur. Re-administration of the drug after a drug-free period of 15 weeks cannot be recommended because of the risk of delayed hypersensitivity reaction.

Infliximab is contraindicated in patients with sepsis, or with clinically manifest infections (including tuberculosis (TB)) and/or abscesses. It is also contraindicated in patients with a history of sensitivity to infliximab or other murine proteins or to any of the excipients. Use during pregnancy or lactation is not recommended.[47]

Infliximab has been marketed in the UK at a cost of £451.20 for a single 100 mg vial. These vials do not contain a preservative – any unused portion of reconstituted solution must be discarded. For a 70-kg patient, the average cost for a single 5 mg/kg infusion is £1804.80 (four vials).

Identification of patients and criteria for treatment

Patients suitable for treatment with infliximab will already have an established diagnosis of Crohn's

disease and have received appropriate medical or surgical treatment. They will be suffering from chronic active disease or fistulising disease but obtaining no benefit from an adequate course of conventional treatment (4–6 months) or surgery. Lack of benefit can be defined as persistent, troublesome symptoms or intolerance to treatment.

Infliximab is suitable for these patients with atypical disease when there are no alternative medical or surgical treatment options. In all cases, patient should have undergone a full assessment by both a gastroenterologist and surgeon experienced in the management of severe Crohn's disease.

Patients who have active sepsis, have a known stricture or abscess or have a history malignant disease should not be treated with infliximab.[48] Additional contraindications include known allergy against murine proteins, pregnancy or breastfeeding.

Personnel involved and setting
Patients suitable for treatment with infliximab will already be under the care of a specialist. They should have been fully assessed by a gastro-intestinal physician and surgeon experienced in the management of severe Crohn's disease. The decision to start infliximab treatment will be made on an inpatient or hospital day-case basis.

Infliximab needs to be reconstituted prior to administration. It is administered as a slow intra-venous infusion over at least 2 hours. An infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter should be used. (Infliximab is incompatible with polyvinyl chloride tubing.[49]) Patients need to be carefully monitored by a nurse or doctor during the infusion in case of an anaphylactic reaction or other acute side-effects. Adequate facilities for the management of allergic reactions should be available.

It would therefore be most appropriate for infliximab to be administered in a hospital setting, where staff are experienced in the reconstitution and administration of intravenous infusions and where patients can be monitored closely during the infusion. A competent team approach is recommended, such as that provided at tertiary centres. It is expected that most patients will be treated on an outpatient basis. Patients with fistu-lising Crohn's disease require repeat infusions at 2 and 6 weeks.

Patients will require follow-up at 2–4 and 8–12 weeks after completion of treatment, with assessment regarding the need for further treatment. Tests for inflammatory markers, full blood count, electrolytes and liver function should be repeated at each visit.[48]

Degree of diffusion
There are no accurate data on the extent of the current usage of infliximab for the treatment of Crohn's disease in England and Wales. Based on sales figures, 16,510 vials were supplied in the UK and Republic of Ireland from September 1999 to May 2001. These sales reflect usage for both licensed indications: Crohn's disease and RA. From these data, it is not possible to calculate the number of patients treated, owing to the different dosages and treatment regimens used in different patient groups and the likelihood that a number of patients will be receiving regular treatment. Schering-Plough Ltd believe that between January 2000 and May 2001, 600–700 patients were treated with infliximab for Crohn's disease. They estimated that use of infliximab in severe active disease and fistulising disease was split equally (M Kehily-Richards, Schering Plough Ltd, Welwyn Garden City, UK; personal communication, 2001).

The University of Birmingham conducted a survey in May/June 2001 of the use of infliximab for the treatment of Crohn's disease among gastro-enterologists in England and Wales. A question-naire (see appendix 1) with personalised letter was sent to all gastroenterologists working in the NHS in England and Wales. In total, 303 question-naires were mailed, and 214 responses were received (a 70.6% response rate). Responding physicians had treated 526 patients with chronic active Crohn's disease (median per gastro-enterologist = 1; interquartile range (IQR), 0–3) and 271 with fistulising Crohn's disease (median per gastroenterologist = 0; IQR, 0–1.75) with infliximab. In some cases, patients were identified as haing been treated as part of an RCT. The numbers of patients currently receiving treatment were much smaller: 203 with chronic active and 70 with fistulising Crohn's disease. Of these patients, 145 (53.1%) were receiving continuous treatment (118 with chronic active and 27 with fistulising disease). Importantly, approximately half of responders identified that funding cur-rently limited their treatment with infliximab of patients with Crohn's disease.

7

Chapter 2

Effectiveness

Methods for reviewing effectiveness

The methods of the review followed the guidance laid out in the West Midlands Development and Evaluation Service Handbook[50] and the NHS Centre for Reviews and Dissemination Report Number 4.[51]

Review questions

The following questions were addressed in this review by assessing existing evidence.

Effectiveness
- How effective is infliximab as a second- or third-line treatment for severe active Crohn's disease in adults who have not responded to conventional treatment?
- How effective is infliximab at reducing the number of draining fistulae in adult patients with fistulising Crohn's disease who have not responded to conventional treatment?
- How effective is infliximab at preventing relapse in adult patients with severe active Crohn's disease or those with fistulising Crohn's disease?

Adverse effects
- What is the frequency and severity of adverse effects associated with the use of infliximab?
- What adverse events are associated with repeated treatment with infliximab?

Cost and cost-effectiveness
- What is the cost-effectiveness of infliximab for the above indications compared with standard practice?

Search strategy

The following electronic databases were searched with a cut-off date of 31 March 2001: Cochrane Library, MEDLINE, EMBASE and Science Citation Index. Search terms included the text words, infliximab, remicade, tumour necrosis factor, tnf, ca2, chimeric ca2, and the index terms, crohns disease, receptors and tumour necrosis factor. A full search strategy is available from the authors on request.

Studies were limited to humans. No language or age restrictions were applied. Altavista and Yahoo search engines were used to search the Internet, and links were followed up. *Scrip*, Food and Drug Administration (FDA) submissions for new drug applications and European Medicines Evaluation Agency (EMEA) reports were searched by hand and the reference lists of identified publications reviewed for further citations.

Studies identified by the search strategy were assessed for inclusion via two stages. First, two reviewers screened titles and abstracts independently for inclusion. Original papers were ordered for all articles that appeared to fulfil the inclusion criteria. Two reviewers then examined the full text of these studies for inclusion. No disagreements occurred (see appendix 2).

Inclusion and exclusion of trials
Inclusion criteria
Studies were included in the final analysis of the systematic review of effectiveness if they met the following criteria.

Study design
RCTs or quasi-RCTs.

Population
Adults aged ≥ 18 years with either severe active Crohn's disease or fistulising Crohn's disease resistant to conventional treatment.

Intervention
Infliximab given as a single dose, treatment course or repeated treatment course.

Comparator
Placebo or other treatment for Crohn's disease.

Publication
All data were to be included irrespective of publication status.

Exclusion criteria
Non-RCT.

Data extraction strategy
Two reviewers independently extracted data using a pre-designed data extraction form. Disagreements were resolved by discussion, with consultation with a third party.

The following data were extracted:

- details of the study populations and baseline characteristics
- details of the intervention, such as dose and frequency of administration
- individual outcomes measured, such as:
  - changes in disease activity (changes in CDAI)
  - changes in PDAI
  - number of fistulae
  - complete response
  - duration of remission
- changes in quality of life
- adverse events reported.

Where possible, data were extracted for the intention-to-treat (ITT) population. When information was missing, further information was sought from the authors or industry.

Quality assessment strategy

Two reviewers independently undertook quality assessments. Disagreements were resolved by discussion, with reference to a third party if disagreement remained. The validity of the studies was assessed by examining the method of randomisation, the comparability of baseline characteristics between different arms, the concealment of allocation, blinding, withdrawals and losses to follow-up for each patient group. A Jadad score was calculated (see appendix 3).

An assessment was made of the clinical relevance of the outcomes reported. Outcomes expected to be of clinical relevance included: CDAI, duration of remission, other Crohn's disease medication used, weight loss/gain, tumours, infections, PDAI, prevention of surgery and IBDQ.

The quality of the reporting of the trials was assessed. When the reporting of a trial was incomplete (e.g. results only reported for some participants or only interim results available), the investigators were contacted for full details. Data from trials that had not finished recruiting were included if available.

Results

Quantity and quality of research available

Number of studies identified

In all, 23 abstracts, posters or full publications that potentially reported relevant trials were identified.[28,52–73] Of these, 21 came from searches of electronic databases[28,53–69,71–73] (ten of these

were also identified by handsearching reference lists), one was identified from the Internet[52] and one from handsearching reference lists, journals and contact with experts.[70] Many were duplicate publications of the same studies. A total of 12 different original studies of infliximab were found.

Number and type of studies included

Five published papers appeared to meet the inclusion criteria,[54,62,66,68,73] two of which referred to one trial.[62,73] Four were reports of RCTs[62,66,68,73] and the fourth was a paper[54] on endoscopic healing in a subgroup of patients enrolled in the larger study by Targan and colleagues (see *Table 3*).[68] Two ongoing trials, which were identified from a single report on the internet, also met the inclusion criteria,[74] but preliminary data were available for only one of these, the ACCENT I study.[75] These studies largely addressed different aspects of use of infliximab for the treatment of Crohn's disease.

Further data on included trials were available from the FDA,[76] EMEA,[46,77] the physicians' desk reference on infliximab[74] and a product monograph produced by Centocor.[49] Data have been extracted from these sources when not available from the primary publication.

Excluded trials

Of the 18 excluded publications (see appendix 4), ten were not RCTs, seven were not clinical trials and, in one, responses in a subgroup of patients were reported by treatment centre.[53] Patients included in this study were enrolled as part of two double-blind RCTs in patients with treatment-resistant, moderate-to-severe Crohn's disease. The author was contacted and confirmed that the patients were enrolled in the studies by Targan and colleagues[68] and Present and colleagues.[62,73] The results of these trials were published in full. It was not possible to differentiate patients between these two trials from the data presented by Baert and colleagues.[53] The data could not, therefore, be included in the analysis.

Design and conduct

Validity

All included studies were double-blind RCTs. The Jadad score for each trial is summarised in *Table 4*. The low score for the ACCENT I trial is probably related to the few data on methodology currently available.

Randomisation was performed centrally by an independent organisation (PPD Pharmaco, Austin,

TABLE 3 *Aspects of treatment evaluated by the four trials meeting the inclusion criteria*

Trial	Number of patients	Type of Crohn's disease		Treatment course		Comments
		Chronic active	Fistulising	Single	Repeated	
Targan *et al.*, 1997[68]	108	Yes	No	Yes	No	Patients who did not respond to blinded infusion by week 4 were allowed to receive a single dose of open-label infliximab Study by D'Haens *et al.*[54] reported data on endoscopic healing for a subgroup of patients enrolled in this trial
Rutgeerts *et al.*, 1999[66]	73	Yes	No	No	Yes	Patients needed to show response to blinded treatment in Targan *et al.* study[68] to be enrolled in this trial
ACCENT I, 2001[75]	573	Yes	No	No	Yes	All patients received single dose of infliximab prior to randomisation
Present *et al.*, 1999[62]	94	No	Yes	Yes	No	

TABLE 4 *Validity score for the included trials*

Study	Truly random allocation	Was concealment adequate?	Was treatment allocation masked from:			Significant difference in completion rates between groups	Jadad score
			Participants	Investigators	Assessors		
Targan *et al.*, 1997[68]	Yes	Yes	Yes	Yes	Yes	No	5
Rutgeerts *et al.*, 1999[66]	Yes	Yes	Unclear	Unclear	Unclear	No	4
ACCENT I, 2001[75]	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	2
Present *et al.*, 1999[62]	Yes	Yes	Yes	Yes	Yes	No	5

Texas, USA) for the three primary studies. Details were not given for the ACCENT I trial. A stratified treatment assignment was used in all four trials. Investigational site was a stratification variable in each trial. Other variables were corticosteroid use during trials and number of fistulae at baseline in the study by Present and colleagues.[62,73]

All trials were described as double-blind. In the study by Targan and colleagues, the infliximab and placebo solutions were prepared at each site by a pharmacist who was aware of treatment assignments. The investigators, all other study personnel and patients, were blinded to treatment assignment during the double-blind phase of the trial.[68] In the fistulising Crohn's disease study by Present and colleagues, all study personnel (including pharmacists) and patients were masked from treatment.[62,73] Data on blinding were not clearly presented for the ACCENT I trial.

ITT analysis was only clearly used in the study by Present and colleagues.[62,73] The study by Rutgeerts and colleagues[66] did not specify whether ITT analysis was used. In this trial, for continuous variables, patients who discontinued regularly scheduled follow-up or underwent a surgical procedure or change in medication related to their Crohn's disease not permitted by the trial protocol had their last observation carried forward.[66] The Targan and colleagues study was not analysed by ITT.[68] Two patients assigned to treatment did not receive it and were not included in the analysis. The remaining patients were analysed according to the treatment to which they were randomised.

A total of 24 patients did not complete the re-treatment trial conducted by Rutgeerts and colleagues: 14 assigned to placebo and ten assigned to infliximab.[66] Reasons for discontinuation were lack of efficacy (12 assigned to placebo and four assigned to infliximab), adverse events (none assigned to placebo and six assigned to infliximab) and other (two assigned to placebo: withdrawal of consent and non-compliance).

In the fistulising Crohn's disease trial conducted by Present and colleagues, six patients completed only two of the planned three infusions (four assigned to placebo, one assigned to infliximab, 5 mg/kg, and one assigned to infliximab, 10 mg/kg).[62,73] Reasons for discontinuation of treatment were lack of efficacy (three assigned to placebo), adverse events (one assigned to infliximab, 10 mg/kg) and other (one assigned to placebo for administration reasons and one assigned to infliximab, 5 mg/kg, for withdrawal of consent).

The ACCENT I trial is ongoing and details on methods of analysis and number of patient withdrawals were not available.

Interventions and comparators

The three fully completed trials incorporated into this review all had a placebo comparator arm and an infliximab, 10 mg/kg, treatment arm. The other doses evaluated are shown in *Table 5*. The study by Targan and colleagues allowed patients who had not achieved a response to their initial infusion at week 4 to receive an additional open-label infusion of infliximab at a dose of 10 mg/kg.[68] Infliximab was administered by slow intravenous infusion over a 2-hour period in all the trials. A more detailed summary of interventions and comparators appears in *Table 6*.

Key characteristics of the included studies

The four trials were undertaken to evaluate largely different aspects of treatment with infliximab and,

therefore, differed in their inclusion and exclusion criteria (*Table 6*).[62,68] Trial profiles for the three fully published trials are given in appendix 5.

In the Phase II study by Targan and colleagues, the short-term efficacy of a single dose of infliximab was evaluated in 108 patients with moderate-to-severe treatment-resistant Crohn's disease (CDAI ≥ 220 despite concurrent treatment with drugs other than infliximab).[68] Patients were randomised to double-blind treatment with a single infusion of placebo ($n = 25$), infliximab, 5 mg/kg ($n = 27$), infliximab, 10 mg/kg ($n = 28$) or infliximab, 20 mg/kg ($n = 28$), and followed-up for 12 weeks.[68] This trial was conducted over 18 sites (13 in the USA and five in Europe). At 13 of these centres, five or fewer patients were enrolled.[76]

The design of this trial was unusual. If patients did not show a clinical response (≥ 70-point reduction in CDAI) at week 4 of the trial, they were enrolled in a parallel, open-label study and received a single infusion of infliximab, 10 mg/kg, and were followed-up for an additional 12 weeks.[68]

Non-responding patients who received open-label infliximab treatment had their results at 4 weeks carried forward to weeks 8 and 12.[76] No account was taken therefore of any late and/or spontaneous responses that may have occurred in any group during the period between the 4- and 12-week assessment.[68]

The trial conducted by Rutgeerts and colleagues[66] was a 36-week extension study of the trial by Targan and colleagues[68] in adult patients with treatment-resistant, moderate-to-severe Crohn's disease. Patients enrolled in the study by Targan and colleagues who demonstrated a clinical response 8 weeks after blinded or open-label treatment were eligible to enrol in the

TABLE 5 *Number of patients who received each of the doses of infliximab evaluated*

Trial		Infliximab dose		
		5 mg/kg	**10 mg/kg**	**20 mg/kg**
Targan *et al.*, 1997[68]	Double-blind	27	28	28
	Open-label	–	48	–
Rutgeerts *et al.*, 1999[66]		–	37	–
ACCENT I, 2001[75]		573	?	–
Present *et al.*, 1999[62]		31	32	–
Total		**631**	**145**[*]	**28**

[*] *48 patients received additional open-label treatment due to a lack of response to initial blinded treatment*

TABLE 6 *Summary of trial characteristics*

	Targan *et al.*, 1997[68]	Rutgeerts *et al.*, 1999[66]	ACCENT I, 2001[75]	Present *et al.*, 1999[62]
Intervention	Infliximab, 5 mg/kg × 1 dose Infliximab, 10 mg/kg × 1 dose Infliximab, 20 mg/kg × 1 dose	Infliximab, 10 mg/kg × 4 doses	Infliximab, 5 mg/kg, at weeks 0, 2 and 6 and 8 weekly Infliximab, 5 mg/kg, at weeks 0, 2 and 6, and 10 mg/kg, 8 weekly	Infliximab, 5 mg/kg × 3 doses Infliximab, 10 mg/kg × 3 doses
Comparator	Placebo × 1 dose	Placebo × 4 doses	Infliximab, 5 mg/kg, at week 0 and placebo at weeks 2 and 6 and 8 weekly	Placebo × 3 doses
Design	RCT	RCT	RCT	RCT
Country	USA and Europe	USA and Europe	USA, Europe and Israel	USA and Europe
Number of centres	18	17	55	12
Number of patients randomised	108	73	573	94
Number given placebo/ infliximab	25/83 Infliximab 5 mg/kg: 27 Infliximab 10 mg/kg: 28 Infliximab 20 mg/kg: 28 Note: 48 patients received an additional infusion of infliximab 10 mg/kg	36/37 Infliximab 10 mg/kg: 37	Commercial-in-confidence, data removed	31/63 Infliximab 5 mg/kg: 31 Infliximab 10 mg/kg: 32
Inclusion criteria	Aged 18–65 years Crohn's disease for ≥ 6 months CDAI score of 220–400 and current treatment or lack of response to • oral corticosteroids ≤ 40 mg/day • sulfasalazine/ mesalazine • azathioprine or 6-mercaptopurine • methotrexate or ciclosporin	As for Targan *et al.* study plus clinical response to infliximab infusion documented by Targan *et al.*	Commercial-in-confidence, data removed	Aged 18–65 years Confirmed Crohn's disease Single or multiple draining abdominal or perianal fistulae for 3 months

continued

TABLE 6 contd *Summary of trial characteristics*

	Targan *et al.*, 1997[68]	Rutgeerts *et al.*, 1999[66]	ACCENT I, 2001[75]	Present *et al.*, 1999[62]
Exclusion criteria	Treatment with ciclosporin, methotrexate or experimental agents within 3 months before screening	As for Targan *et al.* study	Commercial-in-confidence, data removed	Treatment with aminosalicylates, oral corticosteroids, methotrexate, azathiporine, 6-mercaptopurine or antibiotics discontinued < 4 weeks before enrolment
	Symptomatic stenosis or ileal strictures			Concurrent ciclosporin treatment
	Proctocolectomy or total colectomy			Treatment with investigational drugs or use of any medication to reduce concen-tration of TNF-α $\leq$ 3 months before enrolment
	Stoma			
	History of allergy to muric proteins			
	Previous treatment with murine chimeric or humanised monoclonal antibodies			Other complications of Crohn's disease, e.g. current strictures or abscesses
	Treatment with parenteral cortico-steroids or cortico-trophin within 4 weeks before screening			Stoma created < 6 months before enrolment
				History of allergy to murine proteins
				Previous treatment with infliximab
Duration of follow-up	12 weeks	48 weeks from start of Targan *et al.* trial	Commercial-in-confidence, data removed	26 weeks
Reporting intervals	0, 4, 8, 12 and (16) weeks	12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 weeks	Commercial-in-confidence, data removed	0, 2, 6, 10, 14, 18, 26 and 34 weeks

re-treatment extension, which began at week 12 following initial successful treatment. The trial was conducted at 17 study centres in the USA and Europe.[66]

Of the 80 eligible patients, 73 were randomised to double-blind treatment with four infusions of placebo ($n = 36$) or infliximab, 10 mg/kg ($n = 37$), at 8-week intervals (weeks 12, 20, 28 and 36). Patients were followed-up 4-weekly and for a further 12 weeks after their last treatment (week 48). Four of the patients enrolled in the re-treatment trial had shown an initial clinical response to placebo in the study by Targan and

colleagues; one of these patients was retreated with placebo and three were treated with infliximab in the extension study.[66]

The study conducted by Present and colleagues was an evaluation of the efficacy of a three-dose treatment course of infliximab in 94 patients with Crohn's disease with single or multiple draining abdominal or perianal fistulae of at least 3 months' duration.[62,73] The fistulae were required to be distinctly identifiable. At baseline, drawings and photographs were used to document all fistulae present. Patients were randomised to double-blind treatment with placebo ($n = 31$), infliximab,

5 mg/kg (*n* = 31), or infliximab, 10 mg/kg
(*n* = 32), administered as an intravenous infusion
at weeks 0, 2 and 6.[62] The trial was conducted at
seven centres in the USA and five in Europe. At six
of these sites five patients or fewer were enrolled.
Patients were followed-up to 26 weeks.[62,73,74,76]

In the later, larger ACCENT studies, the efficacy
is being evaluated of repeated treatment with
infliximab at 8-week intervals in patients with
moderate-to-severe Crohn's disease (ACCENT I)
and fistulising Crohn's disease (ACCENT II).
Preliminary results were available for responding
patients in the ACCENT I trial.

The ACCENT I trial is an ongoing study with 573
patients with moderate-to-severe active Crohn's
disease. All enrolled patients received an initial
infusion of 5 mg/kg of infliximab at week 0. At
week 2, patients were randomised to one of three
treatment groups: placebo infusion at weeks 2, 6
and every 8 weeks, infliximab, 5 mg/kg, at weeks 2,
6 and every 8 weeks and infliximab, 5 mg/kg,
at weeks 2 and 6 and 10 mg/kg every 8 weeks.
Data were available up to week 30 for patients
who responded to the initial infusion of infliximab,
5 mg/kg. The trial was conducted at 55 centres
in the USA, Europe and Israel.[75,78]

Characteristics of the study population
A summary of the key baseline characteristics
for patients enrolled in the three trials is given in
Table 7. Few data were available for the ACCENT I
trial. In the three completed studies, the patients
enrolled were predominantly white, had suffered
with Crohn's disease for a mean duration of over
10 years and approximately half were male. In
these three trials, the baseline demographic data
did not differ significantly between the active and
placebo treatment groups in terms of age, weight,
race, gender, duration of Crohn's disease and
median/mean CDAI scores. However, in the study
by Targan and colleagues, placebo-treated patients
had the lowest mean CDAI score, shortest mean
duration of illness, highest mean IBDQ and
lowest mean concentration of C-reactive protein
(CRP) numerically.[68]

In all three trials, approximately 55% of patients
had involvement of both the ileum and colon,
and approximately 50% had required previous
surgery for their Crohn's disease. In the study
by Targan and colleagues,[68] significantly more
patients in the placebo group had ileal disease
alone compared with the other groups (*p* = 0.02),
whereas in the study by Present and colleagues,[62,73]
there was a trend for a higher proportion of

infliximab-treated patients to have undergone a
previous segmental resection (21 (68%) treated
with infliximab, 5 mg/kg, 17 (53%) treated with
infliximab, 10 mg/kg, and 12 (39%) treated
with placebo).

Across the three completed trials, 55–62% of
patients had received or were receiving amino-
salicylates, 35–60% corticosteroids, 37–47%
azathioprine or 6-mercaptopurine, and up
to 30% an antibiotic drug.[62,68,73,79]

In total, 92% of patients in the study by Targan and
colleagues[68] and 83% in the study by Present and
colleagues were taking concurrent Crohn's disease
medication at baseline.[76] (In the study by Present
and colleagues, 93% of patients had been aggres-
sively treated with either antibiotic or immuno-
suppressive drugs prior to enrolment.[46]) There
were no significant differences across the groups
with respect to concomitant medication. It was of
note in the study by Present and colleagues that a
greater proportion of patients assigned infliximab,
10 mg/kg, were receiving 6-mercaptopurine or
azathioprine than those assigned 5 mg/kg or
placebo (53, 39 and 29%, respectively), and that
fewer assigned 5 mg/kg were receiving antibiotic
treatment than those assigned 10 mg/kg or
placebo (19, 34 and 35%, respectively).[62,73,76]

In the fistulising Crohn's disease trial conducted
by Present and colleagues,[62] 55.3% of patients had
more than one fistula present at baseline (median
= 3) with even distribution across the treatment
groups.[76] For the whole group, 90% of patients had
perianal fistulae and 10% abdominal fistulae.[73]
Although it was stated that 20 patients enrolled in
the study by Targan and colleagues[68] had a fistula
present at baseline, no further details were given.
No data were available on this variable for patients
enrolled in the ACCENT I trial.

Outcomes measured
These four trials did not have a common primary
outcome (*Table 8*). However, clinical response
and clinical remission were specified primary or
secondary outcome endpoints in all four trials.
A clinical response was defined as a reduction of
at least 70 points in CDAI from baseline without
a change in medication or the need for surgical
intervention for Crohn's disease. This can be
taken as a modest improvement. (A more strin-
gent endpoint of a reduction of ≥ 100 points in
CDAI has been used in previous trials evaluating
other therapies for Crohn's disease.[78]) Clinical
remission was defined as a CDAI score of
< 150 – a widely accepted definition.

TABLE 7 *Summary of patient baseline characteristics*

	Targan *et al.*, 1997[68]	Rutgeerts *et al.*, 1999[66]	ACCENT I, 2001[75]	Present *et al.*, 1999[62]
Number given placebo/ infliximab	25/83	36/37	Commercial-in-confidence, data removed	31/63
Number male/female (% male)	55/53 (51%)	38/35 (52%)	Commercial-in-confidence, data removed	44/50 (47%)
Number of white race (%)	108 (100%)	73 (100%)	Commercial-in-confidence, data removed	86 (91%)
Mean duration of Crohn's disease (years)	All: commercial-in-confidence, data removed Placebo: 10.4 ± 7.7 Infliximab, 5 mg/kg: 12.5 ± 10.3 Infliximab, 10 mg/kg: 11.5 ± 9.6 Infliximab, 20 mg/kg: 13.5 ± 8.8	All: commercial-in-confidence, data removed Placebo: commercial-in-confidence, data removed Infliximab, 10 mg/kg: commercial-in-confidence, data removed	All: commercial-in-confidence, data removed Placebo: commercial-in-confidence, data removed Infliximab: commercial-in-confidence, data removed	All: commercial-in-confidence, data removed Placebo: 12.0 ± 7.9 Infliximab, 5 mg/kg: 13.6 ± 9.5 Infliximab, 10 mg/kg: 11.5 ± 8.2
Intestinal area involved: ileum only/colon only/ ileum and colon	17/33/58	10/23/40	Commercial-in-confidence, data removed	14/26/54
Previous surgery for Crohn's disease	53 (49.1%)	35 (47.9%)	Commercial-in-confidence, data removed	50 (53.2%)
Number of patients with fistulae: 1/> 1	20 (number of fistulae present not stated)	Commercial-in-confidence, data removed (number present not stated)	Commercial-in-confidence, data removed	42/52
Location of fistula: perianal/abdominal	Not stated	Commercial-in-confidence, data removed	Commercial-in-confidence, data removed	85/9
Mean baseline CDAI (± SD)	All: commercial-in-confidence, data removed Placebo: 288 ± 54 Infliximab, 5 mg/kg: 312 ± 56 Infliximab, 10 mg/kg: 318 ± 59 Infliximab, 20 mg/kg: 307 ± 50	All: commercial-in-confidence. data removed Placebo: commercial-in-confidence, data removed Infliximab: commercial-in-confidence, data removed	All: commercial-in-confidence, data removed Placebo: commercial-in-confidence, data removed Infliximab: commercial-in-confidence, data removed	All: not stated Placebo: 192.9 ± 92.0 Infliximab, 5 mg/kg: 184.4 ± 98.5 Infliximab, 10 mg/kg: 184.9 ± 97.5

TABLE 7 contd Summary of patient baseline characteristics

	Targan et al., 1997[68]	Rutgeerts et al., 1999[66]	ACCENT I, 2001[75]	Present et al., 1999[62]
Previous/concurrent medication (n (%))	Corticosteroid: 64 (59.3%) Mercaptopurine/azathioprine: 40 (37.0%) Aminosalicylate: 64 (59.3%) Antibiotic: commercial-in-confidence, data removed	Corticosteroid: commercial-in-confidence, data removed Mercaptopurine/azathioprine: commercial-in-confidence, data removed Aminosalicylate: commercial-in-confidence, data removed Antibiotic: commercial-in-confidence, data removed	Corticosteroid: commercial-in-confidence, data removed Mercaptopurine/azathioprine: commercial-in-confidence, data removed Aminosalicylate: commercial-in-confidence, data removed Antibiotic: commercial-in-confidence, data removed	Corticosteroid: 33 (35.1%) Mercaptopurine/azathioprine: 38 (40.4%) Aminosalicylate: 52 (55.3%) Antibiotic: 28 (29.8%)

TABLE 8 Primary and secondary outcomes

	Targan et al., 1997[68]	Rutgeerts et al., 1999[66]	ACCENT I, 2001[75]	Present et al., 1999[62]
Primary outcomes	≥ 70-point reduction in CDAI at week 4 with no change in concomitant medication (clinical response)	Not specified	Commercial-in-confidence, data removed	≥ 50% reduction from baseline in number of draining fistulae, observed at two or more consecutive study visits
Secondary outcomes	Clinical response over time Duration of response Clinical remission (CDAI < 150) Changes in CDAI, IBDQ, CDEIS and CRP Changes in components of CDAI Proportion of patients discontinued at week 12	Maintenance of clinical response Maintenance of clinical remission Proportion of patients discontinuing due to lack of efficacy Change in CDAI, IBDQ and CRP over time	Commercial-in-confidence, data removed	Complete response (absence of any draining fistulae at two consecutive visits) Time to response Duration of response Changes in CDAI and PDAI Clinical response Clinical remission

In the fistulising Crohn's disease study conducted by Present and colleagues,[62] the primary endpoint was a reduction in the number of draining fistulae by at least 50% over two or more consecutive study visits, without a change in medication or the need for surgery related to Crohn's disease. A minimum of 21 days was required between consecutive study visits. This endpoint was based upon the physical examination of the patient by the investigators. A fistula was considered closed when it no longer drained despite gentle finger compression. For patients with multiple fistulae at baseline to achieve the primary endpoint, ≥ 50% closure of fistulae was required overall; consistent closure of the same fistulae was not required.

Assessment of effectiveness
Moderate–severe active Crohn's disease
Data on the effectiveness of infliximab in the treatment of patients with moderate-to-severe treatment-resistant Crohn's disease was provided chiefly by the study conducted by Targan and colleagues,[68] the follow-up to this study by Rutgeerts and colleagues[66] and the ACCENT I trial.[52,74]

The trial by Targan and colleagues chiefly evaluated the efficacy of a single dose of infliximab but allowed treatment with open-label infliximab at week 4 if patients did not respond to their initial blinded treatment.[68] In the trial by Rutgeerts and colleagues and the ACCENT I study, the maintenance of benefit with repeated infliximab treatment was evaluated.

The studies by Targan and colleagues[68] and Rutgeerts and colleagues[66] were published in full. The ACCENT I trial is ongoing. Preliminary data were available from this trial to week 30 for patients who responded to an initial infusion of infliximab (*n* = 335 (59%)), with limited data available to week 10 for all patients enrolled in the study.[75]

Clinical response (reduction in CDAI of ≥ 70 points)
Single dose
In the study by Targan and colleagues (*n* = 108), the proportion of patients who responded to a single dose of infliximab was significantly higher than with placebo at week 4 and remained significant throughout the 12 weeks of follow-up (*Table 9*).[68] No patients responded after the 4-week evaluation.

Among the patients who responded at the 4-week evaluation, 25% (1/4) of placebo-treated and 37% (20/54) of infliximab-treated patients subsequently lost response by week 12.[76] No data were provided on the health state of these relapsed patients. However, the loss of response seen suggested that repeated dosing was required to maintain an effect.[68]

Consistent treatment effects were seen when the analysis was stratified according to location of disease or concurrent drug regimens. The highest clinical response rate was seen in the 5-mg/kg group, with a trend towards increased benefit versus 10- and 20-mg/kg treatment groups ($p = 0.053$ for 5 mg/kg versus 10 and 20 mg/kg combined at week 4). A retrospective analysis for the number of patients achieving ≥ 100-point reduction from baseline in CDAI also demonstrated significant benefit with treatment (*Table 10*).[76]

TABLE 9 *Response to treatment (≥ 70-point reduction in CDAI) following initial blinded treatment in the Targan* et al. *trial*[68]

Time post-treatment	Placebo (*n* = 25)	Infliximab, 5 mg/kg (*n* = 27)	Infliximab, 10 mg/kg (*n* = 28)	Infliximab, 20 mg/kg (*n* = 28)	All infliximab (*n* = 83)
Week 2	4 (16.0%)	Commercial-in-confidence, data removed	Commercial-in-confidence, data removed	Commercial-in-confidence, data removed	Commercial-in-confidence, data removed
Week 4	4 (16.0%)	22 (81.5%)*	14 (50.0%)†	18 (64.3%)‡	54 (65.1%)*
Week 8	4 (16.0%)	16 (59.3%)	11 (39.3%)	16 (57.1%)	Commercial-in-confidence, data removed
Week 12	3 (12.0%)	13 (48.1%)	8 (28.6%)	13 (46.4%)	34 (41.0%)‡

* p < 0.001 versus placebo
† p < 0.05 versus placebo
‡ p < 0.01 versus placebo

TABLE 10 *Reduction in CDAI*[76]

Reduction in CDAI	Treatment	Treatment effect		*p*
		Placebo	Infliximab	
Week 4				
≥ 70 points	Initial blinded treatment	16%	65.1%	< 0.001
	Open-label infliximab			
	Initial treatment placebo (*n* = 19)	–	57.9%	–
	Initial treatment infliximab (*n* = 29)	–	34.5%	–
≥ 100 points	Initial blinded treatment	16%	51.8%	0.0134
Week 12				
≥ 70 points	Initial blinded treatment	12%	41.0%	< 0.01
≥ 100 points	Initial blinded treatment	12%	38.6%	0.047

In total, 50 patients did not respond to the initial blinded infusion by week 4 – 21 (84%) with placebo and 29 (34.9%) with infliximab (all doses). Of these patients, 48 subsequently received open-label infliximab: 19 patients following an initial placebo infusion and 6, 15 and 8 patients following initial infusions of infliximab, 5, 10 and 20 mg/kg, respectively.

Among the patients receiving placebo initially, the response rate at 4 weeks after the open-label infusion of infliximab was 57.9% (11/19). However, only 34.5% of patients (10/29) who received infliximab as their initial blinded infusion responded to a second dose of infliximab, suggesting that these patients may have been less responsive to anti-TNF therapies.

Repeated dosing
In the re-treatment follow-up of the above trial by Rutgeerts and colleagues, 8-weekly repeated treatment with infliximab was associated with a statistically significant improvement in clinical response at week 36 only; 72.2 versus 44.1% (*p* = 0.018). Data were not given for week 48 but the response rates were 62 versus 37% (*p* = 0.160) at week 44 (8 weeks after the last infusion).[49,66]

Although not reaching the conventional level of statistical significance, patients treated with infliximab who were receiving concurrent treatment with 6-mercaptopurine or azathioprine showed a greater treatment response than those treated with infliximab but not receiving 6-mercaptopurine or azathioprine (75 versus 50%, *p* = 0.17 at week 44).[66]

Clinical remission (CDAI < 150 points)
Single dose
In line with the clinical response, the proportion of patients in clinical remission was significantly higher in each of the infliximab treatment groups compared with placebo at week 4. However, no significant difference was apparent in this endpoint by week 12 (*Table 11*).[68] The location of the disease or concurrent drug treatment had no effect on the response seen. The largest response was apparent with the 5 mg/kg dose of infliximab (*p* = 0.046 versus 10 or 20 mg/kg combined for remission at any time).

For the non-responding patients who received an open-label infusion of infliximab, 10 mg/kg, the remission rate at week 4 following the open-label infusion was 47% for patients initially treated with placebo and 17% for those initially treated with infliximab (*p* = 0.05). This confirmed the reduced responsiveness in this latter group.[68]

Repeated dosing
In the trial by Rutgeerts and colleagues,[66] a statistically significant difference in the proportion of patients in clinical remission between the treatment groups was only apparent at week 28 (60 versus 30.6%, *p* = 0.045) and week 44 (52.9 versus 20%, *p* = 0.013).[46]

In the ACCENT I trial, for patients who demonstrated an initial response to a single infusion of infliximab, 5 mg/kg (*n* = 335), repeated dosing with the drug was associated with a significant increase in the proportion of patients in clinical remission compared with repeated treatment with placebo at week 30.[75]

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TABLE 11 *Patients in clinical remission in the Targan* et al. *trial*[68]

Time post-treatment	Placebo (*n* = 25)	Infliximab, 5 mg/kg (*n* = 27)	Infliximab, 10 mg/kg (*n* = 28)	Infliximab, 20 mg/kg (*n* = 28)	All infliximab (*n* = 83)
Any time	Commercial-in-confidence, data removed	Commercial-in-confidence, data removed	Commercial-in-confidence, data removed	Commercial-in-confidence, data removed	Commercial-in-confidence, data removed
Week 2	1 (4.0%)	Commercial-in-confidence, data removed	Commercial-in-confidence, data removed	Commercial-in-confidence, data removed	22 (26.5%)[*]
Week 4	1 (4.0%)	13 (48.1%)[†]	7 (25.0%)	7 (25.0%)	27 (32.5%)[‡]
Week 8	4 (16.0%)	10 (37.0%)	8 (28.6%)	7 (25.0%)	25 (30.1%)
Week 12	2 (8.0%)	8 (29.6%)	5 (17.9%)	7 (25.0%)	20 (24.1%)

[*] *p = 0.006 versus placebo*
[†] *p < 0.001 versus placebo*
[‡] *p = 0.005 versus placebo*

Duration of response

Single dose
A small cohort of 23 patients enrolled in the Targan and colleagues' trial were evaluated by the FDA, to address the issue of duration of response. These 23 patients were all randomised to blinded treatment with infliximab and classified as responders at week 4. They received no open-label infliximab and no further active treatment in the follow-up study conducted by Rutgeerts and colleagues.[66] These patients were evaluated over 48 weeks. Loss of response was defined as a CDAI of > 150 for patients who were in remission at 4 weeks or a > 25% increase in CDAI score for those with levels of > 150 at week 4. Where data were missing, patients were considered to have lost response. Patients were evaluated at 4-week intervals. The median duration of response was documented as 16 weeks, with the majority of patients experiencing 12 weeks of response through this period. It was noted that the distribution might not have been unimodal.

A cohort of patients appeared to have quiescent disease activity for more than 6 months. Due to the small number of patients involved, it was not possible to identify the factors contributing to this.

Repeated dosing
Data on duration of response with repeated dosing were only available for the re-treatment phase of the study by Targan and colleagues.[68] The duration of response was compared between treatment groups using survival analysis. In this analysis, patients who had a clinical response at any visit during the re-treatment period were followed-up for duration of response. The median time to loss of response did not differ significantly between the treatment groups (> 48 weeks for infliximab versus 37 weeks for placebo, *p* = 0.057).[46]

Measurements of disease activity

Single dose
The trial reported by Targan and colleagues provided data for the change in CDAI score, change in CRP levels and change in IBDQ score seen with treatment at week 4 of the trial (*Table 12*). Significant reductions in CDAI score and CRP levels and a significant increase in IBDQ score from baseline were seen with infliximab treatment at all doses at week 4 compared with placebo.[68]

For the individual components of the CDAI, most improvement was seen in the daily evaluation of the number of liquid or soft stools, abdominal pain/cramps and general well-being.[49] All sub-domains of the IBDQ were improved in patients treated with infliximab compared with placebo.

In the 54 patients who demonstrated an initial response to infliximab treatment, their reduction in CDAI score and improvement in IBDQ was maintained over the 12 weeks of the study.[68] Levels of CRP in responding patients began to rise at 12 weeks to 14.1 ± 2.2 mg/L across the infliximab groups, potentially indicating a relapse of disease.[68]

Repeated dosing
Data were only presented graphically for median values for these endpoints at each 4-week visit in the report by Rutgeerts and colleagues.[66] Generally, the improvements seen with the initial

TABLE 12 *Mean (± SD) values for CDAI, CRP and IBDQ at baseline and week 4 in the Targan* et al. *trial[68]*

Time post-treatment	Placebo (n = 25)	Infliximab, 5 mg/kg (n = 27)	Infliximab, 10 mg/kg (n = 28)	Infliximab, 20 mg/kg (n = 28)	All infliximab (n = 83)
Score on CDAI					
Baseline	288 ± 54	312 ± 56	318 ± 59	307 ± 50	312 ± 55
4 weeks	271 ± 82	166 ± 76[*]	226 ± 115[†]	211 ± 107[*]	201 ± 103[*]
Score on IBDQ					
Baseline	128 ± 29	122 ± 29	116 ± 23	118 ± 28	118 ± 27
4 weeks	133 ± 28	168 ± 36[*]	146 ± 41[‡]	149 ± 35[§]	154 ± 38[¶]
CRP (mg/litre)[**]					
Baseline	12.8 ± 13.9	22.1 ± 23.6	23.2 ± 34.2	22.4 ± 23.9	22.6 ± 27.4
4 weeks	14.8 ± 18.6	5.7 ± 9.3[††]	12.1 ± 18.6	6.9 ± 11.6[*]	8.3 ± 13.9[*]

[*] $p < 0.001$
[†] $p = 0.003$
[‡] $p = 0.02$
[§] $p = 0.03$
[¶] $p = 0.001$
[**] *Levels of CRP below 8 mg/L are considered normal[69]*
[††] $p = 0.004$

treatment appeared to be maintained with repeated treatment. Patients re-treated with placebo showed a gradual loss of the initial treatment benefit, although the CDAI score still remained below the original baseline values by week 48.

Other endpoints
Endoscopic and histological healing
European patients ($n = 30$) enrolled in the trial by Targan and colleagues[68] had full ileocolonoscopy performed both before treatment and 4 weeks after the infusion, to evaluate mucosal healing using the Crohn's Disease Endoscopy Index of Severity (CDEIS). Additionally, a subset of nine of these patients had biopsy samples taken during these procedures. Of the 30 patients, eight were treated with placebo, seven with infliximab, 5 mg/kg, seven with 10 mg/kg and eight with 20 mg/kg. Mean baseline CDEIS scores were lowest in the placebo group (8.4, 15.1, 10.6 and 13.3, respectively). A significant reduction in mean CDEIS from baseline was seen in all three infliximab treatment arms ($p < 0.01$) but not with placebo. The change in CDEIS score was seen to correlate with the change in CDAI ($r = 0.58$, $p = 0.002$) and, to a lesser extent, serum CRP concentrations ($r = 0.47$, $p = 0.011$). Although a mean decrease in ulcerative lesions of 74–96% across the sites was seen, strictures continued to develop despite infliximab treatment. At the histological level, the architectural abnormalities seen remained unchanged in most patients;

however, acute and chronic inflammatory infiltration was reduced, with the complete disappearance of neutrophils.

No data were available on endoscopic and histological healing with repeated dosing.

Steroid withdrawal
The ACCENT I trial is an evaluation of the ability of patients to be withdrawn from their concomitant corticosteroid treatment during continued treatment with infliximab/placebo. Data on this endpoint are commercial-in-confidence and no data were available from the other trials.

Fistulising Crohn's disease
Data on the effectiveness of infliximab in the treatment of patients with fistulising Crohn's disease were provided chiefly by the study by Present and colleagues.[62] In this trial, the efficacy of a single three-dose treatment course of infliximab was evaluated. The ACCENT II trial, which is still ongoing and for which few data are available,[52] will provide data on the efficacy of repeated treatment with infliximab in patients with fistulising Crohn's disease.

Closing of fistulae
The trial by Present and colleagues provided data on the number of patients with at least a 50% reduction in the number of draining fistulae over two or more consecutive study visits (primary

endpoint) and the number of patients with absence of any draining fistulae at two consecutive visits.[73] A significant treatment effect was seen with both doses of infliximab for both of these endpoints (*Table 13*). The difference between the two doses of infliximab was not significant for the ≥ 50% reduction endpoint.

The response seen was irrespective of the number of fistulae present at baseline. The primary endpoint was reached by a significant proportion of patients with single fistulae at baseline (52 versus 8%, $p = 0.02$) and patients with multiple fistulae at baseline (71 versus 39%, $p = 0.03$) compared with placebo. Interestingly, FDA analysis of data indicated that for patients with multiple fistulae, if one fistula responded the others seemed to respond as well. This may be due to the fact that these fistulae are interrelated, such that they share the same source in the intestine.[76]

There was no evidence that long-standing fistulae (> 2 years' duration) were any more resistant to closing than younger fistulae.[76] Infliximab was consistently beneficial, regardless of the concomitant therapy taken by patients. There was an apparent difference in response between men and women. Overall, there was a higher placebo response rate in women as well as a lower treatment response rate. This suggested that there might have been a stronger treatment effect among men. However, this requires confirmation.[62,73,76]

There were no data evaluating the effect of infliximab treatment upon internal healing of the fistula canal. Over the course of the study, 17 patients developed new fistulae (eight treated with placebo, eight treated with infliximab, 5 mg/kg, and one treated with infliximab, 10 mg/kg). New fistulae developed regardless of whether or not the patient had responded to infliximab. This suggests that, for some patients, ongoing disease activity existed that prevented internal healing of the fistulae.[76]

Onset and duration of response

Onset of response was measured as the time from the initial infusion to the first of the two or more consecutive visits at which the primary endpoint was observed. Duration was measured as the maximum period during which the patient had ≥ 50% reduction in draining fistulae over consecutive visits. These could only be measured in 4-week increments in line with the study visits.

The majority of patients treated with infliximab who responded to treatment did so by week 2 (the first evaluation visit). Patients randomised to placebo who responded did so throughout the study (median onset = 6 weeks).[76] The duration of closure of the fistulae varied. In patients who met the response criteria, 7/39 responded over the whole study period of 26 weeks, 7/39 responded over six visits and 5/39 over five visits.[46] The median duration of response was, however, approximately 3 months across all treatment groups (*Table 14*).[62,76]

TABLE 13 *Numbers of patients (%) with reduction in number of fistulae over two consecutive study visits in the Present* et al. *trial*[62]

Change in number of fistulae	Placebo (*n* = 31)	Infliximab, 5 mg/kg (*n* = 31)	Infliximab, 10 mg/kg (*n* = 32)	All infliximab (*n* = 63)
≥ 50% reduction in number of draining fistulae	8 (25.8%)	21 (67.7%)*	18 (56.3%)†	39 (61.9%)*
100% reduction in number of draining fistulae	4 (12.9%)	17 (54.8%)‡	12 (37.5%)†	29 (46.0%)‡

* *p = 0.002 versus placebo*
† *p ≤ 0.05 versus placebo*
‡ *p ≤ 0.001 versus placebo*

TABLE 14 *Median time to onset and duration of closure of fistulae in days (IQR) in the Present* et al. *trial*[62]

	Placebo (*n* = 8)	Infliximab, 5 mg/kg (*n* = 21)	Infliximab, 10 mg/kg (*n* = 18)	All infliximab (*n* = 39)
Onset of response	42 (15–72)	14 (14–42)	14 (14–42)	14 (14–42)
Duration of response	86 (56–104)	84 (31–113)	99 (86–113)	86 (57–113)

By week 22, there was no significant difference in the proportion of patients with ≥ 50% reduction in number of draining fistulae across the treatment groups, providing no evidence for a lasting drug effect. An analysis undertaken by the FDA suggested that the response to placebo was more durable than the response to infliximab.[76]

Crohn's disease activity

The trial by Present and colleagues provided data on the change in CDAI to week 18 for 79 patients enrolled in the trial.[62,73] A CDAI could not be calculated for 15 patients with a stoma at baseline; these data are confidential. Change in PDAI from baseline to week 18 was presented for 85 patients with peri-anal disease at baseline (see *Table 15*). A significant reduction in median PDAI score was apparent with infliximab treatment at both doses compared with placebo at week 2 but not at week 18.[73]

Summary of the evidence and conclusions

Currently, only three small RCTs evaluating the use of infliximab in patients with Crohn's disease have been completed. Preliminary data to week 30 were available from the larger ACCENT I trial. In these trials, largely different aspects of use were addressed.

Targan and colleagues[68] reported the evaluation of the efficacy of a single dose of treatment in 108 patients with moderate-to-severe active Crohn's disease (mean CDAI = 307) unresponsive to conventional treatment (principally cortico-steroids). At baseline, 92% of patients were taking concurrent Crohn's disease medication. Treatment with a single infusion of infliximab, 5–20 mg/kg, was associated with a 65% response rate (≥ 70-point decrease in CDAI) compared with a 16% response rate with placebo at week 4 ($p < 0.001$). A reduction of 70 points in the CDAI can be taken as modest improvement. However, significantly more patients treated with infliximab than

placebo also achieved the more stringent endpoint of ≥ 100-point reduction in CDAI. The response to treatment was seen early, by week 4, and subsequently lost by week 12 in approximately 40% of patients. Analysis of a small subset of responding patients documented a median duration of response of 16 weeks.

In 30 patients who underwent endoscopy, mucosal healing seemed to correlate with positive changes in CDAI score. This has not been seen consistently with other drug treatments; mucosal healing has been seen with azathioprine treatment for at least 6 months but not corticosteroid treatment.

In line with the clinical response, the proportion of patients in clinical remission was significantly greater with infliximab compared with placebo at week 4 (32.5 versus 4%), and CRP levels were significantly reduced. Significant improvements in these variables were no longer apparent by week 12 (remission was lost in approximately 26% of patients). Sustained benefit is, therefore, unlikely with a single dose. The greatest benefit in all variables was seen with a 5 mg/kg dose, which is the licensed dose. This approached statistical significance.

This trial allowed patients who had not responded at week 4 to receive an open-label infusion of infliximab. This confounded the interpretation of the placebo response. It did, however, demonstrate that, for patients who had not responded to initial infliximab treatment, a limited response was seen with a second dose: 35.4 versus 57.9% response for those initially treated with placebo. The factors that determined lack of response were unknown.

The benefit of repeated treatment with infliximab in patients with chronic active Crohn's disease was addressed by the trial undertaken by Rutgeerts and colleagues[66] and the ACCENT I study.[75] In the study reported by Rutgeerts and colleagues,[66] the

TABLE 15 *Median PDAI score (IQR) by treatment group in the Present* et al. *trial*[62]

Time after first infusion (weeks)	Placebo[*]	Infliximab, 5 mg/kg[*]	Infliximab, 10 mg/kg[*]	All infliximab[*]
0	9 (7–10.5)	8 (7–10)	10 (8–12)	9 (7–11)
2	8 (6–10)	6 (3–7)[†]	6 (4–8)[‡]	6 (3.5–8)[§]
18	7 (4–9)	4 (1–7)	5 (3–8)	5 (2–7.5)

[*] *Data for the number of patients in each subgroup removed as commercial in confidence*
[†] *p = 0.02 versus placebo*
[‡] *p = 0.04 versus placebo*
[§] *p = 0.01 versus placebo*

benefit of repeated treatments with infliximab (four doses at 8-week intervals) was evaluated in 73 patients who had all previously demonstrated a response to blinded or open-label treatment in the study by Targan and colleagues.[68] Repeated infliximab treatment appeared to be associated with better maintenance of clinical benefit in terms of clinical response and remission, but results did not consistently achieve statistical significance versus placebo re-treatment. The trial investigators claimed that the study was not fully powered to detect differences and that it had not been anticipated that patients randomised to re-treatment with placebo would take so long to return to baseline disease activity levels.[66] Without a true placebo arm, it was not possible to identify the anticipated benefit of re-treatment.

Data from the ACCENT I trial were preliminary.[75] In this trial, the benefit of a three-dose induction with infliximab, 5 mg/kg (not currently a licensed dose regimen in chronic active Crohn's disease), was evaluated, followed by 8-weekly dosing with infliximab, 5 or 10 mg/kg, compared with a single dose of infliximab, 5 mg/kg. For the whole treatment cohort ($n = 573$), the three-dose induction was associated with a significantly greater response rate at week 10 than the single dose (65 versus 52%, $p = 0.035$). This was not surprising, given the data from the study by Targan and colleagues that demonstrated that maximal benefit was seen 4 weeks after dosing and was then subsequently lost over time. The response seen 4 weeks after completion of the three-dose induction (i.e. week 10) was comparable to the response rate seen 4 weeks after the single-dose induction in the trial by Targan and colleagues.

In the ACCENT I trial, repeated dosing with infliximab in patients who demonstrated a response to the initial 5 mg/kg infusion of infliximab was associated with a significantly greater remission rate than repeated treatment with placebo (42 versus 21%, $p \le 0.003$) at week 30.[75] Data were only presented for this one timepoint. It was not, therefore, clear whether this represented a consistent treatment benefit. Complete trial results would be required to evaluate this and the duration of benefit. Additionally, patients were allowed episodic re-treatment with infliximab if they subsequently lost response. The numbers of patients who required this in each treatment arm were not provided in the preliminary data; this could have a bearing on the interpretation of the results.

In the study reported by Present and colleagues,[62] the benefit of a single treatment course of three

infusions of infliximab was evaluated in 94 patients with fistulising Crohn's disease (90% perianal and 10% abdominal fistulae). Treatment with infliximab, 5–10 mg/kg, was associated with healing of $\ge$ 50% of fistulae in 62% of patients compared with 26% treated with placebo ($p = 0.005$), and complete healing in 46 versus 13% ($p \le 0.001$) for at least two consecutive visits. Thus, 74.4% of patients treated with infliximab who achieved the primary endpoint actually had complete healing of all their fistulae compared with 50% treated with placebo.

Consistent benefit was seen across subgroups of patients defined by demographic and disease characteristics and concomitant medication for Crohn's disease. The response seen was irrespective of the number of fistulae present at baseline and the 'age' of the fistula. The data suggested a stronger treatment effect in men; however, this needs further investigation. As in the active Crohn's disease trials, the greatest benefits were seen with the 5 mg/kg dose of infliximab. The small size of the cohort studied precluded a meaningful effect of a dose–response relationship.

The median onset of response was earlier with infliximab (14 versus 42 days) with the majority of patients who responded doing so by week 2, although duration of response was comparable (median = 3 months) between treatments. Again, this suggested that while infliximab had an initial benefit on closing fistulae, a single set of doses was unlikely to provide durable benefit. No data were provided on continued treatment. This will be provided by the larger ACCENT II trial, which is ongoing.

The endpoint of closure of fistula as defined by no drainage with gentle compression is subjective. Given the small size of the cohorts studied, any changes or inaccuracies in the assessment of this endpoint could markedly affect the analysis.[76] Data on internal healing of the fistula tract were not presented. Magnetic resonance imaging was performed on a subgroup of patients but this data has not been analysed. A number of patients developed new fistulae over the course of the study.

Longer-term data are required to assess continued response to treatment. This trial presented no data on closure of non-cutaneous draining fistulae or on cutaneous fistulae in locations other than perianal or periabdominal, and data cannot, therefore, be extrapolated to other patients.

Clinical effect size
Chronic active Crohn's disease
From the trial by Targan and colleagues, the NNT with a single dose of infliximab, 5–20 mg/kg, for one patient to achieve a reduction in CDAI ≥ 70 points at week 4 was 2.04 (95% CI, 1.5 to 3.2) and for one patient to achieve remission at week 4 was 3.51 (95% CI, 2.4 to 6.3).[68] The limited data from trial by Rutgeerts and colleagues and the ACCENT I trial did not allow the clinical effect size to be calculated for re-treatment.

Fistulising Crohn's disease
From the trial by Present and colleagues, the NNT with three doses of infliximab, 5–10 mg/kg, for one patient to achieve complete healing of their fistulae for at least 21 days was 3.02 (95% CI, 2.0 to 6.2).[62,73]

Adverse effects
Published data on safety in Crohn's disease patients are limited. The number of patients exposed to the licensed dose of 5 mg/kg in the three fully published RCTs was relatively small (*n* = 58). Additionally, the number of patients who received placebo only was small (*n* = 56) and, thus, of limited use as a comparator. Even more limited were the data on the safety of re-treatment. The duration of follow-up was also limited, ranging from an average of 6.9 to 32.5 weeks. Data on adverse events from the ACCENT I trial were too limited to be useful.

Infliximab has been marketed in the USA since August 1998. Across the world, it is estimated that over 100,000 patients have been treated with in-fliximab for all indications.[77] An assessment of safety among 771 patients treated with infliximab in clinical studies (199 for Crohn's disease and 555 for RA) was undertaken by the EMEA.[80] At least five infusions of infliximab were received by 416 patients (103 Crohn's disease patients received three or more infusions). More than half of treated Crohn's disease patients were exposed to infliximab for 14 weeks or longer; 84% received at least 10 mg/kg and 51% at least 20 mg/kg.[80]

Deaths
There were no deaths in the two short-term studies[62,68,73] of patients with severe active Crohn's disease and those with fistulising Crohn's disease. In the re-treatment study, one placebo re-treated patient developed intravascular duodenal β cell lymphoma 9.5 months after the initial infusion of infliximab. Shortly after the patient's last study evaluation, the patient developed sepsis secondary to his chemotherapy and died.[66]

Adverse events
The incidence of adverse events ranged from 60–97% in placebo-treated patients and 65–95% in infliximab-treated patients across the three fully published Crohn's studies. The incidence of adverse events was highest in the re-treatment study for both treatment groups (97 versus 95%).[66] In the overall EMEA safety analysis, reasonably attributable adverse events were reported in 55% of infliximab-treated patients and in 31% treated with placebo.[80]

Adverse events leading to the withdrawal of treatment were only reported for the studies by Present and colleagues and Rutgeerts and colleagues.[62,66,73] In the study in fistulising Crohn's disease, one patient randomised to infliximab, 10 mg/kg, and one treated with placebo withdrew because of adverse events. The infliximab-treated patient developed pneumonia 22 days after the second infusion of infliximab, although the symptoms resolved within 1 week of antibiotic treatment. One patient treated with placebo discontinued the trial after completion of all scheduled infusions because of an adverse experience. This patient reported arthritis and fasciitis, assessed as possibly related to study medication, 1 week after the three placebo infusions.

In the re-treatment study, six patients discontinued treatment with infliximab and none discontinued treatment with placebo owing to adverse events. One patient experienced dyspnoea, pain, nausea, flushing, hypersthesia, vision abnormality and rigors immediately after the first re-treatment infusion. The infusion was discontinued and the condition resolved within 30 minutes. The remaining five patients developed mononucleosis (one patient), cholecystitis (one patient), severe headache (one patient,) extensive hidradenitis (one patient) and lupus arthritis (one patient), and treatment was withdrawn.[66,76]

In the study by Targan and colleagues,[68] the number of patients who suffered an adverse event requiring withdrawal from treatment was not specified. However, it was stated that of the 29 patients who received two infliximab infusions, two had a reaction (chest pain, dyspnoea or nausea) that led to discontinuation of the infusion. These reactions resolved spontaneously within minutes after the infusion was discontinued.

Across the three trials, the most frequently reported adverse events were upper respiratory tract infection, headache, nausea, abdominal pain

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and fatigue. Abscess was noted as a frequent adverse event but only in the trial in fistulising Crohn's disease (*Table 16*). All but one of the patients who developed an abscess responded to treatment (≥ 50% reduction in number of fistulae). The remaining patient showed a partial response. The closure of the fistula may prevent drainage of faecal flora from inflamed bowel and lead to formation of an abscess. The development of abscesses in the infliximab-treated patients appeared to develop more often after cessation of treatment.[62,73,76]

Infusion reactions

Adverse experiences during or within 2 hours of an infusion were reported by 13.1% of patients treated with infliximab and 9.8% treated with placebo in the three completed trials (for a break-down by trial and treatment arm see *Table 17*). The numbers were too small to clearly identify the effect of dosage and frequency of administration on the incidence of infusion reactions. However, the highest incidence was seen in the study by Rutgeerts and colleagues, in which patients received four repeated infusions.[66] The infusion reactions reported included ventricular extra-systoles, bradycardia, fatigue, dizziness, fever, pharyngitis, headache, hypotension, chest pain, injection site pain, dyspepsia, increased gastro-intestinal activity, nausea and vomiting.[76]

In addition, seven patients in the study by Rutgeerts and colleagues (all treated with infliximab)[66] and 11 in the study by Present and colleagues (ten infliximab-treated and one placebo-treated)[62,73] reported adverse experiences on the day of infusion but with an unknown start time. These adverse events included headache, pain, fatigue, hot flushes, pruritus, nausea, rash and influenza-like syndrome.[77]

Data were not presented clearly on the number of infusions that had to be interrupted because of these reactions. American prescribing infor-mation suggests that < 1% of patients discontinue treatment owing to infusion reactions and that all patients recover with treatment and/or discontinuation of infusion. In the overall EMEA safety analysis, infusion reactions were documented in 16% of infliximab-treated Crohn's patients and 6% of placebo-treated patients.[76,81] Of the 1207 infliximab infusions given in clinical trials, 5% were accompanied by non-specific symptoms, such as fevers or chills, 1% by pruritus or urticaria and 1% by cardiopulmonary reactions (chest pain, hypotension, hypertension or dyspnoea) and 0.2% by combined symptoms of pruritus/

urticaria and cardiopulmonary reactions.[80] Nine reactions resulted in discontinuation of infliximab. The incidence of infusion reactions was positively correlated to the number of infusions received and to the presence of human antichimeric antibody (HACA), and negatively correlated to the use of concomitant immunosuppressants.[80] An infusion reaction was experienced by 7% of infliximab-treated patients during initial infusion and 10% during second infusions. Subsequent infusions were not associated with a higher incidence.[76,80]

In a clinical trial of 40 patients with Crohn's disease re-treated following a 2–4 year period without infliximab treatment, ten patients (25%) developed a serum sickness-like delayed hyper-sensitivity reaction 3–12 days after re-treatment. Symptoms included myalgia, polyarthritis, fever and rash. Six patients required hospitalisation and treatment with high-dose steroids. At the time of reaction, patients had high titres of HACA despite all patients being negative for HACA at the time of re-treatment.[80] Nine patients who experienced these events were treated with a liquid formulation of infliximab that is no longer available. It is not clear whether these reactions relate to this specific formulation.[74]

The risk of delayed hypersensitivity following re-administration after a drug-free period of 15 weeks to 2 years is currently unknown. The Summary of Product Characteristics does not recommend, therefore, re-administration after a drug-free interval of 15 weeks. Clinical experience suggests the risks may be small.[81]

Infections

TNF-α plays an important role in the defence against various infections. Infliximab inhibits TNF-α. It may, therefore, affect normal immune responses and predispose patients to opportunistic infections. Infections were reported frequently across the trials, in particular upper respiratory tract infections. Data for the numbers of patients who developed one or more infections are presented in *Table 18* for the three completed trials. Five patients (of whom four were treated with infliximab) devel-oped serious infections: cholecystitis (one patient); furunculosis of the right arm and right leg (one patient); pneumonia (one patient); deleted, commercial-in-confidence (two patients).[62,66,68,73]

The overall EMEA safety analysis indicated that infections were reported by 26% of infliximab-treated patients versus 16% of placebo-treated patients: 4% in each group were considered serious.[46]

TABLE 16 Adverse effects reported in > 10% of patients in any of the treatment groups evaluated

	Type of Crohn's disease						
	Severe active treatment-resistant			**Severe active treatment-resistant**		**Fistulising**	
Trial reference	Targan *et al.,* 1997[68]			Rutgeerts *et al.,* 1999[66]		Present *et al.,* 1999[62]	
Treatment schedule	One dose of treatment with an additional open-label dose in non-responders			Four repeated doses		Treatment course of three doses	
Treatment groups	Placebo (*n* = 25)	Single-dose infliximab (*n* = 102)	Two-dose infliximab (*n* = 29)	Placebo (*n* = 36)	Infliximab, 10 mg/kg (*n* = 37)	Placebo (*n* = 31)	All infliximab (*n* = 63)
Average follow-up (weeks)	6.9	10.4	12.4	30.7	32.5	19.8	21.2
Any adverse events (%)	60.0	74.4	79.3	97.2	94.6	64.5	74.6
Adverse events (n (%))							
Nausea	2 (8.0)	11 (10.8)	5 (17.2)	3 (8.3)	7 (18.9)	0 (0.0)	5 (7.9)
Abdominal pain	2 (8.0)	NR	NR	5 (13.9)	5 (13.5)	0 (0.0)	4 (6.3)
Headache	5 (20.0)	19 (18.6)	3 (10.3)	4 (11.1)	6 (16.2)	7 (22.6)	11 (17.5)
Fatigue	1 (4.0)	6 (5.9)	3 (10.3)	2 (5.6)	5 (13.5)	2 (6.5)	6 (9.5)
Dizziness	2 (8.0)	NR	NR	1 (2.8)	4 (10.8)	3 (9.7)	2 (3.2)
Upper respiratory tract infection	3 (12.0)	8 (7.8)	4 (13.8)	6 (16.7)	9 (24.3)	2 (6.5)	6 (9.5)
Rash (all types)	0 (0.0)	NR	NR	5 (13.9)	4 (10.8)	3 (9.7)	7 (11.1)
Rhinitis	1 (4.0)	3 (2.9)	3 (10.3)	1 (2.8)	4 (10.8)	NR	NR
Anxiety	NR	NR	NR	4 (11.1)	0 (0.0)	NR	NR
Fever	2 (8.0)	NR	NR	5 (13.9)	4 (10.8)	2 (6.5)	3 (4.8)
Abscess	1 (4.0)	0 (0.0)	0 (0.0)	NR	NR	1 (3.2)	7 (11.1)
Anti-ds DNA	0 (0.0)	NR	NR	NR	3 (8.1)	NR	8 (12.7)
Adverse events during or within 2 hours of infusion	0 (0.0)	0 (0.0)	2 (6.9)	5 (13.9)	9 (24.3)	2 (6.5)	4 (6.3)
Adverse events on day of infusion start time unknown	NR	NR	NR	NR	7 (18.9)	1 (3.2)	10 (15.9)
Arthralgia	0 (0.0)	NR	NR	4 (11.1)	2 (5.4)	NR	NR
Influenza-like syndrome	NR	NR	NR	2 (5.6)	4 (10.8)	NR	NR

TABLE 17 Infusion reactions

	Placebo	**Infliximab, 5 mg/kg**	**Infliximab, 10 mg/kg**	**Infliximab, 20 mg/kg**	**All infliximab**
Targan *et al.,* 1997[68]	Commercial-in-confidence, data removed	NR	NR	NR	Commercial-in-confidence, data removed
Rutgeerts *et al.,* 1999[66]	5/36	NA	9/37	NA	9/37
Present *et al.,* 1999[62]	2/31	2/31	2/32	NA	4/63
NA, not applicable					

TABLE 18 *Numbers of patients who developed infections requiring antibiotic treatment*

Trial		Placebo	Infliximab			All infliximab
			5 mg/kg	10 mg/kg	20 mg/kg	
Targan *et al.*, 1997[68]	Double-blind treatment	2/25	3/27	2/28	6/28	11/83
	Open-label treatment	–	–	7/48	–	7/48
Rutgeerts *et al.*, 1999[66]		8/36	–	13/37	–	13/37
Present *et al.*, 1999[62]		3/31	3/31	4/32	–	7/63

Following worldwide launch in February 2001, there have been 28 spontaneous reports of the onset or re-activation of TB suspected to be a reaction to infliximab therapy.[82] Nine reports were from the USA and 19 from Europe, of which one had a fatal outcome. The majority of patients had a prior history of treatment with immunosuppressants, including corticosteroids. However, owing to limited clinical experience with infliximab, the onset (or re-activation) of TB or other opportunistic infections cannot be ruled out.[77,82] The Committee on Safety of Medicines and the EMEA have advised prescribers to be vigilant for both latent and active TB in patients prior to and during treatment with infliximab. Infliximab treatment should be withdrawn in patients with suspected TB until the infection is ruled out or treated.[77,82]

Serious adverse events

Across the three fully completed trials, 21 patients suffered serious adverse events – 14 on infliximab and seven on placebo. Examples included lupus arthritis and chest pain. Only seven of these were considered as possibly or probably related to the study drug. In the overall EMEA safety analysis, adverse events considered serious and reasonably related to infliximab occurred in 3.6% of infliximab-treated and 2.6% of placebo-treated patients (examples included pneumonia, fever, dyspnoea and rashes). These were all medically manageable and without long-term sequelae.[46,80] A case of reversible cholestatic jaundice believed to be related to infliximab treatment has been reported in the literature.[83]

Lymphoproliferative disorders

In addition to the case of non-Hodgkin's lymphoma identified above, a second patient with Crohn's disease developed nodular sclerosing Hodgkin's lymphoma 3 weeks after receiving an infusion of infliximab. Another five cases of lymphoproliferative disorders have been reported in patients with RA or HIV who received

infliximab. All patients had been previously exposed to chronic immunosuppressive therapies.

Lymphoma is rare in patients with Crohn's disease. The data available for infliximab are too limited to accurately assess whether infliximab treatment increases the potential for lymphoproliferative disorders and whether it confers any increased risk compared with other immunosuppressive drugs.[46,80,84]

HACA

The detection of HACA is complicated since the presence of infliximab interferes with the assay. A large proportion of patients enrolled in clinical trials could not be evaluated for HACA owing to the presence of infliximab in postinfusion samples. Very few data were available. Six of 43 evaluable patients (14.0%) in the trial by Targan and colleagues had a positive HACA response,[68] two of 11 (18.2%) in the trial by Rutgeerts and colleagues[66] and three of 50 (6%) in the fistulising study.[73] In the overall safety analysis, HACA developed in 13% of patients with Crohn's disease treated with infliximab.[29,46,80,84]

Patients who are HACA positive appear more likely to experience an infusion reaction (36 versus 11%).[29,74] Concomitant immunomodulator therapy with corticosteroids, azathioprine or 6-mercaptopurine during infliximab therapy appears to protect against HACA formation (10% frequency) compared with patients not taking immunomodulator therapy (23% frequency).[74,85]

Antibodies against double-stranded DNA

Again, there were few data. In the overall safety analysis, antibodies against double-stranded DNA (anti-ds DNA) developed in approximately 9% of patients. Development was not related to either the dose or duration of treatment. Again, baseline treatment with immune modifier therapy was associated with a decreased likelihood of developing anti-ds DNA (3 versus 21%).[46,74,80,84,85]

One patient treated with infliximab for Crohn's disease developed clinical symptoms consistent with lupus-like syndrome (lupus arthritis) requiring discontinuation of infliximab and treatment with corticosteroids. Anti-ds DNA disappeared when infliximab therapy was discontinued.[74,85]

Chapter 3
Economic analysis

Analysis of the company submission and comments

The economic evaluation undertaken on behalf of Schering-Plough Ltd for their submission to the National Institute for Clinical Excellence used two different models for the two disease states under review: severe active and fistulising Crohn's disease.[86] Both models focused on quality of life, the main effect, and combined this with cost data to give incremental cost per quality-adjusted life-year (QALY) estimates for use of infliximab.

Both models mapped disease-specific scores on to utility scores, relying mainly on published* and partly on in-house data. The existence of published utility scores for particular disease states in Crohn's disease is relatively unusual, but these data were based on small numbers, had relatively wide CIs and were sensitive to the methods used to elicit values.

Chronic active Crohn's disease – company model

To analyse the cost-effectiveness of infliximab in chronic active Crohn's disease, a Markov model with seven states was developed using the software package Decision Maker™. This was shared with us. This model used response rates from the clinical trials, combined with transitional probabilities for seven different disease states extracted from Silverstein's 24-year follow-up of a population-based 'inception cohort' of 174 patients with Crohn's disease in Olmstead County, USA.[87] This latter study provided data on the progress of patients from remission through mild and more severe disease states. Utility values for the various health states were also based on a study by Gregor and colleagues,[24] which elicited utility and CDAI scores from Crohn's disease patients in four health states. Using the CDAI scores, these utility values were applied with interpolation to the seven health states in the Olmstead County data.

To make the results relevant to the UK, UK life tables were applied to the USA data.

Efficacy data were based on the two relevant published trials. The model was run until all patients died, with a mean start age of 37 years, based on the Olmstead County data. Thus, the model aggregated health gains over roughly 40 years.

The relatively small differences in QALY scores between most of the seven health states in the model imply relatively low QALY gains in the short term. For instance, the difference in utility between remission (utility = 0.88) and drug-refractory severe disease (utility = 0.74) was 0.14 (based on standard gamble – see below). However, in the model, these translated into greater values (an average of 0.42 QALYs/patient) due to summing them over patients' lifetimes.

Gregor and colleagues,[24] the source of the utility values in the company model, collected CDAI, IBDQ and utility data from a sample of 180 Crohn's disease patients in a single Canadian tertiary centre during 1995–96 that were classified to four health states. The company model linked these to the seven health states outlined in *Table 19*, which put the utility of drug-refractory state at 0.74 and that of remission at 0.88. By interpolation, the company model used 0.86

TABLE 19 *Health states and utility values used in the company model*

	Markov model	Utility estimate
State 1	Drug-dependent severe disease	0.86
State 2	Drug-refractory disease state	0.74
State 3	Drug responsive	0.77
State 4	Medical remission	0.88
State 5	Mild disease	0.86
State 6	Surgical remission	0.88
State 7	Surgery	0.60

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* The modelling of chronic active Crohn's disease used the study by Gregor and colleagues,[24] in which a variety of instruments were used on 180 consecutive patients with Crohn's disease in a Canadian tertiary treatment centre. The modelling of fistulising Crohn's disease relied on a sample of 79 patients in five UK centres using a combination of CDAI and PDAI to estimate utility linked to the study by Gregor and colleagues.[24]

for mild disease.[†‡] The aim of treatment with infliximab is to shift patients from drug-refractory state to a better health state, such as medical remission or mild disease.

Besides the cost of the drug, the differences in the annual cost per patient in each health state had to be taken into account. The only available relevant UK data were from an unpublished study of a small group of 38 UK patients for whom an average cost over 12 months was estimated. This average cost was distributed across the seven health states using relative cost data from the Olmstead County study.

Three treatment options were evaluated: single, episodic and maintenance treatment. The dose of infliximab used throughout the model for all the treatment options was the lower dose of 5 mg/kg for a 70 kg individual. The resulting cost/QALY estimates are shown in *Table 20.*

The review team noted an error in the model submitted by the company. When it was pointed out, it was accepted by the consultant who had conducted the work, and revised results were then submitted. The model used 1-month rather than 2-month costs for the costs of normal care. Adjusting for this raised the incremental cost/QALY from £8000 to £10,400 for episodic versus standard care. The revised figures are shown in *Table 20.* Costs and benefits were discounted at 6% and 1.5%, respectively.

The company model tested the sensitivity of the results to these assumptions by increasing the 'flare' (or relapse) rate, since this puts patients into more severe health states. The company model included a default 10% flare rate and, in the episodic scenario, these patients were re-treated. This was reasonable according to clinical opinion and was consistent with the clinical trial data. Increasing the flare rate to 20% roughly

TABLE 20 *Summary incremental cost/QALY estimates in chronic active Crohn's disease*

		Treatment schedule		
		Episodic	**Single**	**Maintenance**
Cost (£)/QALY (benefits discounted at 1.5% and costs at 6% with 10% flare rate assumed)		10,400	6700	84,400
Sensitivity analyses:	20% flare	19,800	NA	NA
	50% flare	54,800	NA	NA
NA, not applicable				

[†] The rationale for this assumption was that 'it was necessary to arbitrarily assign values for two states – surgery and mild disease. These estimates were based on the assumptions: (i) that surgery was a worse state than drug-refractory disease since the latter patients would often require surgery as treatment for worsening symptoms and (ii) mild disease was only a slightly worse health state than remission.'[86] A more realistic assumption might have been to assign a value intermediate to drug-refractory disease and remission of 0.81.

[‡] The study by Gregor and colleagues,[24] which had as its primary aim 'to derive estimates of utility from a representative sample of patients with Crohn's disease for use in cost–utility models' provides further data that might be used in sensitivity analyses as follows.

- The utility results were sensitive to the three methods of elicitation used: standard gamble, time trade-off and visual analogue scale.
- The health states were set by the investigators and patients in a range of disease states valued as different disease states using different methods (three utility-based and three disease-specific).
- The utility gains between 'chronically active therapy resistant' (i.e. drug-refractory severe disease in the company model) and remission varied by method, with a gain of 0.14 for standard gamble, 0.12 for time trade-off and 0.23 for visual analogue scale.
- All three scales showed significant correlation with each other and with CDAI and IBDQ, with visual analogue scale showing the strongest degree of correlation with these latter scales. The authors, noting the differences between the utility scales, suggested that standard gamble should be used owing to a higher percentage of patients responding to it compared with time trade-off and better congruence with economic theory.
- The authors did not favour the visual analogue scale because of its 'lack of incorporation of patient preference into this method. Patient preference is probably the most important source of variability in preference elicitation.'[86]

The sensitivity of the results was explored using the values for utility gain from each of the elicitation methods by using a utility gain of 0.2 instead of 0.14 in the sensitivity analysis.

doubled the incremental cost/QALY to £20,000 and a flare rate of 50% led to an incremental cost/QALY of £55,000.

Two fundamental aspect of the model are to be stressed. The first is the assumption that patients who move to a state of remission following infliximab treatment then take on the probabilities of moving into more severe disease states based on patients who were in remission (usually those in the early stages of the disease). This is the implication of using the Olmstead County data on transition probabilities. The few trial data available for these patients suggested that they relapse over time (remission lost in 26% of patients by week 12), but details were not provided in the trial reports of the health/disease states into which these patients relapsed. Clinical opinion suggests that these patients might realistically expect to revert to their original drug-refractory state, rather than progress through the various stages of the disease as suggested by the Olmstead County data. Patients in that study were most likely to move into mild rather than to the more severe drug-refractory health state. The lack of relevant observational data on the history of patients treated with infliximab has led to the widespread use of the Olmstead County data in Crohn's disease studies, but this involves some major assumptions. To the extent that patients reverted to the more severe states, the QALY gains would be reduced. The second major assumption is that the time patients spend in the various health states can be aggregated over their lifetimes, which, given the average age used, implies gains spread over about 40 years. Given the reliance on short-term trial data for the effectiveness of infliximab, this is a heroic extrapolation of its benefits.

Fistulising Crohn's disease
A spreadsheet cost–utility analysis was developed by a clinician, Dr Feagan, acting for Schering-Plough Ltd and shared with the review team. This estimated the cost/QALY based on the following factors:

- translating efficacy data from the pivotal trial for fistulising Crohn's disease (using data from Present and colleagues[73]) into time spent with closed fistulae in the first 12 months after treatment (any extension beyond 12 months was noted in the industry submission as likely to improve the cost/QALY value – see below)
- attaching a utility value to this time based on a combination of two disease-specific scores (CDAI and PDAI), using a formula based on unpublished work by Dr Feagan and linked to the published utility scores for Crohn's disease discussed above[24]
- combining this with the drug cost of infliximab, offset by possible savings in surgery, to derive an incremental cost/QALY for infliximab compared with standard treatment
- variations on the above related to providing re-treatment doses to those whose fistulae re-open after 14 weeks, with various assumptions on success and closure rates.

As the model was limited to 12 months, discounting was not relevant. The resulting cost/QALY values were high, from £102,000–123,000 for initial treatment only and from £82,000–96,000 with the most favourable re-treatment assumptions on closure rates (see *Table 21*). The results were relatively insensitive to the costs offset (due to surgery averted), which were based on various UK sources, even when 100% offset was assumed.

The company submission stated that these estimates were conservative, due mainly to limiting the analysis to 12 months because some patients were still receiving benefit at that stage.

TABLE 21 *Incremental cost/QALY for fistulising Crohn's disease*

| Treatment phase | Success rate | Cost (£)/QALY | | |
		No costs offset	50% costs offset	100% costs offset
Initial treatment		123,000	113,000	102,000
Initial treatment plus re-treatment if fistula reopens or flares	90% success	96,000	89,000	82,000
	80% success	100,000	92,000	85,000
	70% success	104,000	96,000	88,000
Initial treatment plus maintenance for patients achieving 100% closure	90% of patients fully closed	117,000	110,000	102,000
	80% of patients fully closed	120,000	112,000	105,000
	70% of patients fully closed	123,000	116,000	108,000

Extension of the results to more than 12 months, however, is unlikely to alter the results by much because only 13% of patients had closed fistulae at 12 months.

No details were provided as to the types of perianal fistulae included in the pivotal study. Expert clinical opinion suggests that infliximab would only be suitable for a small group of severe symptomatic fistulising patients for whom no alternative surgical or medical treatment was available. Use would clearly be most cost-effective in this subgroup. No estimates were provided in the model for this subgroup.

These results are broadly similar to those of Arseneau and colleagues,[88] who reported on a formal modelling exercise comparing infliximab with alternative treatments and showed a cost/QALY of US$350,000–377,000. They noted that reduction in the cost of infliximab to US$304/infusion would reduce the cost/QALY to US$54,000.

Evaluating and re-estimating the cost-effectiveness in chronic active Crohn's disease

The cost-effectiveness of infliximab in chronic active Crohn's disease has been re-estimated. As noted above, relatively low cost/QALY estimates resulted from the model submitted by the company, in which two major assumptions were made: (a) that patients who achieved remission or mild health states due to infliximab then moved through seven health states to death as though they had been naturally in remission; (b) that the patient utility gains were aggregated over their lifetimes or about 40 years. The effects of relaxing these assumptions were explored and are detailed below.

Comparator and health states
The comparator is placebo, as in the company model. To the degree that conventional treatments are effective, this approach would overestimate the effectiveness of infliximab. However, use of infliximab is a last resort for drug-refractory patients for whom the only alternative may be surgery. No data were available on the extent to which infliximab delays surgical intervention. The company model, by using transition state probabilities that included surgery, assumed that infliximab postpones or reduces (depending on the timeframe) the need for surgery. The

implications of making various assumptions on the extent to which surgery is averted or delayed was explored in sensitivity analyses.

Scenarios
Two scenarios were explored: the baseline scenario (scenario 1) was based on the company model estimates for effectiveness, and scenario 2 was based on more optimistic effectiveness estimates with 5 mg doses. In each scenario, cost/QALY of infliximab compared with placebo was estimated for both single-dose and episodic treatment, the latter based on three re-treatments for those who initially respond but subsequently relapse (flare). Optimistic estimates of response for those who are re-treated were employed (100% response).

The two scenarios shared a range of basic assumptions. One was use of both remission and mild health states. Improvements less than remission (remission is defined as CDAI < 150) have been included in both scenarios as in the company model. The company model took an improvement of 70 points on CDAI as a shift to mild disease. No explicit rationale was given for this assumption, which increased the percentage of patients achieving a worthwhile response and so improved the cost/QALY. No literature has been located that justifies allocation of a clinical response of 70 points on the CDAI as mild disease. This optimistic assumption roughly doubled the response rate. As noted above, the utility values for remission and mild disease are almost identical at 0.14 and 0.12, respectively. The latter value, used in the company model, was via interpolation.

In each scenario, duration of response was put at a median of 80 days from a single dose. A mean rather than a median value should be used for estimating QALYs but this was not given in the trial reports or in the company submission. No data were given on duration of clinical response. The company model did not use data on duration but rather applied a flare rate to those who responded. In the absence of mean data, there was no choice but to use median duration. The effect of assuming a longer duration was explored in sensitivity analyses.

Fewer data were available on duration of response for those who are re-treated than for those who had an initial response. Repeated dosing in the clinical trials narrowly failed to show a statistically significant difference ($p = 0.057$) between infliximab and placebo in time to loss of response;

however, this was based on relatively few patients.§ No data were available on duration of clinical response (i.e. mild disease) but, for modelling purposes, this was assumed to be 80 days, equal to that for those patients achieving remission. The scenarios differed in relation to the percentage of patients who achieve these states, but both relied on trial data apart from different dosages.

Scenario 1 – effectiveness

In scenario 1, the same effectiveness estimates were used as in the company model, checked against *Table 11*[68] for the percentage of patients moving into remission and mild health states. The effectiveness estimates in the company model were explained as follows:[86]

> "The 2-month likelihoods of achieving a remission or a response were based on the pooled results for patients evaluated at 4, 8 and 12 weeks. Thus, for the placebo arm, 9.5% achieved a remission and an additional 5.4% a clinical response,¶ and for the pooled infliximab arms, 28.9% achieved a remission and an additional 23.7% a clinical response. Based on the Mayo Clinic data, about 10.2% of patients with a remission would flare during each 2 months. A linear regression analysis of the Rutgeert and colleagues study suggests that about 9.5% of the 55.6% of patients responding flared… We assumed

that 10.2% of patients would flare every 2 months in the episodic treatment arm and they would receive single-dose infliximab at 5 mg/kg and that such treatment would restore remission."

This approach relied on data from the trials (excluding ACCENT I, which has only been published in abstract form) solely on the proportion of patients achieving remission and clinical response, with the flare rate taking into account remission. This seems reasonable but has inherent problems once the time-frame is restricted as outlined above, in that some patients may not have flared by the end of the period.

The company model took an average of the percentage of patients moving into remission for all doses: 28.9% for infliximab and 9.3% for placebo (unweighted average of 4-, 8- and 12-week responses). These figures are shown in *Table 22*; however, a higher average of 38.2% applies to those treated with 5 mg/kg. Since the company model costs patients at 5 mg/kg, it would seem more reasonable to use the response rates for this dose. The effects of this were explored in scenario 2 below.

The company model had 28.9% patients achieving remission** which, subtracting the 9.5% of patients achieving remission on placebo, gave a net value of

TABLE 22 *Efficacy of infliximab versus placebo in trials for patients moving into remission*

	Placebo		Infliximab, 5 mg/kg		Infliximab, 10 mg/kg		Infliximab, 20 mg/kg		All infliximab	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Any time	Commercial-in-confidence, data removed		Commercial-in-confidence, data removed		Commercial-in-confidence, data removed		Commercial-in-confidence, data removed		Commercial-in-confidence, data removed	
Week 2	1	4.0	Commercial-in-confidence, data removed		Commercial-in-confidence, data removed		Commercial-in-confidence, data removed		22	26.5
Week 4	1	4.0	13	48.1	7	25.0	7	25.0	27	32.5
Week 8	4	16.0	10	37.0	8	28.6	7	25.0	25	30.1
Week 12	2	8.0	8	29.6	5	17.9	7	25.0	20	24.1
Average week 4, 8 and 12		9.3		38.2		23.8		25.0	72	28.9

§ Omission of repeated dosages would confine the analysis to single rather than episodic treatment. It could be assumed that repeat dosing leads to remission, either for 100% or some smaller percentage of patients (whether this would be the same percentage as for the first dose and with the same duration is unknown). The company model assumed 100%: 'We assumed that 10.2% of patients would flare every 2 months in the episodic treatment arm and they would receive single-dose infliximab at 5 mg/kg and that such treatment would restore remission'.[86]

¶ The clinical response appeared to be synonymous with transition to the mild disease state in the company model.

** This (a) was a simple average of the three periods and (b) covered the three dosage regimes. For (a), a weighted average of the periods might be more appropriate (29.3%) or the percentage achieving remission in any period (34.9%). Epidemiological input is required as to which, if any, is most appropriate to use. However, the differences are small. For (b), it may be more appropriate to use the data for the dose rate with the best response (5 mg/kg), which was also used in the costing in the company model. This has an anytime response of 51.9% and an average of the four, eight and 12 responses of 38.2%.

19.4%. The model had 23.7% of patients in the treatment arm achieving such a change and 5.4% in the placebo arm, giving a net value of 18.3%. We have not been able to check these figures. We note that inclusion of the percentage moving to mild disease roughly doubles the response rate to 37.7% and, thus, proportionately improves the cost-effectiveness of infliximab.

Scenario 2 – effectiveness

As noted above, higher response rates were reported for the 5 mg dose than for all doses in relation to remission: 38.2 versus 28.9%. No data were provided for the proportion of patients achieving the mild health state. To allow for a similar increase as that observed for remission, the figure for those achieving the mild health state for all doses (23.7%) was increased in proportion to the increase for those achieving remission (38.2/28.9) giving a figure of 31.3%. Combining inclusion of this higher response for both remission and mild disease states increases the percentage of patients achieving a response (to remission or mild health states) from 38% in scenario 1 to 55% in scenario 2. This was the single difference between the two scenarios. Owing to the importance of the assumptions made, scenario 2 should be treated with caution.

Scenario 1 – cost-effectiveness

The above company estimates were combined in the table in appendix 6 to estimate the cost/ QALY for both first dose and for subsequent episodic treatments of those who respond but later relapse (or flare). For remission, the utility gain of 0.14 was applied to the net 19.5% of patients achieving this state because of infliximab which, for a median duration of 80 days, gave a total of 0.60 QALYs for 100 patients. Inclusion of patients achieving mild disease for a net 18.3% of patients (23.7–5.4%) with a utility gain of 0.12 and assuming equal duration of 80 days as for remission, gave a QALY gain of 0.48 for 100 patients. The total QALY gain from those achieving remission or mild health states was thus 1.08 for 100 patients.

Taking 100 patients and a cost/patient of £1457.35 for an average patient weighing 60 kg (based on the company model, which chiefly included drug and administration costs), then the total cost was £145,700 (£1457.35 × 100). Dividing this by the total QALY gain of 1.08 gave a cost/QALY of £135,000 for patients moving to either remission or mild health states. A much higher cost/QALY of £245,000 would apply if the analysis was restricted to

remission but the inclusion of mild disease dramatically improved the cost/QALY to £135,000.

Inclusion of QALY data for those who responded to the first dose but who subsequently relapsed could improve the cost/QALY, depending on the assumptions made on the percentage of those who respond to subsequent doses. If it is assumed that each of these had the same probability as for the first treatment for the same clinical gain and the same average duration of gain, then inclusion of subsequent treatments would make no difference to the cost/QALY estimates within that year (over longer periods the differences in discount rates for benefits and costs would slightly alter this conclusion).

However, the company model took the other extreme assumption that 100% of those who responded to initial treatment responded to subsequent treatment. While the true figure is unknown, the response rate for those patients who have previously responded is likely to be closer to 100% than to the initial response rate for a cohort of patients. The effect of this favourable assumption has been shown (see appendix 6) to generate a cost/QALY for each of these repeated treatments of £51,000/QALY. It should be noted that this effect could only be achieved with patients who have had initial treatment that cost £156,000/QALY. This much higher estimate was due to the relatively high proportion who would not respond, but who would incur costs. A cost/QALY of £156,000 is the baseline estimate for single-dose infliximab.

The figure of £51,000 for responders should be noted as this is the value that would apply with a 100% initial response rate, and thus provides a floor on the cost/QALY within this scenario. It could only be improved by assuming a longer duration of benefit, a higher utility score or costs offset from surgery averted. Each of these was explored in sensitivity analyses.

Assuming three subsequent treatments after an initial treatment (each subsequent treatment assumed to have a 100% response and a duration of 80 days for patients achieving both remission and mild disease states (the most optimistic scenario)), the cost/QALY would be £72,000. This is the baseline estimate for episodic treatment, against which other scenarios and assumptions should be compared.

Scenario 2 – cost-effectiveness

Use of the higher response rates in scenario 2 gave an improved cost/QALY of £93,000 for single-dose treatment and £62,000 for episodic treatment (initial treatment plus three re-treatments). The cost/QALY for responders was £47,000, which, as discussed above, indicates a floor on the cost/QALY within this scenario.

Sensitivity analyses

In each scenario, the sensitivity of key assumptions on the results were tested specifically by altering the utility gain, the duration of response and costs offset of surgery averted. The degree to which the results were sensitive to the response rate was indicated above by the cost/QALY for responders – £51,000 in scenario 1 and £47,000 in scenario 2.

Utility

The utility gains due to infliximab, as in the company model, for remission compared with drug-refractory state were 0.14 and 0.12 for those patients moving to mild disease state. In sensitivity analyses, the effect of increasing the utility gain to 0.20 for all patients responding to infliximab (remission or mild disease) was examined in order to explore the implications of the values being sensitive to the methods of elicitation. It should be noted that assuming a higher utility score than those indicated for standard gamble, and particularly that derived from a visual ana- logue scale, lacks support within health economics, was dismissed by Gregor and colleagues[24] and was not used in the company model.

Duration of response

Duration of response in the trials for remission was put at a median of 80 days from a single dose. Mean rather than median values should be used for estimating QALYs but these were not given in the trial reports or in the company submission. No data were given on duration of clinical response. The company model did not use data on duration but rather applied a flare rate to those who responded. In the absence of mean data, we have had no choice but to use median duration. Since use of the median may underestimate the duration of response and hence the QALY gain, a longer duration of 120 days was explored in the sensitivity analyses.

Surgery averted

The company model, as noted above, took into account the possibility that infliximab may provide an alternative to surgery. It was unclear whether surgery was delayed or avoided. If delayed, then the cost would still be incurred after the delay. The cost/QALY would be little changed by the discounting of the cost of the surgery and by the addition of some short-lived QALY gain.

Only if surgery were permanently averted would the offset of costs occur. Some estimates are required as to the proportion of patients treated with infliximab who would not proceed to surgery because of the treatment. The cost of surgery in the company submission was estimated at between £2200–2700, of which the latter, higher, figure was used. The optimistic assumption was made that 50% of those responding to infliximab in the baseline scenario had surgery averted permanently.

Results

The degree to which the results in both scenarios were sensitive to the duration of benefit, the utility gains from response and the possible costs offset are summarised in *Table 23*, which shows that use of more optimistic assumptions make relatively little difference to the estimated cost/QALY. In scenario 1, the cost/QALY for episodic dosage fell from £72,000 to just under £50,000 with strong assumptions on either duration of benefit or a higher utility gain per patient. The inclusion of costs offset for surgery had less effect, as long as only one surgical intervention was averted. In scenario 2, the cost/QALY fell from £62,000 to just over £40,000 using the same set of optimistic assumptions and was less sensitive to costs offset owing to surgery averted.[††]

Differences from the company model

The cost/QALY estimates above are very much higher than those in the company model, which were about £8000 for an initial dose and £10,000 for episodic treatment. Our estimates in scenario 1, which used the same initial response rates for in- fliximab, are much higher at £135,000 and £72,000.

The main differences from the company model were as follows.

[††]It was suggested that surgery may, in some cases, avert NNT at a recurring cost of about £20,000/patient/annum. However, it has not been included in the model because there were no data on the proportion of patients to whom this might apply.

TABLE 23 *Summary of estimates of incremental cost/QALY of infliximab compared with placebo by scenario and with different assumptions*

	£/QALY	
	Single dose	**Episodic**
Scenario 1 (all doses)	135,333	72,261
Duration 120 days for 80	–	48,174
Utility 0.20 for 0.13	–	46,969
50% surgery averted	–	60,636
Scenario 2 (5 mg/kg)	93,244	62,016
Duration 120 days for 80	–	41,344
Utility 0.20 for 0.13	–	40,310
50% surgery averted	–	50,090

- The company model considered patients over their lifetimes. Our approach limited the timeframe to one in which three re-treatments could occur, which could be 1 or more years.
- The company model had seven health states (including surgery, surgery remission and drug-responsive and drug-dependent severe disease), each with different utilities. Patients who achieved remission or mild health states due to infliximab were assumed to spend time in each of these disease states accumulating QALYs. In contrast, our estimates assumed that patients reverted back to their original drug-refractory states.

Company model – 1-year results

In order to explore the relative impact of these differences, the company model was run for 1 and 5 years, rather than for the rest of the patients' lifetimes. The results, summarised in *Table 24,* show that at 1 year the cost/QALY was relatively high at between £35,000 (single-dose treatment) and £59,000 (re-treatment for those relapsing from either remission or mild disease

states), compared with £8000 and £10,000 over the patients' lifetimes. The differences between these estimates and our higher estimates were, it is surmised, due to the range of health states in the company model, which allows for surgery.

Company model – 5-year results

Running the company model over 5 years reduced these values to £16,000 (single-dose treatment) and £32,000 (episodic treatment), compared with £8000 and £10,000 when run over the patients' lifetimes. This implies that the aggregation of benefits over time plays a key role in the company model.

The higher cost/QALY due to episodic compared with single-dose treatment in the company model differed from our results, which had more favourable results for episodic treatment. It was unclear why this should be so, given that re-treatments were focused on responders who were assumed to continue to respond. It may be caused by the time lags in response but it was not possible to explore this further.

Conclusions

Chronic active Crohn's disease

The company estimates for cost/QALY were based on a range of highly optimistic assumptions for which we can find no evidence. Many of the key assumptions were embedded into a complex model rather than stated explicitly. The key assumptions in the company model appeared to be caused by patients accumulating utility gains over the rest of their lives and in a variety of health states due to infliximab. Curtailing the timeframe to three re-treatments with a variety of health states broadly confirmed our alternative estimates by generating considerably

TABLE 24 *Incremental cost per QALY estimates of single and repeated treatments with infliximab compared with placebo over 1- and 5-year periods*

	Placebo	**Single dose**	**Flare from remission or mild states**
Six cycles or 12 months			
Cost (£/patient)	1186	2530	2892
QALYs (per patient)	0.8312	0.8689	0.86
Incremental cost (£/QALY)		35,371	59,219
30 cycles or 5 years			
Cost (£/patient)	2523	3858	6054
QALYs (per patient)	3.9293	4.0118	4.0387
Incremental cost (£/QALY)		16,179	32,274

higher cost/QALY estimates. Running the company model over 5 years indicated that the bulk of the gains occurred in the longer term.

Re-estimation of the cost-effectiveness using the company estimates for proportion of patients who respond to treatment (both to remission and mild health states), their utility gains and optimistic estimates of the other key parameters (percentages responding to both treatment and re-treatment) gave a cost/QALY for episodic treatment of £72,000. Use of the response rates for the 5 mg/kg dose gave a cost/QALY of £62,000.

The results were relatively insensitive to major changes in key assumptions in utility gains (increased by about 50%), to duration of benefit (increased by about 50%) and the proportion permanently avoiding surgery (50%). Given the lack of robust information about the longer-term effects of infliximab on patient health states, we consider that our estimates of cost-effectiveness are closer to the true position than those provided by the company model. The key issue appears to be duration of benefit, about which the company model is very optimistic.

Fistulising Crohn's disease
While the cost-effectiveness estimates presented by the company were relatively simple, they seemed both reasonable and transparent. The resulting cost/QALY values were high: £102,000–123,000 for initial treatment only and £82,000–96,000 with the most favourable re-treatment assumptions on closure rates. The results were relatively insensitive to the costs offset (due to surgery averted), even when 100% offset was assumed.

Cost impact

The company submission was based on 30,000 patients, of whom 7–20% had severe disease. Of those with severe disease, a further 20% were not treatable (due to contraindications or personal preference). Of these, 4800 patients were identified as suitable for treatment with infliximab, 18% were considered to have fistulae and require three doses, and 84% had severe active disease and would require only one dose. The costs of this totalled £10,400,000.

Clinical expert opinion suggests that far fewer patients should be treated with infliximab – perhaps only 20% of those deemed eligible for treatment above. This would reduce the cost to about £2,000,000. However, higher costs would be incurred if episodic treatment were permitted. Much higher costs would be incurred if, as in the USA, infliximab was used not only for severe disease states but also for milder forms of the disease.

Chapter 4
Factors relevant to the NHS

Infliximab requires reconstitution prior to administration. The best environment for this needs to be considered, that is, ward versus aseptic preparation. This has implications in terms of NHS costs. Vials of infliximab do not contain any preservatives. The infusion of infliximab should be initiated within 3 hours of reconstitution. The treatment of several patients at the same time provides the potential for less drug wastage.

Other guidance

Three groups to date have issued guidance. An international working group produced recommendations for the use of infliximab in 1999.[89] Their key recommendations were that infliximab should not be considered as a first-line therapy. They suggested that infliximab may be used in:

- patients who relapse and fail to respond to steroids or azathioprine (in doses up to 1.5 mg/kg) within 4 months
- steroid-refractory patients who cannot be brought into remission with azathioprine
- patients with fistulising Crohn's disease in whom other treatments, such as surgery, azathioprine and/or metronidazole, have not been effective.

The working party advised that when infliximab is used, the following factors should be heeded.[89]

- Careful monitoring is required and specific tumour surveillance is recommended. Central documentation of all cases treated in the next year is recommended.
- It should be administered in an institution routinely performing intravenous infusions of drugs and a 2-hour surveillance of the patient should be guaranteed to recognise anaphylactic reactions and other acute side-effects.
- A repeat infusion should primarily only be performed if relapse occurs.

In 2001, the American College of Gastroenterology updated their guidelines on the management of Crohn's disease in adults. These now include infliximab.[90] It is suggested that infliximab may be used as an alternative to corticosteroid therapy in patients with moderate–severe Crohn's disease in whom corticosteroids are contraindicated or ineffective.[90] This represents much more widespread use than is currently suggested by the licensed indications.

European guidelines for 2001–2003 on the use of anti-TNF agents in inflammatory bowel disease have recently been published.[91] These were developed from a systematic search of the published literature and interpreted by 20 experts from Europe. The recommendations from this group are broader, and advise the following.

Active Crohn's disease
- Infliximab should be restricted to the treatment of refractory active Crohn's disease. (Refractory Crohn's disease is when a full and adequately dosed course of corticosteroids in addition to immunomodulators, such as azathioprine/ 6-mercaptopurine or methotrexate, has failed or other drugs are not tolerated or not appropriate and surgery is not indicated.)
- No more than two infusions of infliximab should be given within an interval of 4 weeks without evidence of an appropriate clinical benefit.
- Clinical benefits are of limited duration.
- Immunomodulators are the mainstay of remission maintenance therapy.
- Infliximab should not be administered as a preventative therapy in asymptomatic patients.
- Re-administration of infliximab is warranted in patients who relapse under adequate immunosuppressive/immunomodulatory therapy. A switch of immunomodulators/ immunosuppressives or an increase in the dose of immunomodulators is effective in some patients.
- In clinical practice, the re-infusion of infliximab even after more than 14 weeks seems safe and can be beneficial (based on expert committee opinions or experiences category IV evidence).

Fistulising Crohn's disease
- The use of infliximab is warranted if other conservative options for perianal fistulae have been exhausted (including antibiotics).
- Infliximab may also be tried in non-perianal fistula (e.g. enterocutaneous or rectovaginal).

- Infliximab should be given as a three-dose treatment course. In patients with severe fistulising disease, a course of more than three doses of infliximab may be given.
- The presence of abscesses should be excluded and any abscesses found should be drained before treatment with infliximab.
- In order to prevent abscess formation from premature closure of draining fistulae tracks, setons should probably not be removed before the second infusion of infliximab (clinical opinion).
- Cessation of fistulae drainage does not necessarily indicate true healing of fistulae.
- The concomitant use of antibiotics should be considered (clinical opinion).

General

- It is reasonable to consider use of anti-TNF agents in patients with Crohn's disease and refractory oral, skin, eye or joint manifestations.
- Patients receiving infliximab should be closely monitored with similar precautions to those taken in clinical trials.
- Infectious complications should be ruled out before treatment by chest X-ray and draining any abscesses.
- Adrenergic drugs and glucocorticoids should be available during the infusion in case of acute hypersensitivity.
- Further use of anti-TNF is not recommended after delayed hypersensitivity reaction.
- All patients should be monitored closely through regular follow-up appointments.
- Routine use of anti-TNF agents pre-surgery cannot be recommended.
- No live attenuated vaccines should be given within 3 months of anti-TNF therapy.

Chapter 5
Discussion and conclusions

Main results

The key objective in the treatment of Crohn's disease is the maintenance of remission. In chronic active Crohn's disease, a single infusion of infliximab decreased symptoms in about two-thirds of patients and induced remission in one-third within 4 weeks. However, most patients relapsed after 12 weeks. Repeated doses given every 8 weeks maintained remission in at least half of the treated patients. Maintenance therapy will most likely be required to be continued indefinitely. There are few data to support this and a lack of data related to safety over the longer term.

Patients with chronic active Crohn's disease unresponsive to one infusion of infliximab generally did not respond to a further infusion. The factors that determine lack of response are unknown. It has been suggested that non-response to treatment with infliximab is due to an early reactivation of the inflammatory cascade caused by an intrinsic immunological mechanism.[92]

In patients with perianal fistulae, a clinical response was seen in 62% of patients treated with infliximab compared with 26% treated with placebo, with complete healing in approximately 50% of infliximab-treated and 13% of placebo-treated patients. Benefits were seen rapidly (within 2 weeks) and lasted for approximately 3 months, suggesting the need for repeated treatments. Unfortunately, infliximab treatment was not compared to surgical management. Surgery is known to be associated with excellent healing rates in patients with simple perianal fistulae.

In the fistulising Crohn's disease trial,[73] 10% of patients developed an abscess at the fistula site. It has been suggested that this resulted from skin closure without tract closure. Concomitant use of azathioprine or its metabolite 6-mercaptopurine seemed to encourage healing. More research is required to evaluate this.

Infusion reactions can be expected in approximately 7% of patients during their first infusion. Re-treatment leads to sensitisation and a higher incidence (10%) of infusion reactions has been documented with second infusions. Patients who become positive for HACA are also at increased risk of a reaction. To date, all patients have recovered from these reactions. Other potential adverse events that require further evaluation are the risk of severe infections and lymphoproliferative disease.

The placebo arms of the published clinical trials suggest that a number of patients with active disease go into remission without drug therapy by 4 months. Maintenance studies of patients in remission demonstrate that most patients remain in remission for up to 24 months. Longer-term placebo-controlled maintenance trials are, therefore, required to detect a therapeutic advantage accurately.[16]

In all three fully published trials, the majority of patients had involvement of both the ileum and colon. Ileocolic location is associated with the highest morbidity in terms of the need for surgery. Improvement in these patients is, therefore, impressive but further follow-up data are required to determine whether the need for surgery is reduced.

The optimal dose and dosage frequency of infliximab is unclear from the current evidence. A dose of 5 mg/kg appeared at least as effective as higher doses but it is unclear whether lower doses would be equally effective. A dose of 1 mg/kg is known to have reduced efficacy in Crohn's disease. The optimal re-treatment dose has also not been established; this is being addressed by the ACCENT trials.

These issues all have a bearing on the cost-effectiveness of infliximab treatment. Economic models to date have used the lower, 5 mg/kg dose and have evaluated single-dose, episodic and maintenance treatment. A single treatment was associated with the lowest cost/QALY but, given the high likelihood of relapse, is the least likely treatment strategy. Episodic re-treatment, the anticipated treatment approach, in chronic active disease assuming a 10% flare rate gave a cost/QALY of £10,400. This was, however, very sensitive to the actual flare rate.

The costs associated with treating fistulising Crohn's disease with infliximab are much greater, with cost/QALY ranging from £82,000 to £123,000 depending on the number of treatment doses given, the success rate and costs offset. No details were provided as to the types of perianal fistulae included in the pivotal study. Expert clinical opinion suggests that infliximab would only be suitable for a small group of 'severe symptomatic fistulising patients for whom no alternative surgical or medical treatment was available'. Use would clearly be most cost-effective in this subgroup.

Assumptions, limitations and uncertainties

This review was limited because too few data were available on the use of infliximab in patients with severe active or fistulising Crohn's disease unresponsive to conventional treatment. RCT data from completed studies related to just 275 patients, of whom only 58 received infliximab at the licensed dose of 5 mg/kg. Follow-up data were limited to 48 weeks.

In the trials, 'unresponsive to conventional treatment' was limited to medical treatment. The role of infliximab as an alternative to surgery, or in patients in whom surgery has failed, is unknown. Patients enrolled in the fistulising study had predominantly perianal fistulae. Results can only, therefore, be extrapolated to this group of patients. Patients enrolled in the chronic active Crohn's disease trials had relatively moderate disease (mean CDAI = 307 ± 55). The benefit of treatment in patients with more severe disease (CDAI > 400) is unknown.

The effectiveness and safety of long-term treatment with infliximab is unknown. Data were not available to address this. It is not currently known for how long treatment should be continued. Two large trials, ACCENT I and II, are due to report soon. These will evaluate repeated treatment in approximately 850 patients (550 with active and 300 with fistulising Crohn's disease), and will provide valuable data in these areas.

Important issues not addressed by this review
- The effectiveness and cost-effectiveness of infliximab in children and adolescents < 18 years of age were not considered, as this is not currently a licensed indication for infliximab in the UK.
- There are other TNF-α inhibitors that can be expected to come on to the market in the near future for the treatment of Crohn's disease. These have not been considered.
- The effectiveness and cost-effectiveness of infliximab as a first-line treatment in patients with Crohn's disease was not considered.

Recommendations for research

There are a large number of areas in which further research is required.

- The role of infliximab in long-term prevention of surgery for patients with Crohn's disease.
- The effect of infliximab treatment on the healing of internal fistulae tracts.
- The benefit of infliximab in the treatment of non-cutaneous draining fistulae and cutaneous draining fistulae in locations other than perianal or periabdominal.[74]
- The therapeutic advantage of infliximab over the longer term.
- The identification of factors related to poor response. Preliminary data suggest that subsets of patients with Crohn's disease may be identified using micro-satellite halotypes and perinuclear anti-neutrophil cytoplasmic antibody to predict who will respond to anti-cytokine therapy.[29]
- The synergistic benefit of concomitant therapy. For example, does concomitant use of azathioprine or 6-mercaptopurine encourage healing in patients with fistulising Crohn's disease treated with infliximab?
- Comparative trials with newer immuno-suppressants are needed, for example, tacrolimus and thalidomide.
- Investigation of the long-term toxicity of regular or intermittent use of infliximab, including an evaluation of the potential of infliximab to increase development of lymphoproliferative disorders.
- Identification of the minimum effective dose in both active and fistulising Crohn's disease, and optimal re-treatment regimens.
- The use of infliximab as an effective steroid-sparing agent.
- The use of infliximab as an acute treatment followed by long-term maintenance with an immunosuppressant, for example, azathioprine.
- An evaluation of the natural history of Crohn's disease in the UK post-infliximab.

Research in progress
Three treatment trials in Crohn's disease are ongoing or are completed but not yet

reported. ACCENT I is a study in 573 patients with moderate–severe active Crohn's disease without fistulae, in which treatment with a single infusion of infliximab is being compared with maintenance therapy. This trial was due to be completed in December 2000 but Schering-Plough Ltd advised that it is still ongoing. Preliminary results to week 30 were presented in May 2001.[46,52,75,77] ACCENT II is a study in 300 patients with fistulising Crohn's disease. This trial also compares treatment with a single course of infliximab therapy to maintenance treatment. The trial was due to be completed in December 2000, but Schering-Plough Ltd advised that it is still ongoing. They were unable to advise us as to when preliminary results might be expected.[46,52,74] A study of maintenance treatment in children with active Crohn's disease is planned.[46]

Other biological therapies being evaluated in Crohn's disease are:[29]

- CDP-571 (Celltech, Slough, UK) – a 'humanised' monoclonal antibody to human TNF-α
- rhIL-10
- ICAM-1 (antisense to intracellular adhesion molecule-1)
- antisense oligonucleotide (ISIS 2302)
- opreleukin rhIL-II
- priliximab (anti-CD4)
- natalizumab.

Trials are also underway with both etanercept and thalidomide (which inhibits TNF production).

Conclusions

Infliximab has demonstrated short-term efficacy in patients with severe active Crohn's disease and fistulising Crohn's disease resistant to conventional medical treatment. Although the evidence is still limited, consistent results have been shown. Rapid clinical response is seen, but this is short-lived (mean duration = 3 months).

The study by Rutgeerts and colleagues[66] and preliminary data from the ACCENT I trial[75] supported the premise that a re-treatment regimen of infliximab can provide long-term suppression of disease activity in patients with Crohn's disease. However, full data from the ACCENT I trial are required to confirm this. The optimal dose and frequency of dosing also need to be identified. Comparative studies are required, and the tolerability and long-term efficacy of the drug need to be defined to identify its full potential in the treatment of Crohn's disease.

It has been suggested that infliximab be reserved for patients with moderately severe disease who have failed treatment with conventional immunosuppressants and who are not suitable for or who refuse surgery.[48] Its rapid onset of action may be of benefit in controlling flares in Crohn's disease. It may also, therefore, be a useful bridging agent in patients who are starting immunosuppressive therapy. Further research is required to confirm this. Based on these criteria, its use is likely to be limited to a small number of patients with severe disease unresponsive to medical or surgical management. Such restrictive use of infliximab is likely to be most cost-effective.

Acknowledgements

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Appendix 1

Questionnaire: infliximab for Crohn's disease

Name: .... Date: ....

Base hospital: ....

Please indicate below:

1.   Approximately how many patients under your care have **chronic active** Crohn's disease?

☐ 0–100   ☐ 101–500   ☐ 501–1000   ☐ > 1000

2.   How many of these patients have you treated with infliximab?

....

3.   How many are currently receiving treatment?

....

4.   How many of these are receiving continuous treatment?

....

5.   Approximately how many patients under your care have **fistulising** Crohn's disease?

☐ 0–50   ☐ 51–250   ☐ 251–500   ☐ > 500

6.   How many of these patients have you treated with infliximab?

....

7.   How many are currently receiving treatment?

....

8.   How many of these are receiving continuous treatment?

....

9.   Is treatment with infliximab for any of your patients with Crohn's disease restricted by funding?

☐ Yes   ☐ No

Thank you for sparing the time to complete this questionnaire. Please return in the enclosed pre-paid envelope to Rebecca Mason. A copy of the collated responses will be sent to you shortly.

Appendix 2

Flow chart for the identification and inclusion of RCTs from the initial searches

```
┌─────────────────────────┐
│  Identified on searching │
│         n = 372          │
└─────────────────────────┘
             │
             ▼
┌─────────────────────────┐
│   Abstracts inspected    │──────────▶  Excluded
└─────────────────────────┘               n = 349
             │
             ▼
┌─────────────────────────┐
│  Full copies retrieved   │
│         n = 23           │
└─────────────────────────┘
             │
             ▼
┌─────────────────────────┐
│    Papers inspected      │──────────▶  Excluded
└─────────────────────────┘               n = 18
             │
             ▼
┌──────────────────────────────────┐
│ Papers for appraisal and data     │
│       extraction   n = 5          │
└──────────────────────────────────┘
        ╱                    ╲
       ▼                      ▼
┌──────────────┐      ┌──────────────┐
│Chronic active│      │  Fistulising │
│Crohn's disease│     │Crohn's disease│
│    n = 4     │      │     n = 1    │
└──────────────┘      └──────────────┘
       │                      │
       ▼                      ▼
    3 RCTs                  1 RCT
 1 additional data
```
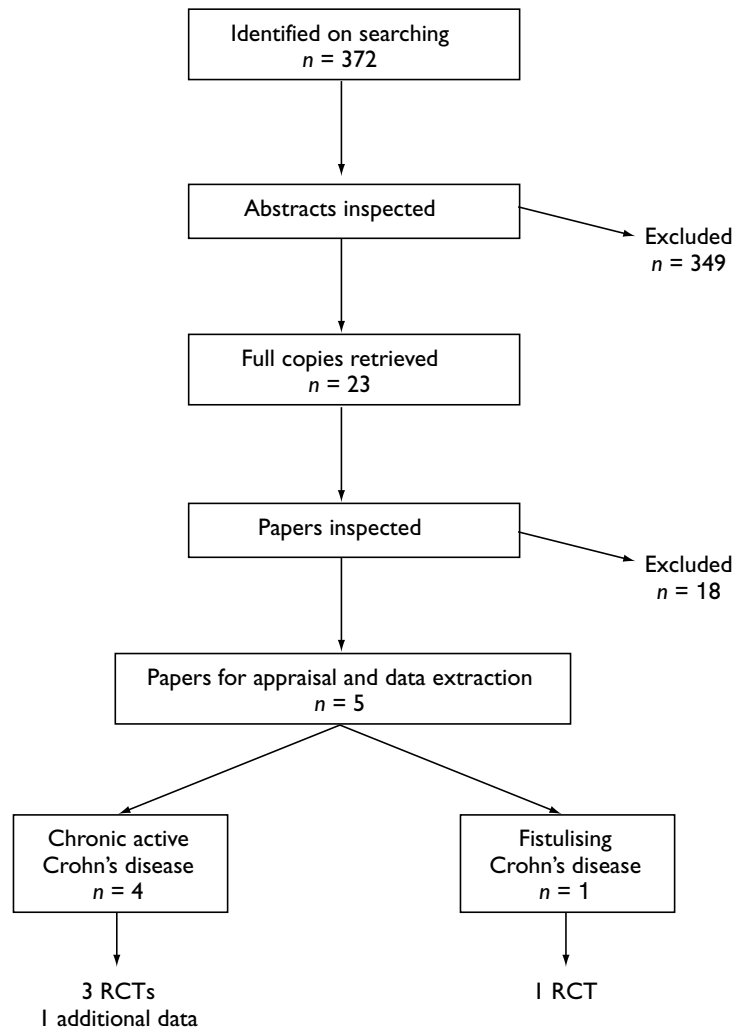
Appendix 3

Quality assessment scale

Jadad score for the evaluation of the quality of clinical trials

1. Was the study described as randomised?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and dropouts?

Scoring of items
Score 1 point for each 'yes' and 0 points for each 'no'.

Give an additional point if:
For question 1, the method to generate the sequence of randomisation was described and it was appropriate (e.g. table of random numbers, computer generated)

and/or:
For question 2, the method of double-blinding was described and it was appropriate (e.g. identical placebo, active placebo, dummy).

Deduct 1 point if:
For question 1, the method to generate the sequence of randomisation was described and it was inappropriate (e.g. patients were allocated alternately, or according to date of birth or hospital number)

and/or:
For question 2, the study was described as double-blind but the method of blinding was inappropriate (e.g. comparison of tablet versus injection with no double dummy).

Appendix 4

Excluded studies with reasons for exclusion

Reference	Reason for exclusion
Baert FJ, D'Haens GR, Peeters M, Hiele MI, Schaible TF, Shealy D, *et al.* Tumor necrosis factor alfa antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. *Gastroenterology* 1999;**116**:22–8.[53]	Not an RCT, but a treatment centre experience
Bourreille A. TNF-alfa et interleukine 1 beta dans les rechutes de maladie de Crohn. *Hepatogastroenterology* 1999;**3**:232–3.[72]	Not a trial
Derkx B, Taminiau J, Tadema S, Stonkhorst A, Wortel C, Tytgat G, *et al.* Tumour-necrosis-factor antibody treatment in Crohn's disease. *Lancet* 1993;**342**:173–4.[55]	Not an RCT
Heller T, James SP, Drachenberg C, Hernandez C, Darwin PE. Treatment of severe esophageal Crohn's disease with infliximab. *Inflamm Bowel Dis* 1999;**5**:279–82.[56]	Not an RCT
Hommes DW, van Dullemen HM, Levi M, van den Ende A, Woody J, *et al.* The effect of monoclonal anti-tumor necrosis factor antibody cA2 on coagulation and fibrinolytic parameters in patients with active Crohn's disease. *Thromb Haemost* 1995;**73**:946.[58]	Not an RCT
Hommes DW, van Dullemen HM, Levi M, van der Ende A, Woody J, Tytgat GN, *et al.* Beneficial effect of treatment with a monoclonal anti-tumor necrosis factor-alfa antibody on markers of coagulation and fibrinolysis in patients with active Crohn's disease. *Haemostasis* 1997;**7**:269–77.[59]	Not an RCT
Hommes DW, van Dullemen HM, Meenan J, van den Ende A, Woody J, *et al.* The effect of monoclonal anti-tumor necrosis factor antibody cA2 on coagulation and fibrinolytic parameters in patients with active Crohn's disease [abstract]. *Gastroenterology* 1995; **108**:A838.[57]	Not an RCT, but an open-label non-comparative study
Kammerer W. Infliximab gegen fisteln bie morbus Crohn. *Pharm Ztg* 1999;**33**(144):32.[60]	Not an RCT
Lofberg R. Treatment of fistulas in Crohn's disease with infliximab. *Gut* 1999;**45**:642–3.[71]	Not a trial
McCabe RP, Woody J, van Deventer S, Targan SR, Mayer L, *et al.* A multicenter trial of cA2 anti-TNF chimeric monoclonal antibody in patients with active Crohn's Disease [abstract]. *Gastroenterology* 2000;**110**:A962.[61]	Not an RCT
Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, *et al.* Infliximab for fistulas: a hole in one? *Inflamm Bowel Dis* 2000;**6**:62–3.[64]	Not a trial
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Appendix 5

Trial profiles

A short-term study of chimeric monoclonal antibody cA2 to TNF-alpha for Crohn's disease, conducted in North America and Europe[68]

```
                          ┌─────────────────┐
                          │  203 screened   │
                          └─────────────────┘
```

Inclusion criteria
Crohn's disease for 6 months
CDAI score of 220–400
Aged ≥ 18 and ≤ 65 years old
At least one of the following:
• use of oral corticosteroids of ≤ 40 mg/day
• use or lack of response to ≥ 2 g/day
  sulfasalazine or ≥ 800 mg mesalazine
• use or lack of response to azathioprine
  or 6-mercaptopurine
• failure to respond to methotrexate
  or cyclosporin

Exclusion criteria
Treatment with cyclosporin, methotrexate or experi-
mental agents within 3 months before screening
Symptomatic stenosis or ileal strictures
Proctocolectomy or total colectomy
Stoma
A history of allergy to muric proteins
Previous treatment with murine chimeric or
humanised monoclonal antibodies
Treatment with parental corticosteroids or
corticotrophin within 4 weeks before screening

```
        ┌──────────────┐
        │ 95 excluded  │ ◄───
        └──────────────┘
```

Patients could continue with:
• mesalazine (≥ 8 weeks) dose if stable for 4 weeks
• corticosteroid ≤ 40 mg/day (≥ 8 weeks) if stable for 2 weeks
• mercaptopurine or azathioprine (≥ 6 months) if stable for 8 weeks
Doses remained stable throughout the study except for
corticosteroids where dose tapering could commence from week 8

Two patients were assigned to
treatment but did not receive it:
one declined to participate and
one did not meet eligibility criteria.
They were not included in analysis

```
        ┌────────────────┐
        │ 108 randomised │
        └────────────────┘
```

Methodology
Screening: CDAI, IBDQ, CRP
concentration at week 1
Immunological investigation:
at baseline and week 12

Intravenous infusion administered over 2 hours

| 25 Placebo | 27 Infliximab, 5 mg/kg | 28 Infliximab, 10 mg/kg | 28 Infliximab, 20 mg/kg |

4 responders | 19 non-responders | 2 ? | 22 responders | 5 non-responders | 14 responders | 14 non-responders | 18 responders | 10 non-responders

Infliximab, 10 mg/kg, open-label

8-week double-blind follow-up

12-week follow-up

Efficacy endpoints
Primary: decrease by ≥ 70 points
in CDAI at week 4

61

Efficacy and safety of re-treatment with anti-TNF antibody (infliximab) to maintain remission in Crohn's disease[66]

```
                    ┌─────────────────────────────┐
                    │ 80 eligible patients screened│
                    └─────────────────────────────┘
```

Inclusion criteria
As for Targan *et al.* study plus patients demonstrating a clinical response to infliximab infusion in the Targan *et al.* study (i.e. adults with moderate-to-severe treatment-resistant Crohn's disease)

Exclusion criteria
As for Targan *et al.* study

Four patients who received initial infusion of placebo showed clinical response

One patient re-treated with placebo

Three patients re-treated with infliximab

7 excluded – main reasons?

73 randomised

Methodology
Design: randomised, double-blind, placebo-controlled, parallel group study
Study visits: 4-week intervals to week 48

Re-treatment commenced at week 12 after response to initial blinded infusion

Four infusions, weeks 12, 20, 28 and 36

36 placebo

37 10 m/kg infliximab

14 withdrawn:
12 due to lack of efficacy and two for other reasons

Ten withdrawn:
four due to lack of efficacy and six due to adverse events

22 (61%) completed

27 (73%) completed

Endpoints
Clinical response (CDAI decrease ≥ 70 points)
Clinical remission (CDAI < 150 points)
Withdrawal due to lack of efficacy
Safety: laboratory values, vital signs, physical examination, adverse events, death, premature discontinuation, anti-ds DNA, HACA

ACCENT I: a Crohn's disease clinical trial evaluating infliximab in a new long-term treatment regimen[75]

```
┌─────────────────────────────────────────────────────────────────┐
│ Inclusion criteria                    Exclusion criteria          │
│ Data removed as commercial-in-confidence  Data removed as         │
│                                       commercial-in-confidence    │
└─────────────────────────────────────────────────────────────────┘

                         ┌──────────────────┐
                         │   573 patients   │
                         │     enrolled     │
                         └──────────────────┘

Week 0                   ┌──────────────────┐
                         │   Infliximab,    │
                         │     5 mg/kg      │
                         └──────────────────┘

Week 2                   ┌──────────────────┐
                         │   573 patients   │
                         │    randomised    │
                         └──────────────────┘

               ┌──────────────────┐    ┌──────────────────┐
               │   n = 188        │    │   n = 385        │
               │   placebo at     │    │ Infliximab, 5 mg/kg, │
Double-blind   │  weeks 2 and 6   │    │  at weeks 2 and 6│
treatment                              └──────────────────┘
period         ┌──────────┐    ┌──────────────┐   ┌──────────────┐
               │ n = 188  │    │   n = ?      │   │   n = ?      │
               │ placebo  │    │Infliximab, 5 mg/kg,│ │Infliximab, 10 mg/kg,│
               │ 8-weekly │    │  8-weekly    │   │  8-weekly    │
               └──────────┘    └──────────────┘   └──────────────┘

Preliminary data
available to week 30  ─────   ─────        ─────   ─────

               ┌──────────┐    ┌──────────┐      ┌──────────┐
Week 54        │% completed│   │% completed│     │% completed│
               │ unknown  │    │ unknown  │      │ unknown  │
               └──────────┘    └──────────┘      └──────────┘

               ┌───────────────────────────────────────┐
               │          Efficacy endpoints           │
               │ Time to loss of response, reduction in│
               │ concomitant corticosteroid use, clinical│
               │ remission, effectiveness of episodic  │
               │ re-treatment, mucosal healing, quality of life│
               └───────────────────────────────────────┘
```

63

Infliximab for the treatment of fistulae in patients with Crohn's disease[62,73]

```
┌─────────────────────────────┐
│   120 patients screened at  │
│ 12 centres in USA and Europe│
└─────────────────────────────┘
```

Inclusion criteria
Aged 18–65 years
Single or multiple draining
abdominal or perianal
fistulas for ≥ 3 months
Confirmed Crohn's disease

Exclusion criteria
Treatment with any of the drugs listed below
discontinued < 4 weeks before enrolment:
– concurrent cyclosporin treatment
– treatment with investigational drugs or use
  of any medication to reduce the concentration
  of TNF-α ≤ 3 months before enrolment
Other complications of Crohn's disease,
e.g. current strictures or abscesses
Stoma created < 6 months before enrolment
History of allergy to murine proteins
Previous treatment with infliximab

Patients could continue with:
• aminosalicylates if stable dose for 4 weeks
• oral corticosteroids ≤ 40 mg/day if stable dose for ≥ 3 weeks
• methotrexate (≥ 3 months) if stable dose for > 4 weeks
• azathioprine or mercaptopurine (≥ 6 months) if stable
  dose for > 8 weeks
• antibiotics if stable dose for > 4 weeks

```
┌──────────────┐
│     94       │
│  randomised  │
└──────────────┘
```

Methodology

Randomised, double-blind, placebo-controlled
Drug administered at weeks 0, 2 and 6
Clinical and laboratory assessments at weeks 2, 6, 10, 14 and 18
Blood samples at weeks 0, 2, 6, 10, 14, 18, 26 and 34

Intravenous
infusions given at
weeks 0, 2 and 6

31 placebo	31 Infliximab, 5 mg/kg	32 Infliximab, 10 mg/kg
Four discontinued after two infusions: three due to lack of efficacy and one due to administrative reasons	One discontinued after two infusions due to withdrawal of consent	One discontinued after two infusions due to adverse events

Duration not
specified

27 (87%) completed	30 (97%) completed	31 (97%) completed

Efficacy endpoints

Primary: reduction of 50% or more from baseline
in number of draining fistulas observed at two or
more consecutive study visits
Secondary: complete response, duration of response,
changes in CDAI, changes in PDAI

Appendix 6

Sensitivity analyses of different scenarios in relation to the treatment of chronic active Crohn's disease with infliximab

Scenario I Chronic active Crohn's disease: cost/QALY re-working the company model for single-dose and episodic treatment of those who respond but relapse (drug response rates as in company model)

	Patients to remission (CDAI < 150)			Patients to mild disease (> 70-point CDAI reduction)				Comments
	Infliximab	Placebo	Net	Infliximab	Placebo	Net	Combined	
Cost/QALY of treating 100 patients with a single initial dose of infliximab (all doses) compared with placebo								
Cost of 100 patients	28.9	9.5	19.4	23.7	5.4	18.3		Trial data as used in company model
Utility gain			0.14			0.12		Remission from Gregor et al.,[24] mild disease from the company model[86]
Duration (days)			80			80		Technology assessment report/FDA (median)
QALD gain/100 patients			217			176		
QALY gain/100 patients			0.60			0.48		
Total QALYs							1.08	Adding 0.60 and 0.48
Cost/100 patients (£)			145,700			145,700	145,700	
Cost/QALY (£)			244,756			302,712	135,333	Combined utility gain, single cost
Subsequent treatment of patients with above responses who 'flare'								
Utility gain			0.13					Average for remission/mild disease
Duration (days)			80					As above
QALDs/patient			10.4					
QALYs/patient			0.028					
Cost/patient (£)			1457					
Cost/QALY (£)			51,135					For subsequent treatments only
Treatment of 100 notional patients, with those moving to remission or mild disease treated for three further episodes in a year								
Net % responding			37.7					Combined remission and mild disease
Utility gain/patient			0.13					Average for remission/mild disease
Duration/patient (days; 80 x 4)			320					
QALDs			1568					
QALYs			4.297					
Cost (£; £1457 x 100 + £1457 x 3 x 37.7)			310,487					
Cost/QALY (£)			72,261					Average for initial and subsequent treatments

Scenario 2 Cost/QALY re-working the company model for single-dose and episodic treatment of those who respond but relapse (drug response rates for 5 mg/kg)

	Patients to remission (CDAI < 150)			Patients to mild disease (> 70-point CDAI reduction)				Comments
	Infliximab	Placebo	Net	Infliximab	Placebo	Net	Combined	
Cost/QALY of treating 100 patients with a single initial dose of infliximab (5 mg doses) compared to placebo								
Cost of 100 patients	38.2	9.5	28.7	31.3	5.4	25.9		Data adjusted for remission only at 5 mg with *pro rata* adjustment for mild disease
Utility gain			0.14			0.12		Remission from Gregor et al.,[24] mild disease from the company model[86]
Duration (days)			80			80		Technology assessment report/FDA (median)
QALD gain/100 patients			321			249		
QALY gain/100 patients			0.88			0.68		Adding 0.88 and 0.68
Total QALYs							1.56	
Cost/100 patients (£)			145,700			145,700	145,700	
Cost/QALY (£)			165,445			213,666	93,244	Combined utility gain, single cost
Subsequent treatment of patients with above responses who 'flare'								
Utility gain			0.14					Average for remission/mild disease
Duration (days)			80					As above
QALDs/patient			11.2					
QALYs/patient			0.031					
Cost/patient (£)			1457					
Cost/QALY (£)			47,483					For subsequent treatments only
Treatment of 100 notional patients, with those moving to remission or mild disease treated for three further episodes in a year								
Net % responding			55					Combined remission and mild disease
Utility gain/patient			0.14					Average for remission/mild disease
Duration/patient (days; 80 x 4)			320					
QALDs			2447					
QALYs			6.705					
Cost (£; £1457 x 100 + £1457 x 3 x 55)			386,105					
Cost/QALY (£)			62,016					Average for initial and subsequent treatments

continued

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