

# **Infliximab for the treatment of Crohn's disease**

**Report commissioned by:** NHS HTA Programme

**On behalf of:** National Institute for Clinical Excellence

**Produced by:** West Midlands Development and Evaluation Service, University of Birmingham, in collaboration with the Medicines Evaluation Unit, Keele University.

**Authors:** Wendy Clark, Information Pharmacist  
Dr Amanda Burls, Senior Clinical Lecturer  
Dr Fujian Song, Research Fellow  
Professor James Raftery, Professor of Health Economics  
Pelham Barton, Lecturer Mathematical Modelling  
Dr Carole Cummins, Senior Lecturer  
Anne Fry-Smith, Information Specialist

**Correspondence to:** Wendy Clark  
Department of Medicines Management  
Keele University  
Keele  
Staffordshire  
ST5 5BG

**Date Completed:** 10<sup>th</sup> July 2001

**Expiry date:** March 2002

## CONTRIBUTIONS OF AUTHORS

Wendy Clark was the lead author. She designed the protocol and piloted and modified the forms used for assessment of eligibility, validity and data extraction. She searched for studies, including hand searching Scip, and contacted authors for further information. She liaised with content experts in the field to obtain background information and support. She assessed studies for eligibility, validity and extracted data from them. She collated and summarised the data and wrote the report.

Amanda Burls was the senior reviewer. She assessed studies for their eligibility and advised Wendy on methodology. She organised the peer review. Amanda read and commented on the draft report and addressed comments from the peer-reviewers.

Fujian Song advised on methodology, assessed studies for validity and independently extracted data from them. He read and commented on the draft report.

James Raftery worked on the economic evaluation and liaised with authors of the models for further information. He read and commented on the draft report.

Pelham Barton analysed the pharmaceutical company economic model.

Carol Cummins helped identify studies and searched the Internet.

Anne-Fry Smith advised on the search strategy and undertook searches of electronic databases.

## CONFLICTS OF INTEREST

### Source of funding

This report was commissioned by the NHS HTA programme funded by the NHS R&D budget.

### Relationship of the reviewer(s) with sponsor

Amanda Burls, Wendy Clark, Fujian Song, James Raftery, Pelham Barton & Carole Cummins have no pecuniary relationship with the companies making or promoting the use of TNF inhibitors.

## ACKNOWLEDGEMENTS

**Robert Allan** Consultant Gastroenterologist, University Hospitals Birmingham NHS Trust, Birmingham B15 2TH, provided us with background information on the management of patients with Crohn's disease, the different manifestations of the disease and the potential place of infliximab. He provided external peer review of the draft report.

**Allan Brown**, Health Economist, CCOHTA, Canada, K2CC 3V4, peer reviewed the draft report.

**Herbert Gröpel**, Internist, Klinikum Nuremberg Nord, 90419 Nuremberg, Germany, peer reviewed the draft report.

**J.R.B Green**, Consultant Gastroenterologist, North Staffordshire Hospital, Stoke on Trent, ST4 6QG peer reviewed the draft report.

**Jack McDonald**, Co-ordinating editor for IBD group, Cochrane Collaboration peer reviewed the draft report.

NOTE

Information that should remain confidential, ie information that is not currently in the public domain, unless permission is received from Schering-Plough is underlined.

## CONTENTS

<b>1.</b>	<b>AIM OF THE REVIEW .....</b>	<b>13</b>
<b>2.</b>	<b>BACKGROUND .....</b>	<b>13</b>
2.1	DESCRIPTION OF CROHN'S DISEASE .....	13
2.1.1	<i>Aetiology</i> .....	13
2.1.2	<i>Presentation</i> .....	13
2.1.3	<i>Complications</i> .....	14
2.1.4	<i>Prognosis</i> .....	14
2.1.5	<i>Determining disease activity</i> .....	15
2.1.6	<i>Classification of Crohn's disease</i> .....	15
2.1.7	<i>Definitions of different severity's of Crohn's disease</i> .....	15
2.1.8	<i>Epidemiology (Prevalence/Incidence)</i> .....	15
2.2	CURRENT SERVICE PROVISION .....	17
2.2.1	<i>Induction of remission (CDAI <math>\leq</math> 150)</i> .....	18
2.2.2	<i>Maintenance Treatment</i> .....	19
2.2.3	<i>Surgical Management</i> .....	20
2.3	ANTI-TNF AND CROHN'S DISEASE .....	20
2.3.1	<i>Technology under evaluation – Infliximab (REMICADE™)</i> .....	20
2.3.2	<i>Identification of patients and criteria for treatment</i> .....	21
2.3.3	<i>Personnel involved and setting</i> .....	21
2.3.4	<i>Degree of Diffusion</i> .....	22
<b>3.</b>	<b>EFFECTIVENESS.....</b>	<b>23</b>
3.1	METHODS FOR REVIEWING EFFECTIVENESS .....	23
3.1.1	<i>Review questions</i> .....	23
3.1.2	<i>Search Strategy</i> .....	23
3.1.3	<i>Inclusion and exclusion of trials</i> .....	24
3.1.4	<i>Inclusion criteria</i> .....	24
3.1.5	<i>Exclusion criteria</i> .....	24
3.1.6	<i>Data extraction strategy</i> .....	24
3.1.7	<i>Quality assessment strategy</i> .....	25
3.2	RESULTS .....	25
3.2.1	<i>Quantity &amp; quality of research available</i> .....	25
3.2.2	<i>Assessment of Effectiveness</i> .....	33
<b>4.</b>	<b>ECONOMIC ANALYSIS.....</b>	<b>47</b>
4.1	ANALYSIS OF COMPANY SUBMISSION AND COMMENTS .....	47
4.1.1	<i>Chronic active Crohn's disease – company model</i> .....	47
4.1.2	<i>Fistulising Crohn's disease</i> .....	49
4.2	EVALUATING AND RE-ESTIMATING THE COST EFFECTIVENESS IN CHRONIC ACTIVE CD .....	50
4.2.1	<i>Comparator and health states</i> .....	51
4.2.2	<i>Scenarios</i> .....	51
4.2.3	<i>Scenario 1: Effectiveness</i> .....	52
SCENARIO 1 USES THE SAME EFFECTIVENESS ESTIMATES AS IN THE COMPANY MODEL, CHECKED AGAINST		
TABLE 11 FOR THE % MOVING INTO REMISSION AND MILD HEALTH STATES .....		
4.2.4	<i>Scenario 2 - effectiveness</i> .....	53
4.2.5	<i>Scenario 1 Cost effectiveness</i> .....	53
4.2.6	<i>Scenario 2: cost effectiveness</i> .....	54
4.3	SENSITIVITY ANALYSIS .....	54
4.3.1	<i>Utility</i> .....	54
4.3.2	<i>Duration of response</i> .....	54
4.3.3	<i>Surgery averted</i> .....	55
4.3.4	<i>Results</i> .....	55
4.4	DIFFERENCES WITH THE COMPANY MODEL .....	56
4.4.1	<i>Company model: one year results</i> .....	56
4.4.2	<i>Company mode: five year results</i> .....	56

4.5 CONCLUSIONS.....	57
4.5.1 <i>Chronic active CD</i> .....	57
4.5.2 <i>Fistulising CD</i> .....	57
4.6 COST IMPACT.....	57
<b>5. FACTORS RELEVANT TO NHS.....</b>	<b>58</b>
5.1 OTHER GUIDANCE.....	58
<b>6. DISCUSSION.....</b>	<b>60</b>
6.1 MAIN RESULTS.....	60
6.2 ASSUMPTIONS, LIMITATIONS AND UNCERTAINTIES.....	61
6.2.1 <i>Important issues not addressed by this Health Technology Assessment</i> .....	61
6.3 NEED FOR FURTHER RESEARCH.....	62
6.3.1 <i>Research in progress</i> .....	62
<b>7. CONCLUSIONS.....</b>	<b>63</b>
<b>8. APPENDICES.....</b>	<b>64</b>
<b>9. REFERENCES.....</b>	<b>76</b>

## LIST OF TABLES

TABLE 1: ANNUAL INCIDENCE OF CROHN'S DISEASE PER 100,000 POPULATION (AS MEASURED DURING 1991-3)	16
TABLE 2: EXPECTED MORBIDITY IN ANY GIVEN YEAR.....	17
TABLE 3: ASPECTS OF TREATMENT EVALUATED BY THE FIVE TRIALS MEETING THE INCLUSION CRITERIA.....	26
TABLE 4: VALIDITY SCORE FOR THE INCLUDED TRIALS.....	26
TABLE 5: NUMBER OF PATIENTS WHO RECEIVED EACH OF THE DOSES OF INFLIXIMAB EVALUATED.....	28
TABLE 6: SUMMARY OF TRIAL CHARACTERISTICS.....	29
TABLE 7: SUMMARY OF PATIENT BASELINE CHARACTERISTICS.....	31
TABLE 8: PRIMARY AND SECONDARY OUTCOMES.....	32
TABLE 9: RESPONSE TO TREATMENT ( $\geq 70$ POINT REDUCTION IN CDAI) FOLLOWING INITIAL BLINDED TREATMENT.....	33
TABLE 10: REDUCTION IN CDAI.....	34
TABLE 11: PATIENTS IN CLINICAL REMISSION.....	35
TABLE 12: MEAN ( $\pm$ SD) VALUES FOR CDAI, CRP AND IBDQ AT BASELINE AND WEEK 4.....	36
TABLE 13: NUMBER OF PATIENTS (%) WITH REDUCTION IN NUMBER OF FISTULAE OVER 2 CONSECUTIVE STUDY VISITS.....	38
TABLE 14: MEDIAN TIME TO ONSET AND DURATION OF CLOSURE OF FISTULAE IN DAYS (IQR).....	39
TABLE 15: MEDIAN PDAI SCORE (IQR) BY TREATMENT GROUP.....	39
TABLE 16: ADVERSE EFFECTS REPORTED IN MORE THAN 10% OF PATIENTS IN ANY OF THE TREATMENT GROUPS EVALUATED.....	42
TABLE 17: INFUSION REACTIONS.....	44
TABLE 18: NUMBER OF PATIENTS WHO DEVELOPED INFECTIONS REQUIRING ANTIBIOTIC TREATMENT.....	45
TABLE 19: HEALTH STATES AND UTILITY VALUES USED IN COMPANY MODEL.....	48
TABLE 20: SUMMARY INCREMENTAL COST PER QALY ESTIMATES IN CHRONIC ACTIVE CROHN'S DISEASE.....	49
TABLE 21: INCREMENTAL COST PER QALY FOR FISTULISING CROHN'S DISEASE.....	50
TABLE 22: EFFICACY OF INFLIXIMAB VERSUS PLACEBO IN TRIALS FOR PATIENTS MOVING INTO REMISSION.....	52
TABLE 23: SUMMARY OF ESTIMATES OF INCREMENTAL COST PER QALY OF INFLIXIMAB COMPARED TO PLACEBO BY SCENARIO AND WITH DIFFERENT ASSUMPTIONS.....	55
TABLE 24: INCREMENTAL COST PER QALY ESTIMATES OF SINGLE AND REPEATED TREATMENTS WITH INFLIXIMAB COMPARED TO PLACEBO OVER 1 AND 5 YEAR PERIODS.....	56

## LIST OF FIGURES

FIGURE 1: RECENT TIME TRENDS IN THE INCIDENCE OF CROHN'S DISEASE.....	16
---	----

## SUMMARY

### Description of proposed service

Infliximab is the first of a new class of drugs, the TNF inhibitors, to be licensed for the treatment of Crohn's disease. Infliximab is indicated for use in adult patients with chronic active Crohn's disease or fistulising Crohn's disease who have not responded to an adequate course of conventional treatment.

Infliximab 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 due to the risk of delayed hypersensitivity.

### Epidemiology and 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 to 25 years. Approximately 31,000 people in England and 1,800 in Wales are estimated to have the disease with around 2,650 new cases diagnosed each year.

Patients with Crohn's disease suffer recurrent attacks with acute flares of the disease interspersed with periods of spontaneous remission. Any part of the gastrointestinal tract can be affected but most commonly the terminal ileum or the ileocaecal region are involved. The disease can be complicated by the development of obstructions, fistulae and perianal disease. Fistulae are 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 or improving quality of life whilst minimising toxicity over the short and long term. Corticosteroids and immunomodulators (chiefly azathioprine or 6-mercaptopurine) form the mainstay of treatment for active Crohn's disease. Both have demonstrated benefit. Treatment is less clear in fistulising Crohn's disease. Enterocutaneous, enteroenteric and enterovisceral fistulae usually result from a mechanical stricture. Surgery will return these 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. Where medical treatment is required the immunomodulatory drugs azathioprine and 6-mercaptopurine are currently considered the most effective, although controlled clinical trial 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.

### Number and quality of studies and direction of evidence

Four randomised-controlled trials are included in this review. Three are completed and one is still on going with preliminary data available to 30 weeks. All trials appeared to be of good methodological quality but this could not be confirmed for the ongoing study.

## Summary of effectiveness

All trials suggested a short-term benefit with infliximab treatment in Crohn's disease. Infliximab use in chronic active Crohn's disease resistant to conventional treatment was evaluated in three trials involving 754 patients (693 receive at least one dose of infliximab). Only the two smaller trials (n=181) are completed, the larger ACCENT I trial (n=573) is yet to be fully reported.

A single dose of infliximab was associated with significant treatment benefit at week 4 (NNT 3 for response defined as  $\geq 70$  point reduction in CDAI) 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 are less clear. The evidence suggests that a positive treatment effect is seen but current data are too limited to confirm this. The full results from the ACCENT I trial will address this.

Only one trial to date has evaluated use in fistulising Crohn's disease. A three-dose treatment course of infliximab resulted in complete healing of perianal/abdominal fistulae for more than 21 days in 46% patients vs. 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. This will be provided by the ACCENT II trial.

## Costs

For a 70kg patient the cost of one dose of infliximab 5mg/kg is approximately £1.8k, with a three-dose course costing approximately £5.4k

## Cost/QALY

The Pharmaceutical company model calculated the cost per QALY in the treatment of chronic active Crohn's disease as £6.7k with a single dose of treatment, £10.4k with episodic re-treatment and £84.4k with maintenance treatment. We believe these to be overestimates due to the assumptions about the way the drug influences the natural history of the disease. (See below)

In fistulising Crohn's disease the cost per QALY values are high, from £102k to £123k for initial treatment only and from £82k to £96K 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 based on clinical opinion seems reasonable. If more frequent flare is seen then costs increase substantially; incremental cost/QALY of £55k with a 50% likelihood of flare.

The fistulising model was relatively insensitive to cost offsets (due to surgery averted), even when 100% offsets assumed.

**Limitations of calculations [assumptions made]**

In developing the model for chronic active Crohn's disease the company have made the implausible assumption that treatment with infliximab will alter the natural course of the disease. There is no observational data available but the clinical trial data suggest that patients return to their pre-treatment disease state with time.

**Other important issues regarding implications**

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 which is not amenable to conventional medical and surgical management. Use of infliximab is therefore likely to be limited to a small group of patients, where benefits over existing treatment can be anticipated.

**Need for further 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.

## ABBREVIATIONS

ACCENT	A Crohn's Disease Clinical Trial Evaluating Infliximab in a new long-term treatment regimen.
Anti-ds DNA	Antibodies to double-stranded DNA
cA2	Infliximab
CDAI	Crohn's disease Activity Index (see glossary)
CDEIS	Crohn's Disease Endoscopy Index of Severity
CI	Confidence Intervals
CSM	Committee on Safety of Medicines
DES	West Midlands Development and Evaluation Service
ECCDS	European Co-operative Crohn's Disease Study
EMA	European Agency for the Evaluation of Medicinal products
GETAID	Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives
GP	General Practitioner
GPRD	General Practitioner Research Database
HACA	Human antichimeric antibody
IBDQ	Irritable bowel disease questionnaire (see glossary)
N/A	Not applicable
NCCDS	National Co-operative Crohn's Disease Study
NHSCRD	NHS Centre for Reviews & Dissemination
NNH	Number-needed-to-harm
NNT	Number-needed to treat
NR	Not reported
ns	Not significant
OR	Odds Ratio
PDAI	Perianal Disease Activity Index (see glossary)
PLA	Placebo
QALY	Quality Adjusted Life Year
RA	Rheumatoid arthritis
SPC	Summary of Product Characteristics
TNF	Tumour Necrosis Factor
URTI	Upper respiratory tract infection

UTI            Urinary tract infection

TB             Tuberculosis

UC            Ulcerative colitis

## GLOSSARY

### **CDAI Crohn's Disease Activity Index**

This is 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.<sup>1</sup>

The index consists of 8 variables (2 subjective) related to the disease. Each of these 8 variables is 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. (As two variables are based on haematocrit and body weight measurements. It is not therefore possible to define a definite numerical upper limit for the score.)

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 vs the physicians subjective overall evaluation of 'how the patient was doing'. A score of 150 or below was taken to represent inactive disease, whereas scores above 450 represented 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 1970s the CDAI has been used widely in clinical trials evaluating interventions in Crohn's disease.

### **CDEIS Crohn's Disease Endoscopic Index of Severity**

The CDEIS 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 10cm visual analogue scale, each segment is scored for the percentage of the segmental surfaces affected by the disease (0% no involvement, 100% complete involvement). Each segment is also scored for the percentage of the segmental surface affected by ulcerations only.<sup>2</sup>

Lower scores indicate endoscopic improvement.

### **IBDQ Irritable Bowel Disease Questionnaire**

The IBDQ was developed in the late 1980s as a tool to measure quality of life in patients with inflammatory bowel disease.<sup>3</sup>

The IBDQ is a 32 item questionnaire, which evaluates; general activities of daily living, intestinal function e.g. bowel habit, abdominal pain, social performance, personal interaction, emotional status. Responses are graded on a 7-point Likert scale; 1 worst function – 7 best function. Scores range from 32 to 224 with a higher score denoting better quality of life. Patients in remission usually score

between 170-190.<sup>4</sup>

Four dimensional scores, cluster items as;

- bowel e.g. loose stools, abdominal pain (10 questions)
- systemic e.g. fatigue, altered sleep pattern (5 questions)
- social e.g. work attendance, need to cancel social events (5 questions)
- emotional e.g. angry, depressed, irritable (12 questions)

The questionnaire takes approximately 15-30 minutes to administer.<sup>3;5</sup>

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

**PDAI Perianal Disease Activity Index**

This is a composite index of the severity of perianal disease as assessed by physicians. It was developed in 1995 because conventional 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. 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 disease activity index (CDAI). In the PDAI a higher score represents more severe disease. The PDAI has demonstrated good correlation with physician and patient global assessment for validity and reliability.<sup>6</sup>

## 1. AIM 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 about the cost and cost-effectiveness of infliximab for the above indications.

## 2. BACKGROUND

### 2.1 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 most commonly the terminal ileum (30-35%) or the ileocaecal region (40%) are 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%.<sup>7-10</sup>

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 emerges.<sup>8</sup>

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. In the National Co-operative Crohn's Disease Study (NCCDS) an average interval of 35 months from the onset of symptoms to diagnosis was documented.<sup>11</sup>

#### 2.1.1 Aetiology

The cause of Crohn's disease is not known 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.<sup>12</sup>

#### 2.1.2 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.<sup>7</sup>

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.<sup>13</sup>

Colonic disease is particularly associated with rectal bleeding, perianal disease and extra intestinal 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.<sup>14</sup> Proctitis however often accompanies ileal disease. Very rarely, the disease affects only the mouth, stomach or duodenum.<sup>7;13</sup>

### 2.1.3 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 eventually cause obstructive symptoms.

Fistulae develop in about one third of patients. They 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).<sup>13</sup> The cause of perianal fistulae is not clear. A spontaneous healing rate is seen, however often surgical management (draining of abscesses) or medical treatment is 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, hepatic disorders) have been documented to develop in more than 15% of patients.<sup>13</sup>, occurring predominantly in patients with colonic Crohn's disease.<sup>7</sup>

### 2.1.4 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.<sup>7;8</sup>

At least 50% of all patients with Crohn's disease require surgical treatment during the first 10 years of their disease; 1 in 12 will require two or more operations during this period. Surgery is usually performed for specific complications (internal obstructions, internal fistulae, toxic megacolon). Only a relatively small number of patients require operations for 'chronic illness' or failure of medical therapy.<sup>13</sup> Following resection for ileal or ileocaecal disease, at least 50% of patients relapse within 10 years and about one half require further surgery.<sup>7;8</sup>

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

### 2.1.5 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,<sup>14</sup> along with disease specific instruments to measure 'quality of life factors'. These include the Crohn's Disease Activity Index (CDAI), Perianal Disease Activity Index (PDAI) and Inflammatory Bowel Disease Questionnaire (IBDQ) which are outlined in the glossary.

### 2.1.6 Classification of Crohn's disease

Crohn's disease is not considered a single homogenous clinical entity. Unfortunately, no simple classification of Crohn's disease has been accepted amongst the experts which distinguishes its principle varieties on the basis of essential differences in clinical behaviour and outcomes.<sup>9</sup>

### 2.1.7 Definitions of different severity's 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. For this report the following working definitions will be used.

#### *Severe active Crohn's disease*

Patients who have a CDAI score >450.<sup>15</sup>

#### *Treatment resistant*

Patients with persisting symptoms (CDAI > 150) despite the introduction of medical treatment (e.g. corticosteroids, azathioprine).

#### *Fistulising Crohn's disease*

Patients with enterocutaneous, enteroenteric, enterovisceral or perianal fistulae.

#### *Remission*

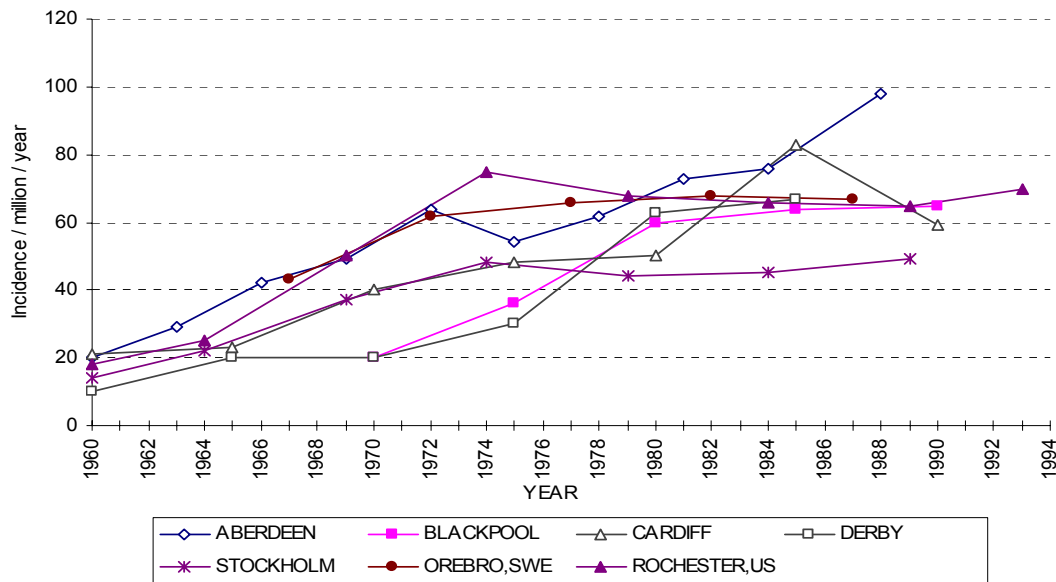
Patients who are asymptomatic or without inflammatory sequelae<sup>14</sup> and with CDAI < 150.

### 2.1.8 Epidemiology (Prevalence/Incidence)

Crohn's disease occurs in all age groups but most commonly presents in those aged 15 to 25 years. Women are slightly more likely to be affected than men are. No marked difference in incidence is apparent across the social classes.<sup>7;16</sup> The disease does however appear to be more common in whites than in blacks and Asians. In particular, there may be an increased incidence (3-6 fold) amongst Ashkenazi Jews.<sup>8</sup>

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 relative) with either Crohn's disease or ulcerative colitis.<sup>7</sup>

**Figure 1: Recent time trends in the incidence of Crohn's disease**



Adapted from GUT 1998; 42: 309-311 with permission from the BMJ Publishing Group and Professor RFA Logan.<sup>17</sup>

Smokers are more likely to develop Crohn's disease than those who do not smoke; relative risk 3:4.<sup>8;18</sup> Other factors recognised to exacerbate Crohn's disease include intercurrent infections and non-steroidal anti-inflammatory drugs (NSAIDs).<sup>7;19</sup>

There are no accurate data on the incidence and prevalence of Crohn's disease. The extent of the disease varies across the world, with highest levels reported in Western Europe and North America. Incidence has been reported to have increased about 5 fold throughout Northern Europe since the 1950s (Figure 1).<sup>17</sup>

The prevalence of Crohn's disease in the western world is estimated at 50 to 100 per 100,000 population with an incidence of 10 per 100,000 per year. In the UK, prevalence is estimated 62.5 per 100,000 (31,095 people in England and in 1,836 Wales) with around 3,000 new cases diagnosed each year (approximately 2,500 people in England and 150 in Wales).<sup>8;20</sup>

**Table 1: Annual Incidence of Crohn's disease per 100,000 population (as measured during 1991-3)**

Age Group	15 – 44	45 – 64	65+
Men	6.0	3.2	2.9
Women	7.7	3.0	2.0

Adapted with permission from the British Society Gastroenterology.<sup>8</sup>

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.

**Table 2: Expected morbidity in any given year**

Stage of Disease	Proportion of Crohn's Disease patients			Estimated No of patients for average HA 500,000
	Swedish Cohort 1987 <sup>21</sup>	Br.Soc.Gastro 1996 <sup>8</sup>	Swedish Cohort 1998 <sup>22</sup>	
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 an operation during the year of diagnosis, 12% during the 1 <sup>st</sup> year, 8% during the 2 <sup>nd</sup> year)		5.7%	16-18

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. The cohort consisted of 174 patients with 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 in post-surgical remission (no- medication), 12.7 years (27%) 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 immunosuppressant treatment.<sup>23</sup> These data have been used to derive utility scores by stage,<sup>24</sup> 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 1966-1969 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 of > 13 years.<sup>13</sup>

## 2.2 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 that are steroid-dependent, being treated with immunosuppressants or requiring surgery, are managed in secondary care.<sup>8</sup>

Crohn's disease is neither medically nor surgically curable. Treatment is therefore aimed at reducing symptoms to maintain/improve quality of life whilst minimising short and long term toxicity.<sup>14</sup> A number of therapeutic agents which have been variably evaluated, are currently used. Unfortunately, differences in study design, patient population, drug regimens and

endpoints hamper the combining and comparison of data collected on these drug therapies in clinical trials.

### 2.2.1 Induction of remission (CDAI $\leq$ 150)

#### *Active Crohn's Disease*

Aminosalicylates, corticosteroids, antibiotics and immunosuppressants have all been evaluated in the treatment of active Crohn's disease. The NCCDS<sup>25</sup> and the European Co-operative Crohn's Disease Study (ECCDS)<sup>26</sup> conducted in the late 1970s/early 1980s provided key data on the efficacy of the aminosalicylates and corticosteroids. Data on other treatments are chiefly provided by later studies. Mesalazine and sulphasalazine are accepted as having only modest efficacy. In the NCCDS and ECCDS trials, 38% vs 26% and 50% vs 37% of patients achieved clinical remission with short term sulphasalazine treatment (16-18 weeks) compared with placebo.<sup>25;26</sup> Similar efficacy has been reported with mesalazine.<sup>27;28</sup> In particular, benefit with sulphasalazine has only been consistently demonstrated in patients with colitis and ileocolitis.<sup>26</sup>

Short-term (4-8 weeks) treatment with corticosteroids forms the mainstay of therapy in active Crohn's disease. In the NCCDS and ECCDS 47% vs. 26% and 83% vs. 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 to 69% over 8-10 weeks) in patients with active disease of the ileum, ileocecal region or ascending colon.<sup>29 30</sup> In severe active disease, hospital admission and intravenous administration of corticosteroids may be required.

Despite a good initial response it is recognised that in those who do respond to oral corticosteroids a proportion will become treatment resistant, and others dependent on treatment, relapsing 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% a partial response and 20% no response. After 1 year 56% of patients were resistant to (20%) or dependent (36%) on corticosteroids.<sup>31</sup>

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 3 randomised controlled trials of azathioprine and 6-mercaptopurine therapy in adult patients (n = 425) with active Crohn's disease. Overall the odds ratio (OR) of a response to azathioprine or 6-mercaptopurine therapy compared to placebo in these patients was 2.36 (95% CI 1.57 to 3.53), NNT 5. These immunosuppressants also demonstrated steroid sparing effects; OR 3.86 (95% CI 2.14 to 6.96), NNT 3. Conversely the odds ratio for a patient suffering an adverse event requiring withdrawal from treatment was 3.01 (95% CI 1.30 to 6.96), NNT 14.<sup>32</sup> In particular treatment with these drugs is 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 and allow steroid withdrawal in 39% of patients dependent on steroids compared with 19% treated with placebo for 16 weeks.<sup>33</sup> The immunosuppressants ciclosporin, 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.<sup>34-36</sup> Larger controlled trials are now underway with tacrolimus.<sup>36</sup>

Other treatments that are used are oral antibiotics (chiefly metronidazole and/or ciprofloxacin) and enteral nutrition. Controlled trials with antibiotic therapy are scarce, with most reporting negative results.<sup>29</sup> Clinical opinion currently considers these drugs modestly effective in mild to moderately active Crohn's disease. They 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 8 trials in 413 patients. Enteral nutrition was found to be inferior to corticosteroids (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.<sup>8</sup>

### ***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.<sup>37</sup>

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 with 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.<sup>29;37</sup> Currently immunomodulatory agents are considered the most effective drugs for the management of fistulising Crohn's disease. Controlled clinical trial data are however limited. The Cochrane Review on azathioprine and 6-mercaptopurine reported a response rate 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 however are required to evaluate whether a significant benefit is seen with treatment.<sup>32</sup> Trials are underway to evaluate the efficacy of tacrolimus in fistulising Crohn's disease after preliminary studies have suggested potential benefit.<sup>36;37</sup>

### **2.2.2 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 with mesalazine are less clear. Two meta-analyses published in 1994 reported a reduction in the relapse rate of approximately 50% with mesalazine predominantly in patients with ileal and ileocolonic disease.<sup>38;39</sup> A more recent meta-analysis reported that mesalazine treatment significantly reduced the symptomatic relapse rate compared to 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.<sup>40</sup>

The use of conventional systemic corticosteroids in patients with clinically quiescent Crohn's disease does 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]).<sup>41</sup>

Azathioprine and 6-mercaptopurine are the mainstay of maintenance therapy. In a pooled analysis, maintenance of remission with azathioprine was seen in 67% of patients vs. 52% 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 NNH was calculated at 19 for withdrawals due to adverse events (OR 4.36 [95% CI 1.63 to 11.67]).<sup>42</sup> 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.<sup>32;43</sup> The results of the GETAID withdrawal trial, expected at the end of 2001, should help to address the issue of optimum duration of therapy.

### 2.2.3 Surgical Management

Between 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
- complications such as fistulae and peri-anal disease.<sup>8</sup>

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.<sup>7 44 14</sup> Despite maintenance therapy, symptoms recur after surgery in about 35% of patients within 5 years and in about 73% of patients within 20 years.<sup>45</sup>

## 2.3 Anti-TNF 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- $\alpha$  is thought to play a central role in the immunopathology 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- $\alpha$ . These antibodies bind to released TNF- $\alpha$  as well as to membrane bound TNF- $\alpha$ .<sup>46 47</sup>

### 2.3.1 Technology under evaluation – Infliximab (REMICADE™)

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to TNF- $\alpha$ , inhibiting its activity. Schering Plough launched Infliximab in the UK on 1st September 1999.

Infliximab is indicated for use in adults (18 years and above) 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'
- 'treatment of fistulising Crohn's disease in patients who have not responded despite a full and adequate course of therapy with conventional treatment'.<sup>48</sup>

Infliximab is also licensed for use in rheumatoid arthritis 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 presented as a powder for solution for infusion that requires reconstitution and dilution before administration. It is given as an intravenous infusion over at least two hours. In severe active Crohn's disease the recommended dose is 5mg/kg as a single infusion. In fistulising Crohn's disease, infliximab is given as an initial 5mg/kg infusion over at least 2 hours followed by additional 5mg/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 due to the risk of delayed hypersensitivity reaction.

Infliximab is contraindicated in patients with sepsis, or with clinically manifest infections (including tuberculosis) 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.<sup>48</sup>

Infliximab has been marketed in the UK at a cost of £451.20 for a single 100mg vial. These vials do not contain a preservative - any unused portion of reconstituted solution must be discarded. For a 70kg patient the average cost for a single 5mg/kg infusion is £1,804.80 (4 vials).

### **2.3.2 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, where 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 a history malignant disease should not be treated with infliximab.<sup>49</sup> Additional contra-indications include known allergy against murine proteins, pregnancy or breast feeding.

### **2.3.3 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 gastrointestinal physician and surgeon experienced in the management of severe Crohn's disease. The decision to start infliximab treatment will be made on an in-patient or hospital day case basis.

Infliximab needs to be reconstituted prior to administration.

Infliximab is administered as a slow intravenous 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 PVC tubing).<sup>50</sup> Patients needed to be carefully monitored by a nurse or doctor during the infusion in case of anaphylactic reaction or other acute side effects. Adequate facilities for the management of allergic reactions should be available.

It will 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, as is provided at tertiary centres. It is anticipated that most patients will be treated on an out-patient basis. Patients with fistulising Crohn's disease require repeat infusions at 2 and 6 weeks.

Patients will require follow-up at 2-4 weeks and 8-12 weeks, after completion of treatment, with assessment regarding the need for further treatment. Inflammatory markers, full blood count, electrolytes and liver function should be repeated at each visit.<sup>49</sup>

#### **2.3.4 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 have been 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 Rheumatoid arthritis. From these data it is not possible to calculate the number of patients treated due 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 believe that between January 2000 and May 2001, 600-700 patients have been treated with infliximab for Crohn's disease. They estimate that use of infliximab in severe active disease and fistulising disease is split 50:50.<sup>51</sup>

The University of Birmingham conducted a survey in May/June 2001 of the usage of infliximab for the treatment of Crohn's disease amongst Gastroenterologists in England and Wales. A questionnaire (Appendix 5) with personalised letter was sent to all Gastroenterologists working in the NHS in England and Wales. In total 303 questionnaires were mailed. 214 responses were received; 70.6% response rate. Responding Physicians had treated 526 patients with chronic active Crohn's disease (median per Gastroenterologist 1, IQR 0 to 3) and 271 with fistulising Crohn's disease (median per Gastroenterologist 0, IQR 0 to 1.75) with infliximab. In some cases it was identified that these patients had been treated as part of a randomised controlled trial. The number of patients currently receiving treatment was 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 disease 27 with fistulising disease. Importantly approximately half of responders identified that funding currently limited their treatment of patients with Crohn's disease with infliximab.

### **3. EFFECTIVENESS**

#### **3.1 Methods for Reviewing Effectiveness**

##### **3.1.1 Review questions**

The following questions are addressed in this review by assessing existing evidence:

##### **Effectiveness**

- Q1 How effective is infliximab as a 2<sup>nd</sup> or 3<sup>rd</sup> line treatment for severe active Crohn's disease in adults who have not responded to conventional treatment?
- Q2 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?
- Q3 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**

- Q4 What is the frequency and severity of adverse effects associated with the use of infliximab?
- Q5 What adverse events are associated with repeated treatment with infliximab?

##### **Cost and Cost-effectiveness**

- Q6 What is the cost-effectiveness of infliximab for the above indications compared to standard practice?

The methods of the review followed the guidance laid out in the West Midlands DES Handbook<sup>52</sup> and the NHSCRD report Number 4 (2<sup>nd</sup> Edition) March 2001.<sup>53</sup>

##### **3.1.2 Search Strategy**

The following electronic databases were searched with a cut-off date of 31<sup>st</sup> March 2001: Cochrane Library, Medline, Embase, Science Citation Index

Search terms included the text words: infliximab; remicade; tumour necrosis factor; tnf; ca2; chimeric ca2 and index terms; crohns disease; receptors; tumour necrosis factor. A full search strategy is available on request.

Studies were limited to humans. No language or age restrictions were applied. Alta Vista and Yahoo search engines were used to search the Internet, and links followed up.

Scrip, FDA submissions for new drug applications, EMEA reports were hand-searched and the reference lists of identified publications reviewed for further citations.

Studies identified by the search strategy were assessed for inclusion via two stages; 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. (Appendix 1).

### 3.1.3 Inclusion and exclusion of trials

#### 3.1.4 Inclusion criteria

Studies were included in the final analysis of the systematic review of effectiveness if they meet the following criteria:

<i>Study design:</i>	Randomised or quasi-randomised controlled trials
<i>Population</i>	Adults aged 18 years and above with either severe active Crohn's disease or fistulising Crohn's disease resistant to conventional treatment.
<i>Intervention:</i>	Infliximab (Remicade™) given as a single dose, treatment course or repeated treatment course.
<i>Comparator:</i>	Placebo, or other treatment for Crohn's disease
<i>Publication</i>	All data to be included irrespective of publication status.

#### 3.1.5 Exclusion criteria

Non-randomised controlled trials.

#### 3.1.6 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 Crohn's disease activity index (CDAI)
  - changes in Perianal disease activity index (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 population (ITT). Where information was missing, further information was sought from the authors or industry.

### 3.1.7 Quality assessment strategy

Two reviewers independently undertook quality assessments. Disagreements were resolved by discussion, with reference to a third party if there remained disagreement.

The validity of the studies was assessed by looking at 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 (Appendix 2).

Assessment was made of the clinical relevance of the outcomes reported. Outcomes anticipated to be of clinical relevance included: CDAI; duration of remission; other Crohn's medication use; weight loss/gain; tumours; infections; PDAI; prevention of surgery; Inflammatory bowel disease questionnaire (IBDQ).

The quality of the reporting of the trial was assessed. Where the reporting of a trial was incomplete (eg. results only reported for some participants, interim results only available), the investigators were contacted for full details. Data from trials that have not finished recruiting were included where available.

## 3.2 Results

### 3.2.1 Quantity & quality of research available

#### *Number of Studies Identified*

Twenty-three abstracts, posters or full publications that potentially reported relevant trials were identified.<sup>28;54-75</sup> Twenty-one came from searches of electronic databases.<sup>28;55-71;73-75</sup> (10 of these were also identified by hand searching reference lists), one from the internet<sup>54</sup> and one from hand searching reference lists, journals, and contact with experts.<sup>72</sup> 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*

Four published papers appeared to meet our inclusion criteria,<sup>56;64;68;70</sup> three were reports of randomised controlled trials and a the forth a paper<sup>56</sup> on endoscopic healing in a subgroup of patients enrolled in the larger Targan study<sup>70</sup>. Two ongoing trials also met the inclusion criteria, (these were identified from a single report on the internet).<sup>54</sup> Preliminary data are currently only available from one of these ongoing trials, the ACCENT I study.<sup>76</sup>

These studies have largely addressed different aspects of use of infliximab for the treatment of Crohn's disease.

**Table 3: Aspects of treatment evaluated by the five 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 <sup>70</sup>	108	√		√		Patients who did not respond to the blinded infusion by week 4 were allowed to receive a single dose of open label infliximab <b>The study by D'Haens<sup>56</sup> reported data on endoscopic healing for a sub-group of patients enrolled in this trial.</b>
Rutgeerts et al <sup>68</sup>	73	√			√	Patients needed to show a response to blinded treatment in the Targan study to be enrolled in this trial
ACCENT I <sup>54</sup>	573	√			√	All patients received a single dose of infliximab prior to randomisation.
Present et al <sup>64</sup>	94		√	√		

**Excluded trials**

Eighteen publications were excluded (Appendix 3); 10 were not controlled trials, 7 were not clinical trials; 1 reported responses in a subgroup of patients by treatment centre.<sup>55</sup> Patients included in this report were enrolled as part of two randomised, double-blind, controlled trials in patients with treatment resistant, moderate to severe Crohn's disease. The author of this report was contacted and identified that the patients were enrolled in the Targan and Present study. The results of these trials are published in full. It is not possible from the data presented in the Baert paper to differentiate patients between these two trials. The data could not therefore be included in our analysis.

**Design & Conduct**

*Validity*

All included studies were randomised, double-blind, controlled trials. The Jadad score for each trial is summarised in Table 4. The low score for the ACCENT I trial probably relates to the limited data on methodology currently available.

**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 <sup>70</sup>	YES	YES	YES	YES	YES	No	5
Rutgeerts et al <sup>68</sup>	Yes	Yes	Unclear	Unclear	Unclear	No	4
ACCENT I <sup>54</sup>	Unclear	Unclear	YES	Unclear	Unclear	Unclear	2
Present et al <sup>64</sup>	Yes	Yes	Yes	Yes	Yes	No	5

Randomisation was performed centrally by an independent organisation (PPD Pharmaco, Austin, Texas) for the 3 primary studies. Details are 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 in the trials by Targan et al<sup>70</sup>, Rutgeerts et al<sup>77</sup> and the ACCENT I study<sup>78</sup>

- last treatment received in the Targan trial for patients enrolled in the trial by Rutgeerts et al<sup>77</sup>
- number of fistulae at baseline in the study by Present et al.<sup>79</sup>

All trials were described as double-blind. In the study by Targan et al the infliximab and placebo solutions were prepared by a pharmacist at each site 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.<sup>70</sup> The same was true for the re-treatment phase of this study.<sup>77</sup> In the fistulising Crohn's disease study by Present et al, all study personnel (including pharmacists) and patients were masked from treatment. Data on blinding are not clearly presented for the ACCENT I trial.

Intention to treat analysis was only clearly used in the study by Present et al.<sup>64</sup> The study by Rutgeerts et al<sup>68</sup> does not specify whether intention-to-treat 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.<sup>68</sup>

The Targan study<sup>70</sup> was not analysed by intention-to-treat. 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.<sup>70</sup>

A total of 24 patients did not complete the re-treatment trial conducted by Rutgeerts et al;<sup>68</sup> 14 assigned to placebo and 10 assigned to infliximab. Reasons for discontinuation were lack of efficacy (12 placebo, 4 infliximab), adverse events (0 placebo, 6 infliximab) and other (2 placebo, withdrawal of consent and non-compliance).

In the fistulising Crohn's disease trial conducted by Present et al, six patients completed only two of the planned three infusions (4 placebo, 1 infliximab 5mg/kg, 1 10mg/kg). Reasons for discontinuation of treatment were lack of efficacy (3 placebo), adverse events (1 infliximab 10mg/kg), other (1 placebo, administration reasons; 1 infliximab 5mg/kg, withdrawal of consent).

The ACCENT I trial is still ongoing, details on, methods of analysis and number of patient withdrawals are not yet available.

### *Interventions and comparators*

The three fully completed trials incorporated into this review all had a placebo comparator arm and a 10mg/kg infliximab treatment arm. The other doses evaluated are shown in Table 5. The Targan study 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 10mg/kg.

In the ACCENT I study all patients received an initial 5mg/kg dose of infliximab and were randomised to continued dosing with infliximab (5mg/kg or 10mg/kg) or placebo.

Infliximab was administered by slow intravenous infusion over a 2-hour period in all the trials.

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

Trial	Infliximab dose		
	5mg/kg	10mg/kg	20mg/kg
Targan et al <sup>70</sup>			
Double blind	27	28	28
Open label		48	
Rutgeerts et al <sup>68</sup>	-	37	-
ACCENT I <sup>76</sup>	573	?	?
Present et al <sup>64</sup>	31	32	-
<b>Total</b>	<b>631</b>	<b>145*</b>	<b>28</b>

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

A more detailed summary of interventions and comparators appears in Table 6 page 29.

#### *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).<sup>64;68;70</sup> Trial profiles for the three fully published trials are given in Appendix 4.

The phase II study by Targan et al<sup>70</sup> evaluated the short-term efficacy of a single dose of infliximab in 108 patients with moderate to severe treatment resistant Crohn's disease (CDAI  $\geq$  220 despite concurrent treatment with drugs other than infliximab). Patients were randomised to double-blind treatment with a single infusion of placebo (n = 25), infliximab 5mg/kg (n = 27), 10mg/kg (n = 28), 20mg/kg (n = 28) and followed up for 12 weeks.<sup>70</sup> This trial was conducted over 18 sites (13 US & 5 European). Thirteen of these centres enrolled 5 or fewer patients.<sup>79</sup>

The design of this trial was unusual. If patients did not show a clinical response ( $\geq$  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 10mg/kg infliximab and were followed up for an additional 12 weeks.<sup>70</sup>

Non-responding patients who received open-label infliximab treatment had their results at 4 weeks carried forward to weeks 8 and 12.<sup>79</sup> No account was therefore taken of any late and/or spontaneous responses which could have occurred in any group during the period between the 4 and 12 week assessment.<sup>70</sup>

The trial conducted by Rutgeerts et al was a 36 week extension study of the Targan trial in adult patients with treatment resistant, moderate to severe Crohn's disease. Patients enrolled in the Targan study who demonstrated a clinical response 8 weeks after blinded or open-label treatment were eligible to enrol in the re-treatment extension which began at week 12 following initial successful treatment. The trial was conducted in 17 study centres in North American and Europe.<sup>68</sup>

Of the 80 eligible patients, 73 were randomised to double-blind treatment with 4 infusions of placebo (n = 36) or infliximab 10mg/kg (n = 37) at 8 week intervals (weeks 12, 20, 28, 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 study had shown an initial clinical response to placebo in the Targan study; 1 of these patients was re-treated with placebo and 3 treated with infliximab in the extension study.<sup>68</sup>

**Table 6: Summary of trial characteristics**

	Targan et al <sup>70</sup>	Rutgeerts et al <sup>68</sup>	ACCENT I <sup>76,78</sup>	Present et al <sup>64</sup>
Intervention	Infliximab 5mg/kg x 1 dose Infliximab 10mg/kg x 1 dose Infliximab 20mg/kg x 1 dose	Infliximab 10mg/kg x 4 doses	Infliximab 5mg/kg week 0,2,6 & 8 weekly. Infliximab 5mg/kg week 0,2,6, 10mg/kg 8 weekly	Infliximab 5mg/kg x 3 doses Infliximab 10mg/kg x 3 doses
Comparator	Placebo x 1 dose	Placebo x 4 doses	Infliximab 5mg/kg week 0 + placebo week 2,6 & 8 weekly	Placebo x 3 doses
Design	RCT	RCT	RCT	RCT
Country	N. America & Europe	N. America & Europe	North America, Europe & Israel	US & Europe
No. of centres	18	17	55	12
No. of patients randomised	108	73	573	94
No. placebo/ infliximab	25/83  Infliximab 5mg/kg – 27 10mg/kg – 28 20mg/kg – 28 NB: 48 patients received an additional infusion of infliximab 10mg/kg	36/37  Infliximab  10mg/kg – 37	Week 2 responders 110/225  Infliximab 5mg/kg – 113 10mg/kg – 112	31/63  Infliximab 5mg/kg – 31 10mg/kg – 32
Inclusion criteria	Aged 18-65 years Crohn's disease ≥6 months. CDAI score between 220 to 400 & current treatment or lack of response to: • oral corticosteroids ≤40mg/d • sulfasalazine/mesalazine • azathioprine or 6-mercaptopurine • methotrexate or ciclosporin	As for Targan study plus Clinical response to infliximab infusion documented in Targan study.	Men & women ≥ 18years of age. CDAI ≥220 and ≤400 Crohn's disease of ≥ 3 months duration.	Aged 18-65 Confirmed Crohn's disease Single or multiple draining abdominal or perianal fistulae for ≥ 3 months.
Exclusion criteria	Treatment with ciclosporin, methotrexate or experimental agents within 3 months before screening. Symptomatic stenosis or ileal strictures. Proctocolectomy or total colectomy. Stoma. A history or allergy to muric proteins. Previous treatment with murine chimeric or humanised monoclonal antibodies. Treatment with parental corticosteroids or corticotrophin within 4 weeks before screening.	As for Targan study	Manifestation of Crohn's disease which may require surgery, or prevent use of CDAI. Draining entero-cutaneous or internal fistula Stoma within 3 months of trial entry. Treatment with ciclosporin, tacrolimus or sirolimus within 4 weeks. Use of any investigational drug within 1 month. Previous administration of infliximab or any other drug targeted at TNF within last 3 months. Serious infections in last 3 months. Active TB requiring treatment within previous 3 years. Malignancy ≤ 5 years. History of lympho-proliferation disease.	Treatment with aminosalicylates, oral corticosteroids, methotrexate, azathioprine, 6 mercaptopurine or antibiotics discontinued < 4 weeks before enrolment. Concurrent ciclosporin treatment. Treatment with investigational drugs or use of any medication to reduce the concentration TNF-α ≤ 3 months before enrolment. Other complications of Crohn's disease, eg current strictures or abscesses. 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 trial.	102 weeks	26 weeks
Reporting intervals	0,4,8,12,(16)	12,16,20,24,28,32,36,40,44,48	0,2,6,10,14,22,30,38,46,54,62,70,78,102	0,2,6,10,14,18,26,34

The study conducted by Present et al<sup>64</sup> evaluated 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. 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 5mg/kg (n = 31) or infliximab 10mg/kg (n = 32) administered as an intravenous infusion at weeks 0, 2 and 6.<sup>64</sup> The trial was conducted over 12 centres in the US (n = 7) and Europe (n = 5). Six of these sites enrolled 5 patients or fewer. Patients were followed-up to 26 weeks.<sup>64;79;80</sup>

The later, larger ACCENT studies have evaluated the efficacy of repeated treatment with infliximab at 8 weekly intervals in patients with moderate to severe Crohn's disease (ACCENT I) and fistulising Crohn's disease (ACCENT II). Preliminary results are now available for responding patients in the ACCENT I trial.

The ACCENT I trial was a 54 week study in 573 patients with moderate to severe active Crohn's disease (CDAI  $\geq$  220 and  $\leq$  400). All enrolled patients received an initial infusion of 5mg/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 through to week 54.
- infliximab 5mg/kg at weeks 2, 6 and every 8 weeks through to week 54.
- infliximab 5mg/kg at weeks 2 and 6 and 10mg/kg every 8 weeks through to week 54.

Additionally, patients who initially responded to infliximab therapy but subsequently lost response were eligible for episodic re-treatment with single doses of infliximab beginning at or after week 14. Patients who failed to respond at week 2 and also failed to respond at later evaluation visits were not eligible for crossover.

In all patients who demonstrated a clinical response with the initial dose of infliximab, concomitant corticosteroid doses could be reduced from week 6.

Data are currently available up to week 30 for patients who responded to the initial infusion of infliximab 5mg/kg. Of these 335 patients, 110 were randomised to placebo (weeks 2, 6 and 8 weekly), 113 to continued treatment with infliximab 5mg/kg (weeks 2, 6 and 8 weekly) and 112 to two further doses of infliximab 5mg/kg (weeks 2 and 6) followed by 8 weekly dosing with 10mg/kg. The trial was conducted over 55 centres in North America, Europe and Israel.<sup>76;78</sup>

### *Characteristics of the study population*

A summary of the key baseline characteristics for patients enrolled in the three trials is given in Table 7. Very limited data are 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 the 3 trials, the baseline demographic data did not differ significantly between the active and placebo treatment groups in terms of age, weight, race, sex, duration of Crohn's disease and median/mean CDAI scores. However in the Targan study numerically, 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.

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 et al<sup>70</sup>, significantly more patients in the placebo group had ileal disease alone

compared to the other groups ( $p = 0.02$ ), whereas in the study by Present et al there was a trend for a higher proportion of infliximab treated patients to have undergone a previous segmental resection, 21 (68%) infliximab 5mg/kg, 17 (53%) 10mg/kg and 12 (39%) placebo,  $p = 0.074$ .

Across the three completed trials 55-62% of patients had/were receiving aminosalicylates, 35-60% corticosteroids, 37-47% azathioprine or 6-mercaptopurine and 20-30% antibiotics<sup>64;70;77</sup>

In total 92% of patients in the study by Targan et al<sup>70</sup> and 83% in the study by Present et al<sup>64</sup> were taking concurrent Crohn's disease medication at baseline.<sup>79</sup> (93% of patients in the Present et al study had been aggressively treated with either antibiotics or immunosuppressive drugs, prior to enrolment.<sup>47</sup>) There were no significant differences across the groups with respect to concomitant medication. Of note in the study by Present et al, a greater proportion of patients assigned infliximab 10mg/kg were receiving mercaptopurine or azathioprine than those assigned 5mg/kg or placebo (53% vs 39% vs 29%), and fewer assigned 5mg/kg were receiving antibiotic treatment than those assigned 10mg/kg or placebo (19% vs 34% vs 35%).<sup>64;79</sup>

**Table 7: Summary of Patient Baseline Characteristics**

	Targan et al <sup>70</sup>	Rutgeerts et al <sup>68</sup>	ACCENT I <sup>78</sup>	Present et al <sup>64</sup>
No. placebo/ infliximab	25/83	36/37	110/225	31/63
No. male/female (% male)	55/53 (51%)	38/35 (52%)	NR	44/50 (47%)
Race – White (%)	108 (100%)	73 (100%)	NR	86 (91%)
Mean duration of Crohn's disease (years) - all - placebo - infliximab	12.0 ± 9.1 10.4 ± 7.7 5mg/kg 12.5 ± 10.3 10mg/kg 11.5 ± 9.6 20mg/kg 13.5 ± 8.8	12.0 ± 9.0 13.2 ± 9.8 10mg/kg 10.9 ± 8.1	NR	12.4 ± 8.5 12.0 ± 7.9 5mg/kg 13.6 ± 9.5 10mg/kg 11.5 ± 8.2
Intestinal area involved: ileum only/colon only/ ileum & colon	17/33/58	10/23/40	NR	14/26/54
Previous surgery for Crohn's disease	53 (49%)	35 (48%)	NR	50 (53.2%)
No of patients with fistulae 1/>1	20 Number of fistulae present not stated	13 Number present not stated	NR	42/52 85/9
Location of fistula perianal/abdominal	Not stated		NR	85/9
Mean baseline CDAI (± SD) - all - placebo - infliximab	307 ± 55 288 ± 54 5mg/kg 312 ± 56 10mg/kg 318 ± 59 20mg/kg 307 ± 50		Median (range) 297 (193 – 488)	Not stated 192.9 ± 92.0 5mg/kg 184.4 ± 98.5 10mg/kg 184.9 ± 97.5
Previous/ concurrent medication: Corticosteroid (%) Mercaptopurine/ azathioprine (%) Aminosalicylate (%) Antibiotic (%)	64 (59.3%) 40 (37.0%) 64 (59.3%)		62% 29%	33 (35.1%) 38 (40.4%) 52 (55.3%) 28 (29.8%)

In the fistulising Crohn's disease trial conducted by Present et al<sup>64</sup> 55.3% of patients had more than one fistula present at baseline (median of 3 fistulae) with even distribution across the treatment groups.<sup>79</sup> The majority of patients (68.1%) had a maximum duration of draining of any fistulae of greater than 1 year.<sup>81</sup> For the whole group, 90% of patients had perianal fistulae and 10% abdominal fistulae.<sup>64</sup>

Whilst it is stated that 20 patients enrolled in the study by Targan et al<sup>70</sup> had a fistula present at baseline no further details are given. No data are 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 (and  $\geq 25\%$  for ACCENT I trial) in CDAI from baseline without a change in medication or the need for surgical intervention for Crohn's disease.<sup>78</sup> This can be taken as a modest improvement. (A more stringent endpoint of a reduction of  $\geq 100$  points in CDAI has been used in previous trials evaluating other therapies for Crohn's disease).<sup>78</sup>

Clinical remission was defined as a CDAI score  $< 150$ . This is widely accepted.

In the fistulising Crohn's disease study conducted by Present et al<sup>64</sup> 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 investigators physical examination of the patient; 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 a  $\geq 50\%$  closure of fistulae was required overall, consistent closure of the same fistulae was not required.

**Table 8: Primary and Secondary Outcomes**

	Targan et al <sup>70</sup>	Rutgeerts et al <sup>88</sup>	ACCENT I <sup>78</sup>	Present et al <sup>64</sup>
Primary Outcomes	$\geq 70$ point reduction in CDAI at week 4 with no change in concomitant medication (clinical response)	No specified	Time to loss of response	$\geq 50\%$ reduction from baseline in number of draining fistulae, observed in two or more consecutive study visits
Secondary Outcomes	Clinical response over time. Duration of response. Clinical Remission (CDAI $< 150$ ). Change in CDAI, IBDQ, CDEI scores and CRP values. Changes in components of CDAI. Proportion of patients discontinued at week 12.	Maintenance of clinical response. Maintenance of clinical remission. Proportion of patients discontinuing because of lack of efficacy. Change in CDAI, IBDQ & CRP over time.	Reduction in concomitant corticosteroid use. Clinical remission. Effectiveness of episodic re-treatment. Mucosal healing. Quality of life.	Complete response (absence of any draining fistulae at two consecutive visits). Time to response. Duration of response. Changes in CDAI & PDAI scores. Clinical response. Clinical remission

### 3.2.2 Assessment of Effectiveness

#### *Moderate to 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 is provided chiefly by the study conducted by Targan et al,<sup>70</sup> the follow-up of this study by Rutgeerts et al<sup>68</sup> and the ACCENT I trial<sup>54</sup>.

The trial by Targan et al 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. The Rutgeerts trial and ACCENT I study evaluated the maintenance of benefit with repeated infliximab treatment.

The Targan and Rutgeerts studies are published in full. The ACCENT I trial is still ongoing. Preliminary data are 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.<sup>76</sup>

#### *Clinical response (Reduction in CDAI $\geq$ 70 points)*

##### *Single dose*

In the Targan study (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).<sup>70</sup> No patients responded after the 4 week evaluation.

Among the patients who responded at the 4 week evaluation 25% (1 of 4) placebo treated and 37% (20 of 54) of infliximab treated patients subsequently lost response by week 12.<sup>79</sup> No data are provided on the health state of these 'relapsed' patients. However the loss of response seen suggests that repeated dosing is required to maintain an effect.<sup>70</sup>

**Table 9: Response to treatment ( $\geq$  70 point reduction in CDAI) following initial blinded treatment**

Time post treatment	Placebo n = 25	Infliximab 5mg/kg n = 27	Infliximab 10mg/kg n = 28	Infliximab 20mg/kg n = 28	All infliximab n = 83
Week 2	4 (16.0%)	20 (74.1%)	12 (42.9%)	15 (53.6%)	47 (56.6%)*
Week 4	4 (16.0%)	22 (81.5%)*	14 (50.0%) <sup>†</sup>	18 (64.3%) <sup>#</sup>	54 (65.1%)*
Week 8	4 (16.0%)	16 (59.3%)	11 (39.3%)	16 (57.1%)	43 (51.8%) <sup>†</sup>
Week 12	3 (12.0%)	13 (48.1%)	8 (28.6%)	13 (46.4%)	34 (41.0%) <sup>#</sup>

\*p < 0.001 vs placebo

<sup>#</sup>p < 0.01 vs placebo

<sup>†</sup>p < 0.05 vs placebo

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 5mg/kg dosage group, with a trend towards increased benefit vs 10mg/kg & 20mg/kg treatment. (p=0.053 for 5mg/kg vs 10mg/kg and 20mg/kg combined at week 4).

A retrospective analysis for the number of patients achieving  $\geq$  100 point reduction from baseline in CDAI also demonstrated significant benefit with treatment (Table 10).<sup>79</sup>

**Table 10: Reduction in CDAI**

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

In total 50 patients did not respond to the initial blinded infusion by week 4; 21 (84%) placebo, 29 (34.9%) infliximab 5mg to 20mg/kg. Forty-eight of these patients subsequently received open label infliximab: 19 patients following an initial placebo infusion, 6, 15 & 8 following an initial infusion of infliximab 5mg/kg, 10mg/kg and 20mg/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 of 19). However, only 34.5% of patients (10 of 29) who received infliximab as their initial blinded infusion responded to a second dose of infliximab, suggesting that these patients may be less responsive to anti-TNF therapies.

#### *Repeated dosing*

In the re-treatment follow up of the Targan trial (Rutgeerts study), 8-weekly repeated treatment with infliximab was associated with a statistically significant improvement in clinical response at week 36 only; 72.2% vs 44.1% (p = 0.018). Data are not given for week 48, but at week 44 (8 weeks after the last infusion), the response rates were 62% vs 37%, p = 0.160.<sup>50;68</sup>

Whilst not reaching the conventional level of statistical significance, patients treated with infliximab who were receiving concurrent treatment with 6 mercaptopurine/azathioprine showed a greater treatment response than those treated with infliximab but not receiving 6 mercaptopurine/azathioprine; 75% vs 50%, p = 0.17 at week 44.<sup>68</sup>

In the ACCENT I trial for all enrolled patients (n = 573), a three-dose induction with infliximab 5mg/kg at weeks 0, 2 and 6 and was associated with a significantly greater response rate at week 10 than a single infusion of infliximab at week 0 (65% vs 52%, p = 0.035).<sup>82</sup> No further data are available for this endpoint.

Sixty percent of responders at week 2 who continued on infliximab 5mg/kg are stated to have maintenance of clinical response at week 30. No data are provided for initial responders in the single treatment arm.<sup>82</sup>

#### *Clinical Remission (CDAI < 150)*

##### *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 to placebo at week 4. However, no significant difference was apparent in this endpoint by week 12.<sup>70</sup> (Table 11)

**Table 11: Patients in clinical remission**

Time post treatment	Placebo n = 25	Infliximab 5mg/kg n = 27	Infliximab 10mg/kg n = 28	Infliximab 20mg/kg n = 28	All infliximab n = 83
Any time	1 (4.0%)	14 (51.9%)*	7 (25.0%)	8 (28.6%) <sup>††</sup>	29 (34.9%) <sup>†</sup>
Week 2	1 (4.0%)	10 (37.0%)	5 (17.9%)	6 (21.4%)	22 (26.5%) <sup>†</sup>
Week 4	1 (4.0%)	13 (48.1%)*	7 (25.0%)	7 (25.0%)	27 (32.5%) <sup>#</sup>
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 < 0.001 vs placebo    #p = 0.005    †p = 0.006    ††p < 0.05    ‡p = 0.003

The location of the disease or concurrent drug treatment had no effect on the response seen. The largest response was apparent with the 5mg/kg dose of infliximab (p=0.046 vs 10mg/kg or 20mg/kg combined for remission at any time)

For the non-responding patients who received an open-label infusion of infliximab 10mg/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 confirms the reduced responsiveness in this later group.<sup>70</sup>

#### *Repeated dosing*

In the Rutgeerts trial, a statistically significant difference in the proportion of patients in clinical remission between the treatment groups was only apparent at week 28 (60% vs 30.6% p = 0.045) and week 44 (52.9% vs 20% p = 0.013).<sup>47</sup>

In the ACCENT I trial, for patients who demonstrated an initial response to a single infusion of infliximab 5mg/kg (n = 335), repeated dosing with infliximab was associated with a significant increase in the proportion of patients in clinical remission compared to repeated treatment with placebo, 42% vs 21% p ≤ 0.003 at week 30.<sup>76</sup> Response to the two infliximab doses did not differ significantly (39% 5mg/kg, 45% 10mg/kg p=0.386).

#### *Duration of response*

##### *Single dose*

Following a single dose using survival analysis techniques, the median time to loss of response was calculated as 0 days with placebo, 80 days with infliximab 5mg/kg, 25 days with 10mg/kg and 83 days with 20mg/kg.<sup>77</sup>

A small cohort of 23 patients enrolled in the Targan 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 were classified as responders at week 4. They received no open-label infliximab and no further active treatment in the follow-on study conducted by Rutgeerts et al.<sup>68</sup> These patients were evaluated over 48 weeks. Loss of response was defined as CDAI > 150 for patients who were in remission at 4 weeks or a > 25% increase in CDAI score for those with levels > 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 response through this time period. It was noted that the distribution may not be unimodal.

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

#### *Repeated dosing*

Data on duration of response with repeated dosing are only currently available for the re-treatment phase of the Targan study. The duration of response was compared between the 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 vs 37 weeks for placebo,  $p = 0.057$ .<sup>47</sup>

#### *Measurements of disease activity*

##### *Single dose*

The trial report by Targan et al provides data for the change in CDAI score, change in C-reactive protein (CRP) levels and change in IBDQ score seen with treatment at week 4 of the trial. (Table 12)

**Table 12: Mean ( $\pm$  SD) values for CDAI, CRP and IBDQ at baseline and week 4**

Variable	Placebo n = 25	5mg of cA2/kg n = 27	10mg of cA2/kg n = 28	20mg of cA2/kg n = 28	All cA2 groups n = 83
Score on Crohn's disease Activity Index					
Baseline	288 $\pm$ 54	312 $\pm$ 56	318 $\pm$ 59	307 $\pm$ 50	312 $\pm$ 55
4 weeks	271 $\pm$ 82	166 $\pm$ 76 <sup>†</sup>	226 $\pm$ 115 <sup>§</sup>	211 $\pm$ 107 <sup>†</sup>	201 $\pm$ 103 <sup>†</sup>
Score on Inflammatory Bowel Disease Questionnaire					
Baseline	128 $\pm$ 29	122 $\pm$ 29	116 $\pm$ 23	118 $\pm$ 28	118 $\pm$ 27
4 weeks	133 $\pm$ 28	168 $\pm$ 36 <sup>†</sup>	146 $\pm$ 41 <sup>*</sup>	149 $\pm$ 35 <sup>**</sup>	154 $\pm$ 38 <sup>‡</sup>
C-reactive protein (mg/litre)					
Baseline	12.8 $\pm$ 13.9	22.1 $\pm$ 23.6	23.2 $\pm$ 34.2	22.4 $\pm$ 23.9	22.6 $\pm$ 27.4
4 weeks	14.8 $\pm$ 18.6	5.7 $\pm$ 9.3 <sup>††</sup>	12.1 $\pm$ 18.6	6.9 $\pm$ 11.6 <sup>†</sup>	8.3 $\pm$ 13.9 <sup>†</sup>

<sup>†</sup>  $p < 0.001$       <sup>‡</sup>  $p = 0.001$       <sup>§</sup>  $p = 0.003$       <sup>\*</sup>  $p = 0.02$       <sup>\*\*</sup>  $p = 0.03$       <sup>††</sup>  $p = 0.004$

Levels of CRP below 8mg/l are considered normal.<sup>70</sup>

A significant reduction in CDAI score, CRP levels and increase in IBDQ score from baseline was seen with infliximab treatment at all doses at week 4 compared to placebo.

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.<sup>50</sup> All sub domains of the IBDQ were improved in patients treated with infliximab compared to placebo.<sup>50</sup>

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.<sup>70</sup> Levels of C-reactive protein, in responding patients, began to rise at 12 weeks to 14.1  $\pm$  2.2mg/l across the infliximab groups, potentially indicating a relapse of disease.<sup>70</sup>

#### *Repeated dosing*

Data are only presented graphically for median values for these endpoints at each 4 week visit in the Rutgeerts study report. Generally the improvements seen with the initial treatment appeared to be maintained with repeated treatment. Patients re-treated with placebo showed a gradual loss of the initial treatment benefit, although by week 48 IBDQ and CDAI scores still remained below the original baseline values.

For the ACCENT I trial data are presented graphically for the median CDAI and IBDQ scores to week 30 for patients who demonstrated a response to treatment at week 2. As in Rutgeerts trial the improvements seen with initial treatment appeared to be maintained with repeated 8 weekly dosing. In the placebo re-treatment arm a gradual loss of the original treatment benefit was apparent although again by week 30 these scores remained below the original baseline levels.<sup>76</sup>

### *Other Endpoints*

#### *Endoscopic and histological healing*

European patients (n = 30) enrolled in the Targan trial had full ileocolonoscopy performed 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 9 of these patients had biopsy samples taken during these procedures.

Of the 30 patients, 8 were treated with placebo, 7 infliximab 5mg/kg, 7 – 10mg/kg and 8 – 20mg/kg. Mean baseline CDEIS scores were lowest in the placebo group (8.4, 15.1, 10.6, 13.3 respectively). A significant reduction in mean CDEIS from baseline was seen in all three infliximab treatment arms (p < 0.01) but not 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). Whilst 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 available on endoscopic & histological healing with repeated dosing

#### *Steroid withdrawal*

The ACCENT I trial evaluated the ability for patients to be withdrawn from their concomitant corticosteroid treatment during continued treatment with infliximab/placebo. At week 30 for patients receiving corticosteroids at baseline: 37% on infliximab 10mg/kg, 31% on 5mg/kg and 11% on placebo had had their steroid treatment withdrawn.<sup>76</sup>

No data are available for this endpoint from the other two trials.

### ***Fistulising Crohn's Disease***

Data on the effectiveness of infliximab in the treatment of patients with fistulising Crohn's disease are provided chiefly by the study by Present et al<sup>64</sup>. This trial evaluated the efficacy of a single three-dose treatment course of infliximab. The ACCENT II trial, which is still ongoing, will provide data on the efficacy of repeated treatment with infliximab in patients with fistulising Crohn's disease.<sup>54</sup>

### *Closing of fistulae*

The trial by Present et al provides 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. 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  $\geq 50\%$  reduction endpoint. However the 5mg/kg group demonstrated a higher response rate than the 10mg/kg group for complete response ( $p = 0.045$ ).<sup>81</sup>

**Table 13: Number of patients (%) with reduction in number of fistulae over 2 consecutive study visits**

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

\* $p \leq 0.001$  vs placebo

<sup>†</sup> $p \leq 0.05$  vs placebo

<sup>#</sup> $p = 0.005$  vs placebo

<sup>‡</sup> $p = 0.002$

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% vs 8%,  $p = 0.02$ ) and patients with multiple fistulae at baseline (71% vs 39%),  $p = 0.03$ ) compared to 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 inter-related such that they share the same source in the intestine.<sup>79</sup>

There was no evidence that long standing fistulae ( $> 2$  year duration) were any more resistant to closing than younger fistulae.<sup>79</sup> 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 suggests that there may be a stronger treatment effect among men. This requires confirmation.<sup>64;79</sup>

There are 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 (8 treated with placebo, 8 treated with infliximab 5mg/kg and 1 treated with infliximab 10mg/kg). New fistulae developed regardless of whether or not the patient had shown a response to infliximab. This suggests that for some patients ongoing disease activity exists preventing internal healing of the fistulae.<sup>79</sup>

### *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 a  $\geq 50\%$  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). Patient's randomised to placebo who responded did so throughout the study (median onset 6 weeks).<sup>79</sup> 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 6 visits and 5/39 over 5 visits.<sup>47</sup> The median duration of response was however approximately three months across all of the treatment groups (Table 14).<sup>64;79</sup>

**Table 14: Median time to onset and duration of closure of fistulae in days (IQR)**

	Placebo n = 8	Infliximab 5mg/kg n = 21	Infliximab 10mg/kg n = 18	Total 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  $\geq 50\%$  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.<sup>79</sup>

#### *Crohn's disease activity*

The Present trial provides data on the change in CDAI to week 18 for 79 patients enrolled in the trial. CDAI could not be calculated for 15 patients who had a stoma at baseline.

Change in PDAI from baseline to week 18 is presented for the 85 patients with perianal disease at baseline. A significant reduction in median PDAI score was apparent with infliximab treatment at both doses compared to placebo at week 2, but not at week 18.

**Table 15: Median PDAI score (IQR) by treatment group**

Time post 1 <sup>st</sup> infusion	Placebo n = 29	Infliximab 5mg/kg n = 27	Infliximab 10mg/kg n = 29	Total infliximab n = 56
0	9 (7-10.5)	8 (7-10)	10 (8-12)	9 (7-11)
2	8 (6-10)	6 (3-7)*	6 (4-8) <sup>†</sup>	6 (3.5-8) <sup>#</sup>
18	7 (4-9)	4 (1-7)	5 (3-8)	5 (2-7.5)

\*p = 0.02 vs placebo

<sup>†</sup>p = 0.04 vs placebo

<sup>#</sup>p = 0.01 vs placebo

#### ***Summary of the evidence and conclusions***

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

The study reported by Targan et al<sup>70</sup> evaluated 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 corticosteroids). At baseline 92% of patients were taking concurrent Crohn's disease medication. Treatment with a single infusion of infliximab 5 – 20mg/kg was associated with a 65% response rate ( $\geq 70$  point decrease in CDAI) compared to 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  $\geq 100$  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 to placebo at week 4 (32.5% vs 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% patients). Sustained benefit is therefore unlikely with a single dose.

The greatest benefit in all variables was seen with the 5mg/kg dose, 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 confounds 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% response vs 57.9% for those initially treated with placebo. The factors that determine lack of response are not known.

The benefit of repeated treatment with infliximab in patients with chronic active Crohn's disease was addressed by the trial undertaken by Rutgeerts et al and the ACCENT I study. The study reported by Rutgeerts et al<sup>68</sup> evaluated the benefit of repeated treatment with infliximab (4 doses at 8 week intervals) in 73 patients who had all previously demonstrated a response to blinded or open-label treatment in the Targan study.<sup>70</sup> 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 vs placebo re-treatment. The trial investigators claim 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.<sup>68</sup>

Without a true placebo arm it is not possible to identify the anticipated benefit of re-treatment.

Data from the ACCENT I trial are still preliminary. This trial evaluated the benefit of a three-dose induction with infliximab 5mg/kg (not currently a licensed dosage regimen in chronic active Crohn's disease) followed by 8 weekly dosing with infliximab 5mg/kg or 10mg/kg, compared to a single dose of infliximab 5mg/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% vs 52%; p=0.035). This is not surprising given the data from the Targan study that demonstrates that maximal benefit is seen 4 weeks after dosing and then is subsequently lost over time. The response seen 4 weeks after completion of the three-dose induction (ie week 10) is comparable to the response rate seen 4 weeks after the single dose induction in the Targan trial.

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

The study reported by Present et al<sup>64</sup> evaluated the benefit of a single treatment course of three infusions of infliximab in 94 patients with fistulising Crohn's disease (90% perianal, 10% abdominal fistulae). Treatment with infliximab 5 – 10mg/kg was associated with healing of  $\geq 50\%$  of fistulae in 62% of patients compared to 26% treated with placebo ( $p = 0.005$ ), and complete healing in 46% vs 13% ( $p \leq 0.001$ ) for at least 2 consecutive visits. Therefore 74.4% patients treated with infliximab who achieved the primary endpoint actually had complete healing of all their fistulae compared to 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. There was a suggested stronger treatment effect in men, this needs further investigation. As in the active Crohn's disease trials the greatest benefits were seen with the 5mg/kg dose of infliximab. The small size of the cohort studied precludes a meaningful effect of a dose response relationship.

The median onset of response was earlier with infliximab (14 days vs 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 suggests that whilst infliximab has an initial benefit on closing fistulae, a single set of doses is unlikely to provide durable benefit. No data are provided on continued treatment. This will be provided by the larger ACCENT II trial which is still ongoing.

The endpoint 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 can markedly affect the analysis.<sup>79</sup>

The study did not present data on internal healing of the fistula tract. MRI was performed on a sub-group 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 presents no data on closure of non-cutaneous draining fistulae or on cutaneous fistulae in locations other than perianal or peri-abdominal. It cannot therefore be extrapolated to these patients.

### ***Clinical effect size***

#### *Chronic active Crohn's disease*

From the Targan trial the number of patients who need to be treated with a single dose of infliximab 5mg to 20mg for one patient to achieve a reduction in CDAI  $\geq 70$  points at week four is 2.04 (95% CI 1.5 to 3.2) and for one patient to achieve remission at week four is 3.51 (95% CI 2.4 to 6.3)

The limited data from the Rutgeerts and ACCENT I trials do not allow the clinical effect size to be calculated for re-treatment.

### *Fistulising Crohn's disease*

From the trial by Present et al, the number of patients who need to be treated with three doses of infliximab 5mg to 10mg/kg for one patient to achieve complete healing of their fistulae for at least 21 days is 3.02 (95% CI 2.0 to 6.2).

### **Adverse Effects**

Published data on safety in Crohn's disease patients are limited. The number of patients exposed to the licensed dose of 5mg/kg in the three fully published randomised controlled trials was relatively small (n = 58). Additionally, the number of patients who have received only placebo is small (n = 56) and therefore of limited use as a comparator. Even more limited are the data on the safety of re-treatment. The duration of follow-up is also limited ranging from an average follow-up of 6.9 weeks to 32.5 weeks. Data on adverse events from the ACCENT I trial are currently 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 infliximab for all indications.<sup>83</sup>

An assessment of safety amongst 771 patients treated with infliximab in clinical studies (199 Crohn's disease, 555 rheumatoid arthritis) was undertaken by the EMEA. Four hundred and sixteen patients received at least five infusions of infliximab (103 Crohn's patients received three or more infusions). More than half of Crohn's treated patients were exposed to infliximab for 14 weeks or longer; 84% received at least 10mg/kg and 51% at least 20mg/kg.

### *Deaths*

There were no deaths in the two short-term studies<sup>64;70</sup> in 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  $\beta$ -cell lymphoma 9½ months after the initial infusion of infliximab. Shortly after the patient's last study evaluation he developed sepsis secondary to his chemotherapy and died.<sup>68</sup>

### *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% vs 95%).<sup>68</sup>

**Table 16: Adverse effects reported in more than 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 <sup>70</sup>			Rutgeerts et al <sup>68</sup>		Present et al <sup>64</sup>	
Treatment schedule	1 dose of treatment with additional open label dose in non-responders			4 repeated doses		Treatment course of 3 doses	
Treatment groups	PLA n = 25	One dose cA2 n=102	Two doses cA2 n=29	PLA n = 36	10mg/kg cA2 n = 37	PLA n = 31	Total cA2 n = 63
Average follow-up (weeks)	6.9	10.4	12.4	30.7	32.5	19.8	21.2
Any adverse event	60.0%	74.4%	79.3%	97.2%	94.6%	64.5%	74.6%
<b>Adverse event:</b>							
Nausea	2 (8.0%)	11(10.8%)	5 (17.2%)	3 (8.3%)	7 (18.9%)	0 (0%)	5 (7.9%)
Abdo. pain	2 (8.0%)	NR	NR	5 (13.9%)	5 (13.5%)	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%)
URTI	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%)	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%)	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	NR	NR	1 (3.2%)	7 (11.1%)
Antibodies to DNA	0 (0%)	NR	NR	NR	3 (8.1%)	NR	8 (12.7%)
AE during or within 2 hours of infusion	0 (0%)	0	2 (6.9%)	5 (13.9%)	9 (24.3%)	2 (6.5%)	4 (6.3%)
AE on day of infusion start time unknown	NR	NR	NR	NR	7 (18.9%)	1 (3.2%)	10 (15.9%)
Arthralgia	0% (0%)	NR	NR	4 (11.1%)	2 (5.4%)	NR	NR
Flu like syndrome	NR	NR	NR	2 (5.6%)	4 (10.8%)	NR	NR

In the overall EMEA safety analysis, reasonably attributable adverse events were reported in 55% of infliximab treated patients and 31% treated with placebo.<sup>85</sup>

Adverse events leading to the withdrawal of treatment are only reported for the studies by Present et al<sup>64</sup> and Rutgeerts et al.<sup>68</sup> In the study in fistulising Crohn's disease, one patient randomised to infliximab 10mg/kg and one treated with placebo withdrew due to adverse events. This patient developed pneumonia 22 days after the second infusion of infliximab. The symptoms resolved within a week of antibiotic treatment. One patient treated with placebo discontinued the trial after completion of all scheduled infusions due to 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 6 patients discontinued treatment with infliximab and none treatment with placebo due 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 5 patients developed mononucleosis (1 patient), cholecystitis (1 patient), severe headache (1 patient,) extensive hidradenitis (1 patient), lupus arthritis (1 patient), and treatment was withdrawn.<sup>79 68</sup>

The study by Targan et al<sup>70</sup> does not specifically identify the number of patients who suffered an adverse event requiring withdrawal from treatment. However, it is stated that of the 29 patients who received two infliximab infusions, 2 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 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 had responded to treatment ( $\geq 50\%$  reduction in number of fistulae). The remaining patient had shown 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.<sup>64;79</sup>

### *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. Refer to Table 17 for a breakdown by trial and treatment arm.

**Table 17: Infusion Reactions**

	Placebo	Infliximab 5mg/kg	Infliximab 10mg/kg	Infliximab 20mg/kg	Total Infliximab
Targan et al <sup>70</sup> Blinded Open Label	2/25	NR	NR	NR	11/83 7/48
Rutgeerts et al <sup>68</sup>	5/36	N/A	9/37	N/A	9/37
Present et al <sup>64</sup>	2/31	2/31	2/32	N/A	4/63

The numbers are 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 Rutgeerts study where patients received 4 repeated infusions.

The infusion reactions reported included ventricular extrasystoles, bradycardia, fatigue, dizziness, fever, pharyngitis, headache, hypotension, chest pain, injection site pain, dyspepsia, increased GI activity, nausea and vomiting.<sup>79</sup>

Additionally, 2 patients in the Targan et al study, 7 patients in the Rutgeerts study (all treated with infliximab) and 11 in the Present study (10 infliximab treated and 1 placebo treated) reported adverse experiences on the day of infusion but with an unknown start time. These adverse events included headache, chest pain, pain, fatigue, hot flushes, pruritis, nausea, rash and flu syndrome.<sup>79</sup>

Data are not clearly presented on the number of infusions that had to be interrupted due to these reactions. American prescribing information suggests that less than 1% of patients discontinued treatment due to infusion reactions and all patients recovered with treatment and/or discontinuation of infusion.<sup>80</sup> In the overall EMEA safety analysis, infusion reactions were documented in 16% infliximab treated Crohn's patients and 6% placebo treated patients.<sup>79;85</sup> Of the 1207 infliximab infusion 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.<sup>80, 85</sup> 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.<sup>85</sup>

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.<sup>79;85</sup>

In a clinical trial of 40 patients with Crohn's disease re-treated following a 2-4 year period without infliximab treatment, 10 patients (25%) developed a serum sickness-like delayed hypersensitivity 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.<sup>85</sup> 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.<sup>80</sup>

The risk of delayed hypersensitivity following re-administration after a drug free period of 15 weeks to 2 years is currently not known. The SPC therefore does not recommend re-administration after a drug free interval of 15 weeks. Clinical experience suggests the risks may be small.<sup>86</sup>

### *Infections*

TNF $\alpha$  plays an important role in the defence against various infections. Infliximab inhibits TNF $\alpha$ . 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.

Table 18 presents data for the number of patients who developed one or more infections in the three completed trials. In total 5 patients developed serious infections, 4 on infliximab; cholecystitis.(1 patient)<sup>68</sup> furunculosis of the right arm and right leg (1 patient), pneumonia (1 patient).<sup>64</sup>, salmonella colitis (1 patient)<sup>70</sup> and 1 on placebo; paravesical abscess.

**Table 18: Number of patients who developed infections requiring antibiotic treatment**

Trial	Placebo	Infliximab			Total Infliximab
		5mg/kg	10mg/kg	20mg/kg	
Targan et al: Double-blind treatment	2/25	3/27	2/28	6/28	11/83
Open-label treatment			7/48		7/48
Rutgeerts et al	8/36		13/37		13/37
Present et al	3/31	3/31	4/32		7/63

The overall EMEA safety analysis indicates that infections were reported by 26% of infliximab treated patients vs 16% of placebo treated: 4% in each group were considered serious.<sup>47</sup>

Following world-wide launch to February 2001 there have been 28 spontaneous reports of the onset or re-activation of tuberculosis (TB) suspected to be a reaction to infliximab therapy.<sup>87</sup> Nine cases in North America and 19 in Europe, of which 1 had a fatal outcome. The majority of patients had a prior history of treatment with immunosuppressants including corticosteroids. However, due to limited clinical experience with infliximab the onset (or re-activation) of TB or other opportunistic infections cannot be ruled out.<sup>83;87</sup> The CSM and 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.<sup>83;87</sup>

### *Serious Adverse Events*

Across the three fully completed trials, 21 patients suffered serious adverse events; 14 on infliximab and 7 with placebo. Examples include lupus arthritis & chest pain. Only 7 of these were considered as possibly or probably related to study drug.

In the overall EMEA safety analysis, adverse events considered serious and reasonably related to infliximab occurred in 3.6% of infliximab treated patients and 2.6% placebo treated (examples included pneumonia, fever, dyspnoea and rashes). These were all medically manageable and without long term sequelae.<sup>47;85</sup>

A case of reversible cholestatic jaundice, believed to be related to infliximab treatment, has been reported in the literature.<sup>88</sup>

### *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 5 cases of lymphoproliferative disorders have been reported in patients with rheumatoid arthritis 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 with infliximab are too limited to accurately assess whether infliximab treatment increases the potential for lymphoproliferative disorders and whether it confers any increased risk compared to other immunosuppressive drugs.<sup>47;85;89</sup>

### *Human Antichimeric Antibody Responses (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 due to the presence of infliximab in post infusion samples. Very limited data are available. Six of 43 evaluable patients (14.0%) in the Targan trial had a positive HACA response, 2 of 11 (18.2%) in the Rutgeerts trial and 3 of 50 (6%) in the fistulising study. In the overall safety analysis, HACA developed in 13% of patients with Crohn's disease treated with infliximab.<sup>30;47;85;89</sup>

Patients who are HACA positive appear more likely to experience an infusion reaction (36% vs 11%).<sup>30;80</sup>

Concomitant immune modifier therapy with corticosteroids, azathioprine or 6-mercaptopurine during infliximab therapy appeared to protect against HACA formation (10% frequency) compared with patients not taking immune modifier therapy (23% frequency).<sup>80;90</sup>

### *Antibodies against double-stranded DNA (anti-ds DNA)*

Again data are limited. In the overall safety analysis 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 antibodies against double-stranded DNA (3% vs 21%).<sup>47;80;85;90</sup>

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. Antibodies to double-stranded DNA disappeared when infliximab therapy was discontinued.<sup>80;90</sup>

## 4. ECONOMIC ANALYSIS

### 4.1 Analysis of company submission and comments

The economic evaluation undertaken on behalf of Schering-Plough for their submission to NICE used two different models for the two disease states under review: severe active and fistulising. Both models focus on quality of life, the main effect and combine these with cost data to give incremental cost per QALY estimates for use of infliximab.

Both models map disease specific scores onto utility scores, relying mainly on published<sup>a</sup>, 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 are based on small numbers, relatively wide confidence intervals, and sensitive to the methods used to elicit values.

#### 4.1.1 Chronic active Crohn's disease – company model

To analyse the cost effectiveness of infliximab in chronic active Crohn's disease a Markov model with 7 states was developed in the software package 'Decision Maker'. This was shared with us. This modelled response rates from the clinical trials combined with transitional probabilities for 7 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<sup>23</sup>. 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 Gregor et al, 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 7 health states in the Olmstead county data.

To make the results relevant to the UK, British life tables were applied to the US 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, based on the Olmstead data. Thus the model aggregated health gains over roughly 40 years.

The relatively small differences in QALY scores between most of the 7 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 translate into greater values (0.42 QALYs average per patient) due to summing them over patients' lifetimes.

---

<sup>a</sup> The modelling of chronic active CD used Gregor et al 1997 'An evaluation of utility measurement in Crohn's Disease', which used a variety of instruments on 180 consecutive patients with CD in a Canadian tertiary treatment centre. The modelling of fistulising CD relied on a sample of 79 patients in five UK centres and used a combination of CDAI and PDAI to estimate utility linked to Gregor et al (1997) cited above.

Gregor et al (1997) , the source of the utility values in the company model, collected both CDAI, IBDQ and utility data from a sample of 180 Crohn's Disease patients in a single Canadian tertiary centre in 1995-6, classified into four health states. The company model linked these to the 7 health states outlined in Table 19 below, 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 for 'mild'<sup>a,b</sup>. 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'.

**Table 19: Health States and utility values used in 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

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 was from an unpublished study of a small group of 38 UK patients for whom an average cost over 12 months were estimated. This average cost was distributed across the 7 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 through out the model for all the treatment options was the lower dose of 5mg/kg for a 70kg individual.

The resulting cost per QALY estimates are shown below.

<sup>a</sup> The rationale for this assumption was: 'It was necessary to arbitrarily assign values for two states surgery and mild disease. These estimates were based on the assumptions 1) that surgery was a worse state than drug refractory disease since the latter patients would often require surgery as treatment for worsening symptoms and 2) mild disease was only a slightly worse health state than remission.' (p.44 company submission). A more realistic assumption might be to assign a value intermediate to drug refractory and remission that is 0.81.

<sup>b</sup> The Gregor study, which had as its primary aim 'to derive estimates of utility form a representative sample of patients with Crohn's Disease for use in cost utility models' provides further data which might be used in sensitivity analysis 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 different disease states using different methods (3 utility based, 3 disease specific)
- the utility gains between 'chronically active therapy resistant' (= drug refractory severe disease' in the company model) and 'remission' varied by method, with a gain of 0.14 for Standard Gamble, 0.12 from 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 VAS showing the strongest degree of correlation with these latter scales, The authors of the study noting the differences between the utility scales suggested that Standard Gamble should be used due to higher % of patients responding to it compared to Time Trade Off and better congruence with economic theory
- the authors did not favour VAS of its 'lack of incorporation of patient preference into this method. Patient preference is probably the most important source of variability in preference elicitation' (p.272).
- the sensitivity of the results is explored below using the values for utility gain from each of the elicitation methods by using a utility gain of 0.2 for 0.14 in the sensitivity analysis

**Table 20: Summary incremental cost per QALY estimates in chronic active Crohn's disease**

	Treatment Schedule		
	Episodic	Single	Maintenance
Cost (£) per QALY (benefits discounted @t 1.5% and costs at 6%) (10% flare rate assumed)	10.4k	6.7k	84.4k
Sensitivity analysis	20% flare	N/A	N/A
	50% flare	54.8k	N/A

A mistake in the model submitted by the company was noted by the review team, and when pointed out was accepted by the consultant who had carried out the work who submitted a revised results. The model used one month rather than two-month costs for the costs of normal care. Adjusting for this raised the incremental cost per QALY from £8k to £10.4k 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 a 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 up rate to 20% roughly doubled the incremental cost/QALY of £20k and a flare up rate of 50% lead to an incremental cost/QALY of £55k.

Two fundamental aspect of the model are to be stressed. 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 naturally in remission (usually those in the early stages of the disease). This is the implication of using the Olmstead data on transition probabilities. The limited trial data available for these patients suggests that they relapse over time (remission lost in 26% patients by week 12) but details were not provided in the trial reports of the health/disease states into which these patients relapse. Clinical opinion suggested that these patients might realistically expected to revert to their original drug refractory state, rather than progress through the various stages of the disease as suggested in the Olmstead 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 data in CD 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 around 40 years. Given the reliance on short-term trial data for the effectiveness of infliximab, this is a heroic extrapolation of its benefits.

#### 4.1.2 Fistulising Crohn's disease

A spreadsheet cost-utility analysis was developed by a clinician, Dr Feagan, acting for the company and shared with the review team. This estimated the cost per QALY based on:

- (a) translating efficacy data from the pivotal trial for fistulising Crohn's ( using data from Present et al) 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 per QALY value –see below.)

- (b) 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 CD discussed above (Gregor et al).
- (c) combining this with the drug cost of infliximab, offset by possible savings in surgery, to derive an incremental cost per QALY for infliximab compared to standard treatment,
- (d) 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.

**Table 21: Incremental cost per QALY for fistulising Crohn's disease**

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

As the model was limited to 12-months, discounting was not relevant.

The resulting cost per QALY values were high, from £102k -£123k for initial treatment only and from £82k-£96k with the most favourable re-treatment assumptions on closure rates.

The results were relatively insensitive to the cost offsets (due to surgery averted), which were based on various UK sources, even when 100% offsets were assumed.

The company submission stated that these estimates were conservative, due mainly to limiting the analysis to 12 months as some patients were still receiving benefit at that stage. Extension of the results to more than 12 months, however, is unlikely to alter the results by much as 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 infliximab could be more suitable for a small group of ‘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 in Arseneau et al (2001) which reported on a formal modelling exercise comparing infliximab with alternative treatments and showed a cost per QALY ranging from \$350k to \$377k. The authors noted that reduction in the cost of infliximab to \$304 per infusion would reduce the cost per QALY of \$54k.

**4.2. Evaluating and re-estimating the cost effectiveness in chronic active CD**

This section re-estimates the cost effectiveness of infliximab in chronic active CD. As noted above, the relatively low cost per QALY estimates resulted from the model submitted by the company which made two major assumptions: a) that patients who achieved remission or mild health states due to infliximab then moved through 7 health states to death as though they had been naturally in remission and b) aggregated the patient utility gains over their lifetimes, or around 40 years. The effects of relaxing these assumptions are explored below.

#### 4.2.1 Comparator and health states

The comparator is with 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 as a last resort for 'drug refractory' patients for whom the only alternative may be surgery. No data are available on the extent to which infliximab delays surgical interventions. The company model, by using transition state probabilities which include surgery, assumes that infliximab postpones or reduces (depending on the time frame) the need for surgery. The implications of making various assumptions on the extent to which surgery is averted or delayed is explored below in sensitivity analysis.

#### 4.2.2 Scenarios

Two scenarios are explored; the baseline Scenario 1 is based on the company model estimates for effectiveness. Scenario 2 is based on more optimistic effectiveness estimates with 5 mg doses. In each scenario, cost per QALY of infliximab compared to placebo is estimated for both single dose and for episodic treatment, the latter based on 3 re-treatments for those who initially respond but subsequently relapse (flare). Optimistic estimates of response for those who are re-treated are employed (100% respond).

The two scenarios share a range of basic assumptions. One has to do with 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 takes an improvement of 70 points on CDAI as a shift to 'mild'. No explicit rationale has been made for this assumption which increases the % of patients achieving a worthwhile response and so improves the cost per QALY. No literature has been located justifying allocation of a clinical response of 70 points on the CDAI as 'mild'. This optimistic assumption roughly doubles the response rate. As noted above the utility values for remission and mild 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 80 days from a single dose (p.36 above). Mean rather than median value should be used for estimating QALYs but this is not given in the trial reports or in the company submission. No data are given on duration of 'clinical response'. The company model does not use data on duration, but rather applies a 'flare' rate to those who respond. In the absence of mean data we have had no choice but to use median duration. The effect of assuming a longer duration is explored in sensitivity analysis.

Fewer data are 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 statistically significant difference ( $p=0.057$ ) between infliximab and placebo in time to loss of response but this was based on relatively few patients<sup>a</sup> (p.35 and 36 above). No data are available on duration of 'clinical response' (= 'mild') but for modelling purposes this has been assumed at 80 days, equal to that for those patients achieving remission.

---

<sup>a</sup> Omission of repeated dosages would confine the analysis to single rather than episodic treatment. It can be assumed that repeat dosage leads to remission, either for 100% or some smaller % of patients. The company model assumes 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 5mg/kg and that such treatment would restore remission'.

The scenarios differ in relation to the % of patients who achieve these states, but both rely on trial data but for different dosages.

### 4.2.3 Scenario 1: Effectiveness

Scenario 1 uses the same effectiveness estimates as in the company model, checked against Table 11 for the % moving into remission and mild health states.

The effectiveness estimates in the company model were explained as follows:

‘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<sup>a</sup>, 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's et al 1999 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.’ (page 42 company submission).

This approach relies on data from the two trials (excluding Accent 1 which has only been published in abstract) solely on the proportion of patients achieving ‘remission’ and ‘clinical response’, with the flare rate taking account of remission. This seems reasonable but has inherent problems once the time frame is restricted as outlined above 1 in that some patients may not have ‘flared’ by the end of the period.

The company model takes an average of the % 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). As shown in Table 22, these figures can be derived from Table 11, but a higher average 38.23 % applies to those treated with 5mg/kg. Since the company model costs patients at 5mg/kg it would seem more reasonable to use the response rates for this dose. The effects of this are explored in Scenario 2 below.

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

	Placebo		Inflix 5 mg/kg		Inflix 10 mg/kg		Inflix 20 mg/kg		All Inflix	
	No	%	no	%	no	%	No	%	No	%
Any time	1	4	14	51.9	7	25	8	28.6	29	34.9
Week2	1	4	10	37	5	17.9	6	21.4	22	26.5
Week 4	1	4	13	48.1	7	25	7	25	27	32.5
week 8	4	16	10	37	8	28.6	7	25	25	30.1
week 12	2	8	8	29.6	5	17.9	7	25	20	24.1
									72	
Av. wk. 4,8 & 12		9.33		38.23						28.9

The company model had 28.9% patients achieving remission<sup>b</sup> which subtracting the 9.5% of patients achieving remission on placebo gives a net 19.4%. It also had 23.7% of patients in

<sup>a</sup> The ‘clinical response’ appears to be synonymous with transition to the ‘mild’ disease state in the company model.

<sup>b</sup> This is a) simple average of the three periods and b) covers the 3 dosage regimes. Re a) a weighted average of the periods might be more appropriate (29.3%) or the % achieving remission in any time period (34.9%). Epidemiological input is required as to which if any is most appropriate to use. However the differences are

the treatment arm achieving the 'mild' health state (derived from Table 9) and 5.4% in the placebo arm giving a net 18.3% of patients responding. We note that inclusion of the % moving to mild roughly doubles the response rate to 37.7% and thus proportionately improves the cost effectiveness of infliximab.

#### 4.2.4 Scenario 2 - effectiveness

As noted above, higher response rates were reported for the 5mg dose than for all doses in relation to remission, 38.23% compared to 28.9% and 24.7% compared with 23.7% for those achieving mild health state. Inclusion of this higher response for both remission and mild states increases the % patients achieving a response (to 'remission' or to 'mild' health states) from a net 38% in scenario 1 to 48% in scenario 2. This is the single difference between the two scenarios.

#### 4.2.5 Scenario 1 Cost effectiveness

The above company estimates are combined in Table A6-1 in Appendix 6 to estimate the cost per 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 due to infliximab which for a median duration of 80 days gives a total of 0.60 QALYs for the 100 patients. Inclusion of patients achieving 'mild' disease state for a net 18.3% of patients (23.7%-5.4%) with utility gain of 0.12 and assuming equal duration of 80 days as for remission, gives a QALY gain of 0.48 for the 100 patients. The total QALY gain from those achieving remission or mild health states is thus 1.08 for 100 patients.

Taking 100 patients and a cost per patient of £1,457.35 for average patient weighing 60 kg (based on the company model – see p.46 of company submission), then the total cost is £145.7k ( £1,457.35\*100). Dividing this by the total QALY gain of 1.08 gives a cost per QALY of £135k for patients moving to either 'remission' or 'mild' health states. A much higher cost per QALY of £245k would apply if the analysis was restricted to remission but the inclusion of 'mild' dramatically improves the cost per QALY to £135k.

Inclusion of QALY data for those who respond to the first dose but who subsequently relapse can improve the cost per QALY, depending on the assumptions made on the % of these who respond to subsequent doses. If we assumed that each of these have the same probability as for the first treatment, for the same clinical gain, and same average duration of gain, then inclusion of subsequent treatments would make no difference to the cost per 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 takes the other extreme assumption– that 100% of those who respond to initial treatment respond to subsequent treatment. While the true figure is unknown, the response rate of 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 is shown in Appendix 6, Table A6-1 to generate a cost per QALY for each of these repeated treatments of £51k per QALY. It should be noted that this effect can only be achieved on patients who have had initial treatment which cost £135k per QALY.

---

small. Re b) it may be more appropriate to use the data for the dose rate with the best response (5mg/kg) which is also used in the costing in the company model. This has an any time response of 51.9% and an average of the 4,8 and 12 responses of 38.2%.

This much higher estimate is due to the relatively high proportion who did not respond, but who incurred costs. £135k per QALY is the baseline estimate for single dose infliximab.

The figure of £51k 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 per QALY within this scenario. It could only be improved by assuming a longer duration of benefit, a higher utility score or cost offsets from surgery averted. Each of these is explored in sensitivity analysis.

Assuming 3 subsequent treatments after an initial treatment, each subsequent treatment with 100% response, with duration 80 days for patients achieving both remission and mild states (the most optimistic scenario) then the cost per QALY would be £72k. This is the baseline estimate for episodic treatment, against which other scenarios and assumptions should be compared.

#### **4.2.6 Scenario 2: cost effectiveness**

Use of the higher response rates in scenario 2 give an improved cost per QALY of £105k for single dose and £65k for episodic treatment (initial treatment plus 3 re-treatments). The cost per QALY for responders is £51k, which as discussed above indicates a floor on the cost per QALY within this scenario.

### **4.3 Sensitivity analysis**

In each scenario, the sensitivity of key assumptions on the results are tested, specifically by altering the utility gain<sup>a</sup>, the duration of response and cost offsets of surgery averted. The degree to which the results are sensitive to the response rate has been indicated above by the cost per QALY for responders, which was £51k in both scenario 1 and 2 (due to each scenario assuming a 100% response rate).

#### **4.3.1 Utility**

The utility gains due to infliximab, as in the company model, for 'remission' compared to 'drug refractory state' were 0.14 and 0.12 for those patients moving to 'mild. In sensitivity analysis we explored the effect of increasing the utility gain to 0.20 for all patients responding to infliximab (remission or mild), 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 Visual Analogue Scale, lacks support within health economics, was dismissed by Gregor et al, and was not used in the company model.

#### **4.3.2 Duration of response**

Duration of response in the trials for remission was put at a median 80 days from a single dose (p.36 above). Mean rather than median value should be used for estimating QALYs but this is not given in the trial reports or in the company submission. No data are given on duration of 'clinical response'. The company model does not use data on duration, but rather applies a 'flare' rate to those who respond. In the absence of mean data we have had no choice but to use median duration. Since use of the median may understate the duration of response

---

<sup>a</sup>

and hence the QALY gain, we have explored longer duration of 120 days in sensitivity analysis.

### 4.3.3 Surgery averted

The company model, as noted above, takes into account the possibility that infliximab may provide an alternative to surgery. It is not clear whether surgery is delayed or avoided. If delayed, then the cost is still incurred. The cost per QALY would be little be changed by the discounting of the cost of the surgery, and by the addition of some short lived QALY gain.

Only if surgery was permanently averted would cost offsets occur. Some estimates are required as to the proportion of patients treated with infliximab who would not proceed to surgery due to the treatment. The cost of surgery in the company submission is put at between £2.2k and £2.7k, of which we have used the latter higher figure. We have taken the optimistic assumption that 50% of those responding to infliximab in the baseline scenario had surgery averted permanently.

### 4.3.4 Results

The degree to which the results in both Scenarios are sensitive to the duration of benefit, the utility gains from response and to possible cost offsets are summarised in Table 23 below which shows that use of more optimistic assumptions make relatively little difference to the estimated cost per QALY. In Scenario 1 the cost per QALY for episodic dosage falls from £72k to between £46k and £60k with strong assumptions on either duration of benefit or a higher utility gain per patient. The inclusion of cost offsets for surgery has less effect, as long as only one surgical intervention is averted.

In scenario 2, the cost per QALY falls from £65k to between £42k and £53k on the same set of optimistic assumptions and is less sensitive to cost offsets due to surgery averted<sup>a</sup>.

**Table 23: Summary of estimates of incremental cost per QALY of infliximab compared to placebo by scenario and with different assumptions**

	£/QALY	
	Single dose	Episodic
<b>Scenario 1</b> (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
<b>Scenario 2</b> (5mg)	104,950	64,984
duration 120 for 80		43,323
utility 0.20 for 0.13		42,240
50% surgery averted		53,139

<sup>a</sup> It has been suggested to us that surgery may in some cases avert PNT at a recurring cost of around £20k per patient per annum. However, lacking data on the proportion of patients to whom this might apply, it has not been included in the model.

#### 4.4 Differences with the company model

The cost per QALY estimates above are very much higher than those in the company model, which were around £8k for initial dose and £10k for episodic treatment. Our estimates in scenario 1, which uses the same initial response rates for infliximab are much higher at £135k and £72k.

The main differences with the company model were as follows:

- The company model considers patients over their lifetimes. Our approach has limited the time period to one in which 3 re-treatments could occur, which could be one or more years.
- The company model has 7 health states (including surgery, surgery remission, drug responsive and drug dependent severe disease) each with different utilities. Patients who achieve 'remission' or 'mild' health states due to infliximab are assumed to spend time in each these disease states accumulating QALYs. By contrast our estimates assume that patients revert back to their original drug refractory states.

##### 4.4.1 Company model: one year results

In order to explore the relative impact of these differences, we ran the company model for one and five years rather than for the rest of each patient's lifetimes. The results, summarised in Table 24 show that at one year the cost per QALY was relatively high at between £35k (single dose) and £39k (re-treatment for those relapsing from either remission or mild states), compared to £8k and £10k over the patients' lifetimes. The differences between these estimates and our higher estimates are, we surmise, due to the range of health states in the company model, which include surgery.

##### 4.4.2 Company mode: five year results

Running the company model over 5 years reduces these values to £16k (single dose) and £21k, compared to £8k and £10k 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 per QALY with episodic compared to single dose in the company model differs from our results which had more favourable results for episodic treatment. It is not clear why this should be so, given that re-treatments are focussed on responders who are assumed to continue to respond. It may be due to the time lags in response but it has not been possible to explore this further.

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

	six cycles or 12 months		
	Placebo	single dose	Flare from remission or mild
Cost (£/patient)	1,186	2,520	2,715
QALYs (per patient)	0.8312	0.8689	0.87
Incremental £/QALY		35,371	38,902

	30 cycles or five years		
Cost (£/patient)	2,523	3,858	4,781
QALYs (per patient)	3.9293	4.0118	4.0368
Incremental £/QALY		16,179	21,006

## 4.5 Conclusions

### 4.5.1 Chronic active CD

The company estimates for cost per QALY are based on a range of highly optimistic assumptions for which we can find no evidence. Many of the key assumptions are embedded in a complex model rather than stated explicitly. The key assumptions in the company model appear to be due to patients accumulating utility gains over the rest of their lives and in a variety of health states due to infliximab. Curtailing the time period to three re-treatments with a variety of health states broadly confirms our alternative estimates by generating considerably higher cost per QALY estimates. Running the company model over five years indicates that the bulk of the gains occur 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 to 'mild'), their utility gains and optimistic estimates of the other key parameters (% responding to both treatment and to re-treatment) gives a cost per QALY for episodic treatment of £72k per QALY. Use of the response rates for the 5 mg/kg dosage gives a cost per QALY of £64k.

The results were relatively insensitive to major changes in key assumptions in utility gains (increased by around 50%), to duration of benefit (increased around 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 believe 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, on which the company model is very optimistic.

### 4.5.2 Fistulising CD

While the cost effectiveness estimates presented by the company are relatively simple, they seem both reasonable and transparent. The resulting cost per QALY values were high, from £102k -£123k for initial treatment only and from £82k-£96k with the most favourable re-treatment assumptions on closure rates.

The results were relatively insensitive to the cost offsets (due to surgery averted), even when 100% offsets were assumed.

## 4.6 Cost impact

The company submission was based on 30,000 patients, of whom 7%-20% had severe disease of whom a further 20% were not treatable (contraindications or personal preference). Of these 4,800 patient 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 came to £10.4m.

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

## 5. FACTORS RELEVANT TO NHS

Infliximab requires reconstitution prior to administration. The best environment for this needs to be considered, i.e. ward vs 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.

### 5.1 Other guidance

Three groups to date have issued guidance.

An international working group produced recommendations for the use of infliximab in 1999.<sup>91</sup> Their key recommendations were that infliximab should not be considered a first line drug. They suggested that infliximab may be used in:

- Patients who relapsed and fail to respond to steroids or azathioprine (in doses up to 1.5mg/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 advise that when infliximab is used:

- Careful monitoring is required and specific tumour surveillance 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 two-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.<sup>91</sup>

In 2001 the American College of Gastroenterology updated their guidelines on the management of Crohn's disease in adults. These now include infliximab. It is suggested that infliximab may be used as an alternative to corticosteroid therapy in patients with moderate to severe Crohn's disease, in whom corticosteroids are contraindicated or ineffective.<sup>92</sup> This represents much more widespread use than is currently suggested by the licensed indications.

European guidelines for 2001-3 on the use of anti-tumour necrosis factor agents in inflammatory bowel disease have recently been published.<sup>93</sup> These were developed from a systematic search of the published literature and interpreted by 20 experts from Europe. The recommendations from this group are more broad ranging. They advise that:

*Active Crohn's disease*

- Infliximab should be restricted to the treatment of refractory active Crohn's disease. (Refractory Crohn's disease is defined if a full and adequately dosed course of corticosteroids in addition to immunomodulators [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/ immunosuppressive 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's 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 (eg 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 as taken in clinical trials
- Rule out infectious complications before treatment, chest X-ray, drain any abscesses
- Adrenergic drugs and glucocorticoids should be available during the infusion in the 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 to be given within three months of anti-TNF therapy.

## 6. DISCUSSION

### 6.1 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 2/3<sup>rds</sup> of patients and induced remission in a 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 limited 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 do not respond to a further infusion. The factors that determine lack of response are not known. 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.<sup>94</sup>

In patients with perianal fistulae, a clinical response was seen in 62% of patients treated with infliximab compared to 26% treated with placebo, with complete healing in approximately 50% infliximab and 13% placebo treated of patients. Benefits are seen rapidly (within 2 weeks) and last 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, 10% of patients developed an abscess at the fistula site. It has been suggested 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 anticipated 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 for a reaction. To-date all patients have recovered from these reactions. Other potential adverse events which 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.<sup>16</sup>

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 not clear from the current evidence. A dose of 5mg/kg appears at least as effective as higher doses but it is not clear whether lower

doses would be equally effective. A 1mg/kg dose 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 5mg/kg dose and have evaluated one off, episodic and maintenance treatment. A single treatment is 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 gives a cost per QALY of £10.4k. This is 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 £82k to 123k depending on the number of treatment doses given, the success rate and cost offset. No details were provided as to the types of perianal fistulae included in the pivotal study. Expert clinical opinion suggests infliximab would only be suitable for a small group of '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.

## **6.2 Assumptions, limitations and uncertainties**

This review is limited by the small amount of data available on the use of infliximab in patients with severe active or fistulising Crohn's disease unresponsive to conventional treatment. Controlled trial data from completed studies relate to just 275 patients of whom only 58 received infliximab at the licensed dose of 5mg/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 not known. Patients enrolled in the fistulising study had predominantly perianal fistulae. Results can therefore only be extrapolated to this group of patients.

Patients enrolled in the chronic active Crohn's trials had relatively moderate disease (mean CDAI  $307 \pm 55$ ). The benefit of treatment in patients with more severe disease CDAI  $> 400$  is not known.

The effectiveness and safety of long term treatment with infliximab is not known. 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 active Crohn's disease, 300 fistulising Crohn's disease). These will provide valuable data in these areas.

### **6.2.1 Important issues not addressed by this Health Technology Assessment**

1. We have not considered the effectiveness and cost-effectiveness of infliximab in children and adolescents  $< 18$  years of age, as this is not currently a licensed indication in the UK.

2. There are other TNF $\alpha$  inhibitors that can be anticipated to come onto the market in the near future for the treatment of Crohn's disease. These have not been considered in this report.
3. We have not considered the effectiveness and cost-effectiveness of infliximab as a first line treatment in patients with Crohn's disease.

### 6.3 Need for further research

There are a large number of areas where further research is required. Areas that need to be addressed are:

- 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 peri-abdominal.<sup>80</sup>
- The therapeutic advantage of infliximab over the longer term
- The identification of factors related to poor response. Preliminary data suggest that sub-sets of patients with Crohn's disease may be identified using micro-satellite haplotypes and perinuclear anti-neutrophil cytoplasmic antibody (pANCA) to predict which sub-sets will respond to anti-cytokine therapy.<sup>30</sup>
- 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 immunosuppressants, e.g. tacrolimus and thalidomide.
- Long-term toxicity of regular or intermittent use of infliximab including an evaluation of potential for 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 dosage 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 eg azathioprine
- An evaluation of the natural history of Crohn's disease in the UK post infliximab.

#### 6.3.1 Research in progress

We know of three treatment trials in Crohn's disease that are ongoing, or are completed but not yet reported.

- ACCENT I is a study in 573 patients with moderate to severe active Crohn's disease without fistulae, where treatment with a single infusion of infliximab will be compared to maintenance therapy. This trial was due to be completed in December 2000. Schering Plough advise us that the trial is still ongoing. Preliminary results to week 30 were presented in May 2001.<sup>47;51;54;78</sup>
- ACCENT II is a study in 300 patients with fistulising Crohn's disease. This trial will also compare treatment with a single course of infliximab therapy to maintenance treatment. This trial was due to be completed in December 2000. Schering Plough advise us that the

trial is still ongoing. They have not been able to advise us as to when preliminary results are expected.<sup>47;51;54</sup>

- A study of maintenance treatment in children with active Crohn's disease is planned.<sup>47</sup>

Other biological therapies being evaluated in Crohn's disease are:<sup>30</sup>

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

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

## 7. 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. Whilst the evidence is still limited, consistent results have been shown. Rapid clinical response is seen but this is short lived (mean duration ~ 3 months).

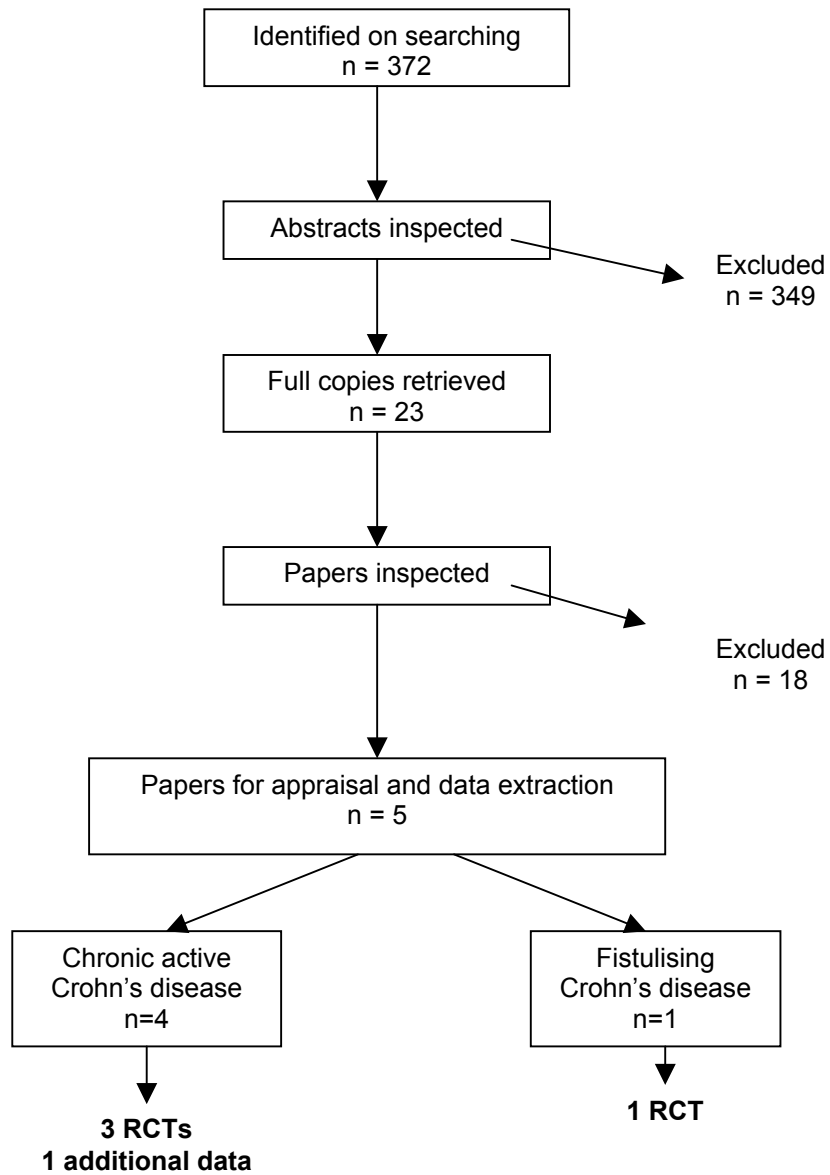
The study by Rutgeerts et al and preliminary data from the ACCENT I trial support the premise that a re-treatment regimen of infliximab can provide long term suppression of disease activity in patients with Crohn's disease. However, full data from the ACCENT I trial are required to confirm this. The optimal dose and frequency of dosing also needs to be identified.

Comparative studies are required and the tolerability and long-term efficacy of the drug need to be defined to identify the full potential of this drug 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.<sup>49</sup> 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 use is likely to be limited to a small number of patients with severe disease unresponsive to medical or surgical management. (Currently in England and Wales only 140 patients are receiving treatment with infliximab) It will also be important to consider the best environment for treatment, larger centres are likely to be best placed to provide the multidisciplinary approach required. Such restrictive use of infliximab is likely to be most cost-effective.

## **8. APPENDICES**

**Appendix 1 : Flow chart of identification and inclusion of RCTs from initial searches.**



## Appendix 2: Quality Assessment Scale

### Jadad score for the evaluation of 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:**

Give a score of one point for each 'yes' and no points for each 'no'.

*Give an additional point if :*

- For question one, the method to generate the sequence of randomisation was described and it was appropriate (table of random numbers, computer generated etc).

And/or:

- If for question two the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy etc)

*Deduct one point if:*

- For question one, the method to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number)

And/or

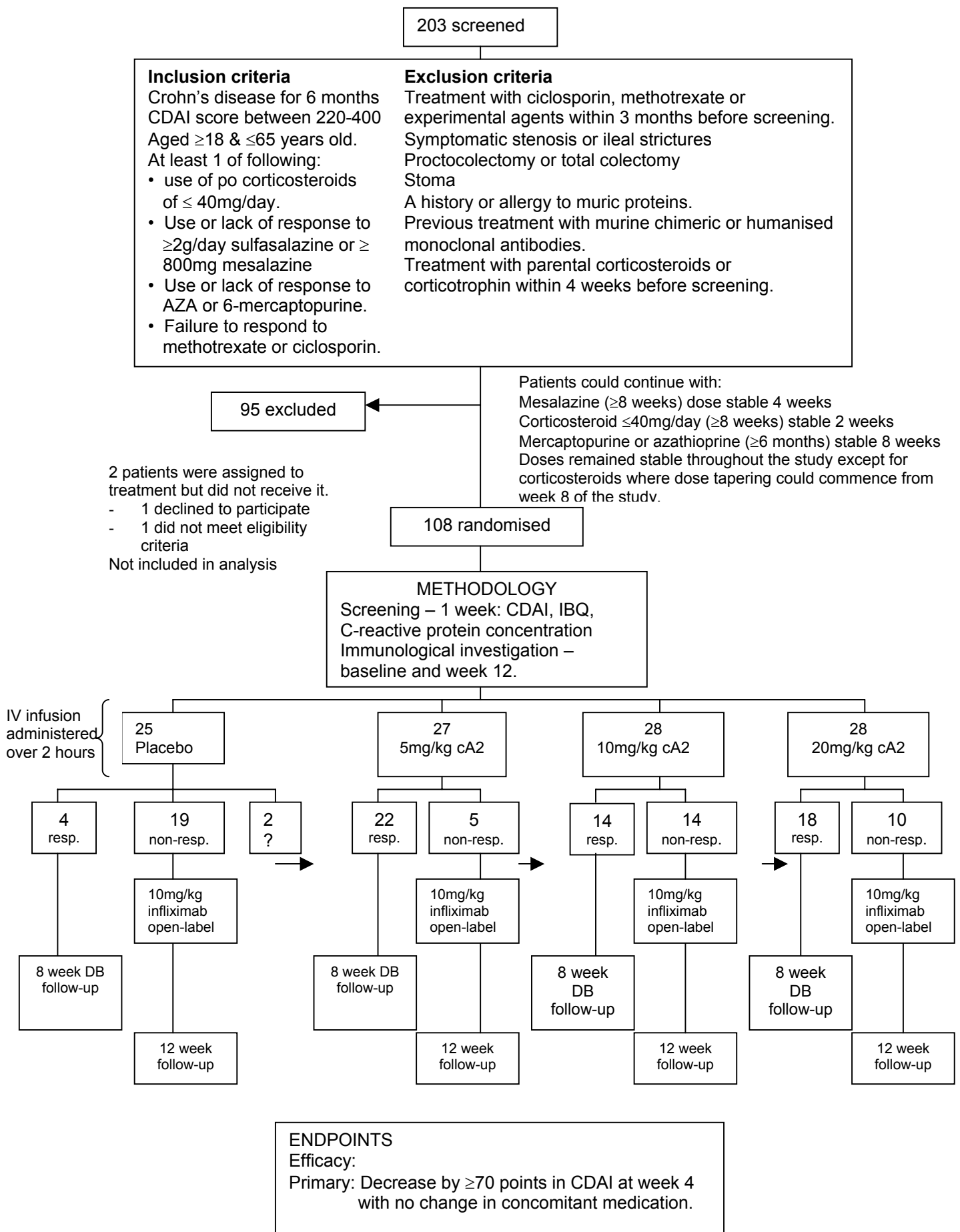
- For question two, the study was described as double blind but the method of blinding was inappropriate (e.g. comparison of tablet vs. injection with no double dummy)

**Appendix 3: Excluded studies with reason for exclusion**

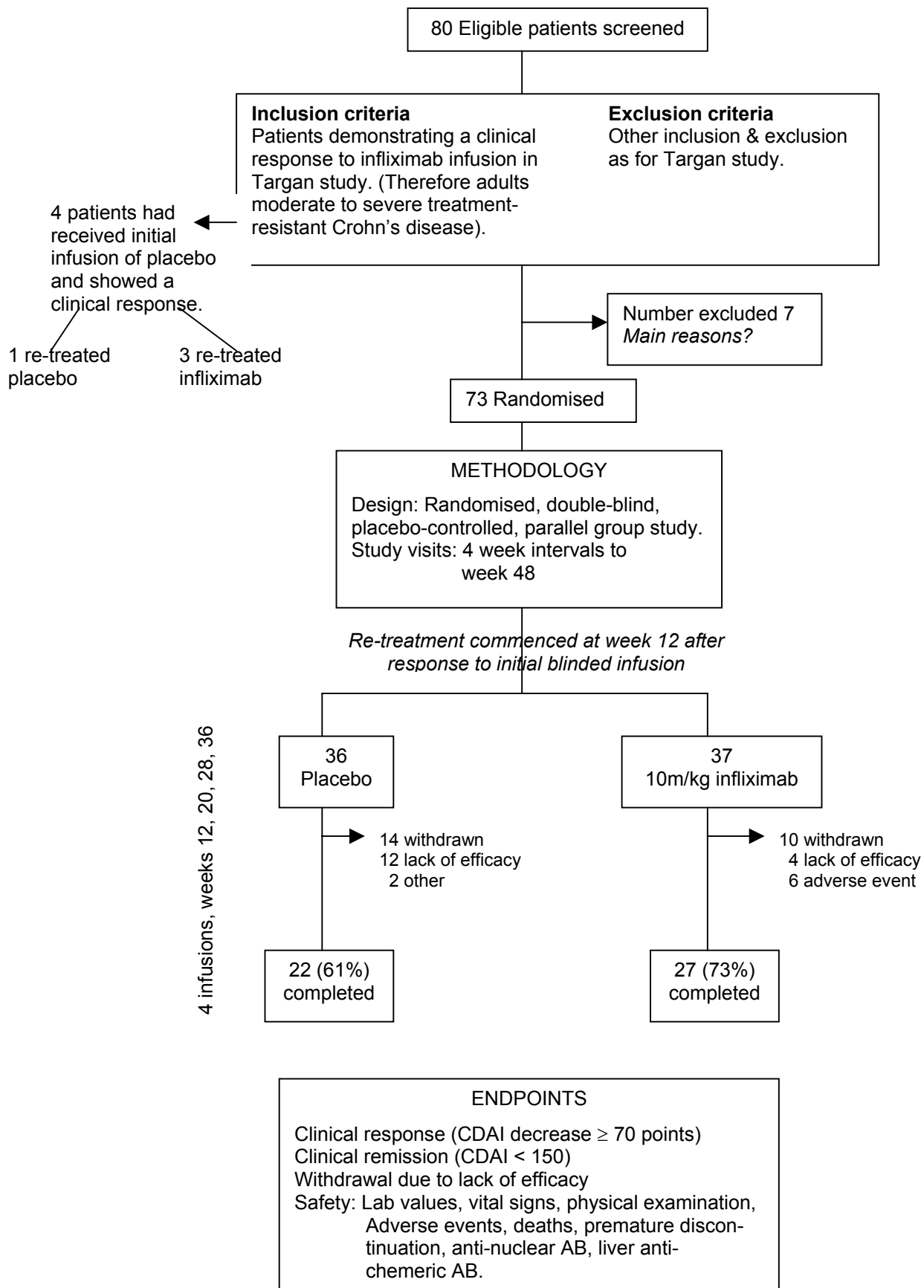
Reference	Reason for exclusion
McCabe R.P, et al. A multicentre trial of cA2 anti TNF chimeric monoclonal antibody in patients with active Crohn's disease. <i>Gastroenterology</i> 1996; <b>110</b> :A962.	Not a controlled trial
Derx B, Taminau J, Tadema S, Stonkhorst A, Wortel C, et al. Tumour-necrosis-factor antibody treatment in Crohn's disease. <i>Lancet</i> 1993; <b>342</b> (8864):173-174.	Not a controlled trial
Ricart E, Panaccione R, Loftus EV, et al. Successful management of Crohn's disease of the ileoanal pouch with infliximab. <i>Gastroenterology</i> 1999; <b>117</b> :429-432.	Not a trial
van Dullemen HM, van Deventer SJH, Hommes DW, Bijl HA, Jansen J, et al. Treatment of Crohn's Disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). <i>Gastroenterology</i> 1995; <b>109</b> :129-135	Not a controlled trial
Baert FJ, D'Haens GR, Peeters M, Hiele MI, Schaible TF, et al. Tumor necrosis factor alfa antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. <i>Gastroenterology</i> 1999; <b>116</b> :22-28.	Not a controlled trial treatment centre experience
Heller T, James SP, Drachenberg C, Hernandez C, Darwin PE. Treatment of severe esophageal Crohn's disease with infliximab. <i>Inflammatory Bowel Diseases</i> 1999; <b>5</b> (4):279-282.	Not a controlled trial
Hommes DW, van Dullemen HM, Levi M, van der Ende A, Woody J, 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. <i>Haemostasis</i> 1997; <b>27</b> :269-277.	Not a controlled trial
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. <i>Thrombosis &amp; haemostasis</i> 1995; <b>73</b> :946.	Not a controlled trial
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. <i>Gastroenterology</i> 1995; <b>108</b> :A838.	Not RCT – open-label non-comparative study
Kammerer W. Infliximab gegen fisteln bie morbus Crohn. <i>Pharm Ztg</i> 1999; <b>33</b> (144):32.	Not a controlled 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. <i>Gastroenterology</i> 2000; <b>110</b> (4):Abs A962.	Not a controlled trial
Present DH. Review article: the efficacy of infliximab in Crohn's disease - healing of fistulae. <i>Aliment Pharmacol Ther</i> 1999; <b>13</b> (Suppl.4):23-28.	Not a trial
Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, et al. Infliximab for fistulas: a hole in one? <i>Inflammatory Bowel Diseases</i> 2000; <b>6</b> (1):62-63.	Not a trial
Rasmussen SN, Petersen JA. Behandling af morbus Crohn med anti-tumornekrosis-faktor-alfa. <i>Ugeskrift for Laeger</i> 1999; <b>1761</b> :4026-4029.	Not a trial
Stack WA, Mann SD, Heath RAJ, Sopwith M, Freeman J, et al. A controlled trial of anti-tumor necrosis factor alfa antibody for crohn's disease. <i>Gastroenterology</i> 1997; <b>113</b> (3):1042-1043.	Not a controlled trial
Lofberg R. Treatment of fistulas in Crohn's disease with infliximab (comments). <i>Gut</i> 1999; <b>45</b> :642-643.	Not a trial
Bourreille A. TNF-alfa et interleukine 1 beta dans les rechutes de maladie de Crohn. <i>Hepato-Gastro</i> 1999; <b>3</b> (6):232-233.	Not a trial
Van den Bosch F, Kruithof E, De Vos M, De Keyser F, Veys EM, et al. Crohn's disease with spondyloarthritis: Effect of tumor necrosis factor-alfa blockade (infliximab) on articular symptoms. <i>Rheumatology &amp; Gastroenterology</i> 2000.	Not a trial

**Appendix 4: Trial Profiles**

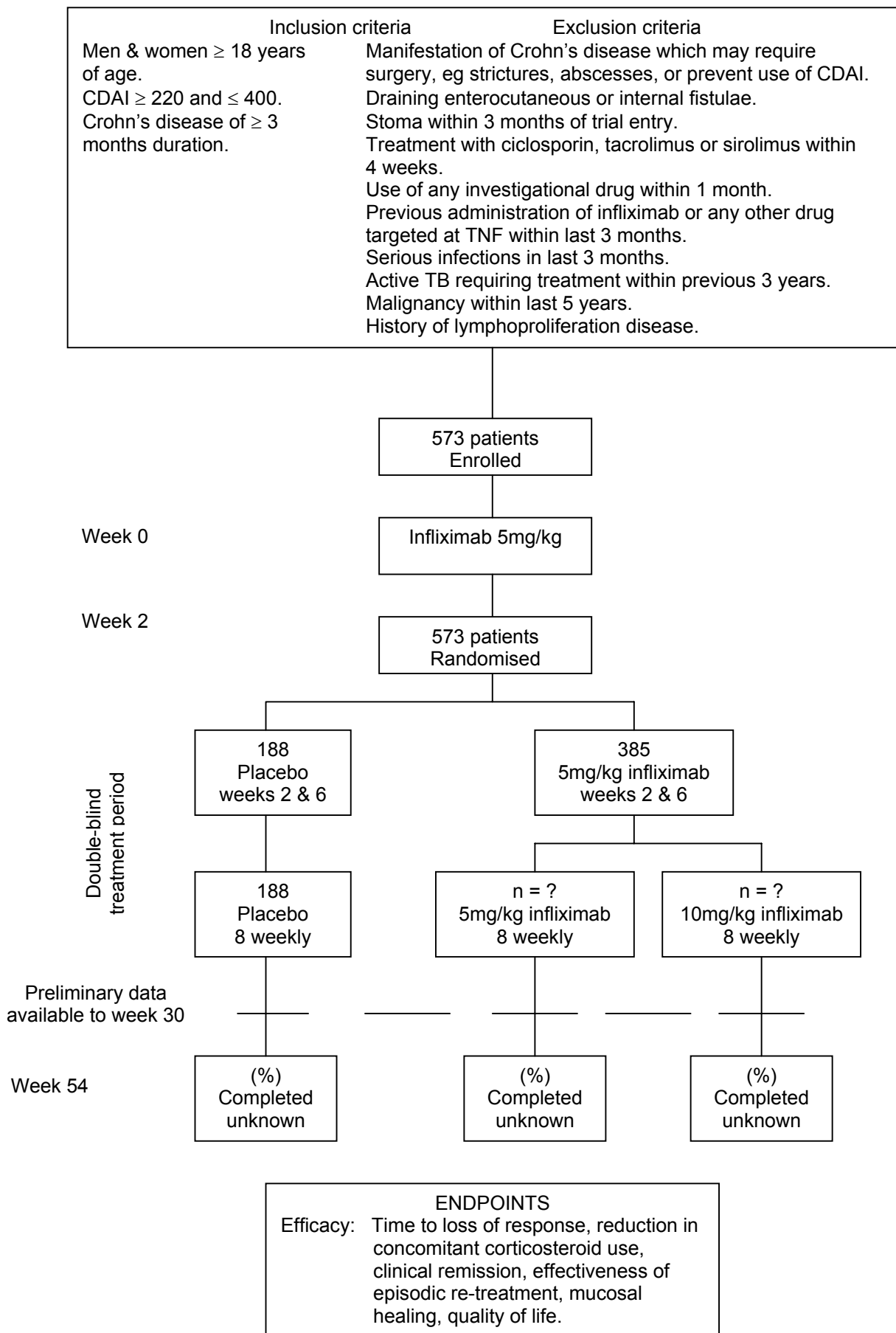
A short-term study of chimeric monoclonal antibody cA2 to tumour necrosis factor  $\alpha$  for Crohn's disease, conducted in North America and Europe.<sup>70</sup>



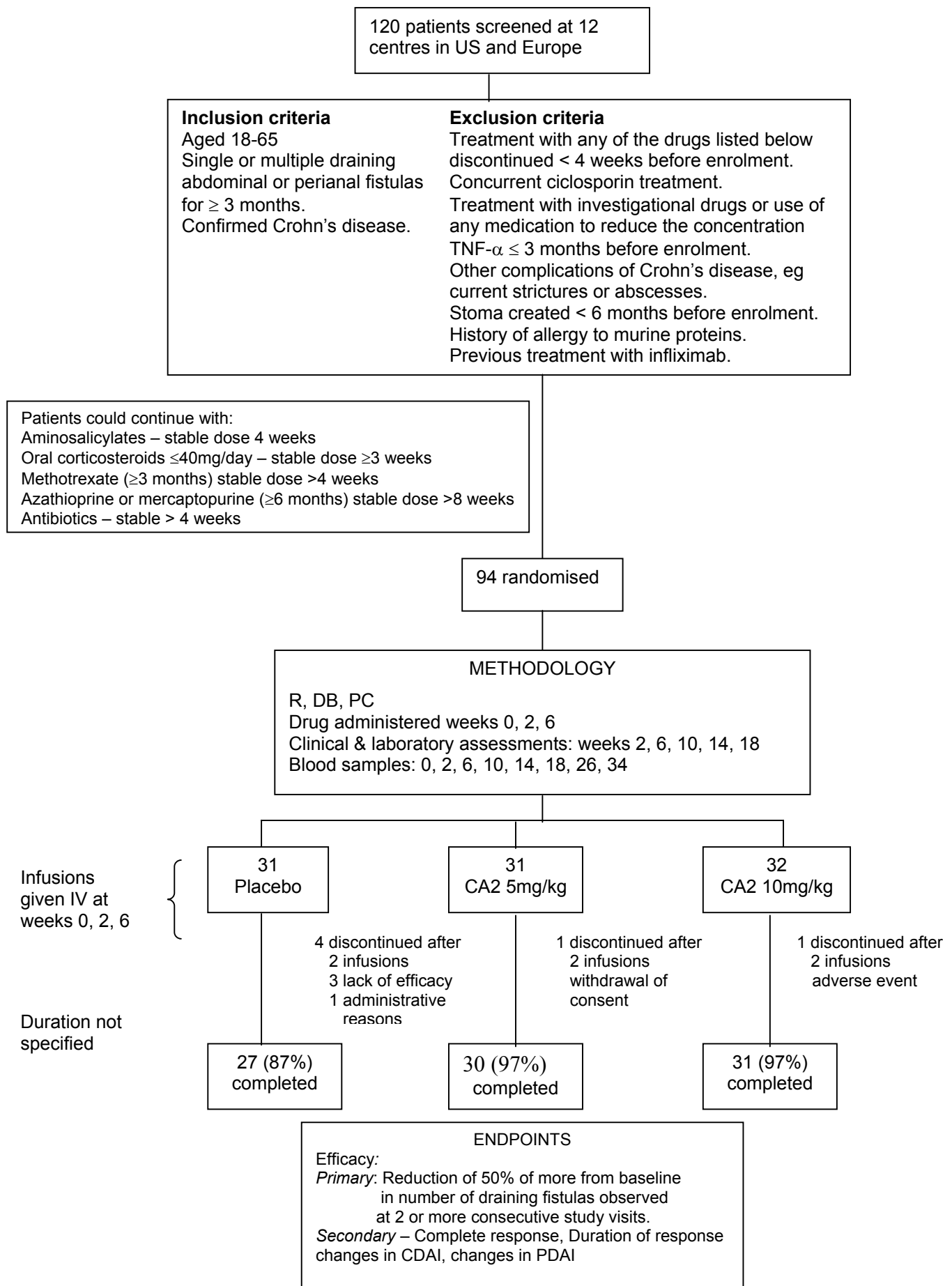
**Efficacy and safety of re-treatment with Anti-tumour necrosis factor antibody (infliximab) to maintain remission in Crohn's disease.**<sup>68</sup>



A randomised, controlled trial of infliximab in the long-term treatment of patients with moderate to severe active Crohn's disease. (ACCENT I trial).<sup>78</sup>



Infliximab for the treatment of fistulas in patients with crohn's disease.<sup>64</sup>





**Appendix 6: Sensitivity analyses of different scenarios in relation to the treatment of chronic active Crohn's disease with infliximab.**

**Table A6-1: Scenario 1. Chronic active CD: Cost per QALY re-working the company model for single dose and 3 episodic treatments of those who respond but relapse (drug response rates as in company model)**

Cost per QALY of treating 100 patients with single initial dose Infliximab (all doses) compared to placebo.									
Patients to remission (CDAI<150)			Patients to 'mild' (>_70 point CDAI reduction)				Comments		
	Infliximab	placebo	net	Infliximab	placebo	net			
	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, mild from company model		
Duration(days)			80			80	TAR/FDA (median)		
QALD gain in 100 patients			217			176			
QALYs gain in 100 patients			0.60			0.48			
total QALYs							1.08		
cost of 100 patients			145,700			145,700	145,700		
£/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 remission/mild		
Duration(days)			80				as above		
QAL Days per patient			10.4						
QALYs per patient			0.028						
cost			1,457						
£/QALY			51,135				for subsequent treatments only		
Treatment of 100 notional patients, with those moving to remission or mild treated for 3 further episodes in year									
Net % responding			37.7				combined remission + mild		
Utility gain per patient			0.13				average remission/mild		
Duration days per patient (80*4)			320						
QAL Days			1,568						
QALYs			4.297						
Cost (£1,457* 100+ £1,457*3*37.7)			310,487						
Cost per QALY			72,261				average initial and subsequent treatments		

**Table A6-2:** Scenario 2. Cost per QALY re-working the company model for single dose and 3 episodic treatments of those who respond but relapse (drug response rates for 5mg/kg)

Cost per QALY of treating 100 patients with single initial dose Infliximab (5mg doses) compared to placebo.								
patients to remission (CDAI<150)			Patients to 'mild' (>_70 point CDAI reduction)					
	Infliximab	placebo	net	Infliximab	placebo	net	totals	Comments
% responding	38.2	9.5	28.7	24.70	5.4	19.3	48.0	data adjusted for 5mg dose
Utility gain			0.14			0.12		Remission from Gregor, mild from company model
Duration(days)			80			80		TAR/FDA (median)
QALD gain in 100 patients			321			185		
QALYs gain in 100 patients			0.88			0.51		
total QALYs							1.39	
cost of 100 patients			145,700			145,700	145,700	
£/QALY			165,445			287,028	104,950	combined utility gain, single cost
Subsequent treatment of patients with above responses who 'flare'								
Utility gain			0.13					average remission/mild
Duration(days)			80					as above
QAL Days per patient			10.4					
QALYs per patient			0.028					
Cost			1,457					
£/QALY			51,135					for subsequent treatments only
Treatment of 100 notional patients, with those moving to remission or mild treated for 3 further episodes in year								
Net % responding			48					combined remission + mild
Utility gain per patient			0.13					average remission/mild
Duration days per patient (80*4)			320					
QAL Days			1,997					
QALYs			5.471					
Cost (£1,457* 100+ £1,457*3*48)			355,508					
								average initial and subsequent treatments
net cost			355,508					
Cost per QALY			64,984					

## 9. REFERENCES

- 1 Best WR, Bectel JM, Singleton JW, Kern F. Development of a Crohn's disease activity index. *Gastroenterology* 1976; **70**:439-444.
- 2 Anon. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. *Gut* 1989; **30**:983-989.
- 3 Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989; **96**:804-810.
- 4 Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. *Hepatology* 1996; **24**:2.
- 5 Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. *Gastroenterology* 1994; **106**:287-296.
- 6 Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new Disease Activity Index. *J Clin Gastroenterol* 1995; **20**(1):27-32.
- 7 Jewell D. Crohn's Disease. *Medicine* 1998; **26**(9):87-92.
- 8 Anon. Inflammatory bowel disease. *Br Soc Gastroenterology Clinical Guidelines* 1996.
- 9 Sachar DB, Andrews HA, Farmer RG, Pallone F, Pena AS, et al. Proposed classification of patient subgroups in Crohn's disease. *Gastroenterology International* 1992; **5**(3):141-154.
- 10 D'Haens G, Rutgeerts P. Treatment of Active Crohn's Disease. *Research and Clinical Forum* 2000; **22**(2):69-75.
- 11 Hagop S, Mekhjian S, Switz M, Melnyk, et al. Clinical features and natural history of Crohn's disease. *Gastroenterology* 1979; **77**:898-906.
- 12 Sartor RB. New therapeutic approaches to Crohn's disease. *New England Journal of Medicine* 2000; **342**(22):1664-1666.
- 13 Farmer RG, Whelan G, Fazio VW. Long-term follow-up of patients with Crohn's disease. *Gastroenterology* 1985; **88**(1818):1825.
- 14 Hanauer SB, Meyers S. Management of Crohn's disease in adults. *Am J Gastroenterology* 1997; **92**(4):559-565.
- 15 Hanauer SB, Cohen RD, Becker RV, Larson LR, Vreeland MG. Advances in the management of Crohn's disease: economic and clinical potential of infliximab. *Clinical Therapeutics* 1998; **20**(5):1009-1029.
- 16 Wall GC, Heyneman C, Pfanner TP. Medical options for treating Crohn's disease in adults: Focus on antitumor necrosis factor- $\alpha$  chimeric monoclonal antibody. *Pharmacotherapy* 1999; **19**(10):1138-1152.
- 17 Logan RFA. Inflammatory bowel disease incidence: up, down or unchanged? *Gut* 1998; **42**:309-311.
- 18 Sutherland LR, Ramcharan S, Bryant H, Fick G. Effect of cigarette smoking on recurrence of Crohn's disease. *Gastroenterology* 1990; **98**:1123-1128.
- 19 Kaufmann HJ, Taubin HL. Non-steroidal Anti-inflammatory drugs activate quiescent inflammatory bowel disease. *Ann Intern Med* 1987; **107**:513-516.
- 20 Anon. Background information on Crohn's Disease. *National Association for Colitis and Crohn's Disease* 2000.
- 21 Munkholm P, Langholtz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. *Scandinavian J Gastroenterology* 1995; **30**:699-706.

- 22 Andersson P, Olaison G, Bodemar G, Almer S, Arvidsson M, et al. Low symptomatic load in Crohn's disease with surgery and medicine as complementary treatments. *Scandinavian J Gastroenterology* 1998; **33**:423-429.
- 23 Silverstein MD, Loftus EV, Sandborn WJ, Tremaine WJ, Feagan BG, Nietert PJ, et al. Clinical course and costs of care for crohn's disease: markov model analysis of a population-based cohort. *Gastroenterology* 1999; **117**:49-57.
- 24 Gregor J, McDonald JWD, Klar N, et al. An evaluation of utility measurement in Crohn's disease. *Inflammatory Bowel Diseases* 1997; **3**:265-276.
- 25 Summers RW, Switz DM, Sessions JTJ, Becktel JM, Best WR, et al. National Cooperative Crohn's disease study: Results of Drug Treatment. *Gastroenterology* 1979; **77**:847-869.
- 26 Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, et al. European Cooperative Crohn's disease study (ECCDS): Results of drug treatment. *Gastroenterology* 1984; **86**:249-266.
- 27 Salomon P, Kornbluth A, Aisenberg J, Janowitz HD. How effective are current drugs for Crohn's disease? *J Clin Gastroenterol* 1992; **14**(3):211-215.
- 28 Ricart E, Panaccione R, Loftus EV, et al. Successful management of Crohn's disease of the ileoanal pouch with infliximab. *Gastroenterology* 1999; **117**:429-432.
- 29 Rutgeerts P. Medical therapy of inflammatory bowel disease. *Digestion* 1998; **59**:453-469.
- 30 Lang KA, Peppercorn MA. Promising new agents for the treatment of inflammatory bowel disorders. *Drugs R&D* 1999; **1**(3):237-244.
- 31 Munkholm P, Langholz E, Davidsen M, Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut* 1994; **35**:360-362.
- 32 Sandborn W, Sutherland L, Pearson D, May G, Modigliani R, et al. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. *The Cochrane Library* 2000; **4**(1):15.
- 33 Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate for the treatment of Crohn's disease. *New England Journal of Medicine* 1995; **332**:292-297.
- 34 Lowry PW, Sandborn WJ, Lipsky JJ. Mycophenolate mofetil for Crohn's disease? *Lancet* 1999; **354**:3-4.
- 35 Rutgeerts P, Baert F. New strategies in the management of inflammatory bowel disease. *Acta Clinica Belgica* 1999; **54**(5):274-280.
- 36 Sandborn WJ. Therapy for Crohn disease. *Current Opinion in Gastroenterology* 2000; **16**:318-323.
- 37 Lichtenstein GR. Treatment of fistulizing Crohn's Disease. *Gastroenterology* 2000; **119**:1132-1147.
- 38 Messori A, Brignola C, Trallori G, Rampazzo R, Bardazzi G, et al. Effectiveness of 5-Aminosalicylic acid for maintaining remission in patients with Crohn's disease: A meta-analysis. *Am J Gastroenterology* 1994; **89**(5):692-698.
- 39 Steinhart AH, Hemphill D, Greenberg GR. Sulfasalazine and mesalazine for the maintenance therapy of Crohn's disease: A meta-analysis. *Am J Gastroenterology* 1994; **89**(12):2116-2124.
- 40 Camma C, Giunta M, Rosselli M, Cottone M. Mesalamine in the maintenance treatment of Crohn's disease: A meta-analysis adjusted for confounding variables. *Gastroenterology* 1997; **113**:1465-1473.
- 41 Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintaining remission of Crohn's disease. *The Cochrane Library* 2000; **4**:1-10.
- 42 Pearson DC, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. *The Cochrane Library* 2000; **4**:1-10.

- 43 Modigliani R. Immunosuppressors for inflammatory bowel disease: how long is long enough? *Inflammatory Bowel Diseases* 2000; **6(3)**:251-257.
- 44 Hanauer SB. Medical therapy for Crohn's disease. *Current Opinion in Gastroenterology* 1999; **15**:308-314.
- 45 Onrust SV, Lamb HM. Infliximab: A review of its use in Crohn's disease and rheumatoid arthritis. *BioDrugs* 1998; **10(5)**:397-422.
- 46 van Hogezaand RA, Verspaget HW. The future role of anti-tumour necrosis factor-alfa products in the treatment of Crohn's Disease. *Drugs* 1998; **56(3)**:299-305.
- 47 Committee for Proprietary Medicinal Products. Remicade. *European Public Assessment Report (EPAR)* 1999; **CPMP/1901/99**.
- 48 Centocor B.V. Remicade 100mg powder for concentrate for solution for infusion. *Summary of Product Characteristics* 2000.
- 49 Bell SJ, Kamm MA. Review article: the clinical role of anti-TNF-alfa antibody treatment in Crohn's disease. *Aliment Pharmacol Ther* 2000; **14**:501-514.
- 50 Centocor B.V. Remicade: Lyophilized concentrate for IV infusion. *Product Monograph* 2000.
- 51 Schering Plough. Infliximab. *Personal communication* 2001.
- 52 Dept of Public Health & Epidemiology. West Midlands Development and Evaluation Service (DES) Handbook. *DPHE 1999 Report No 8* 1999; **2.2**:1-142.
- 53 Anon. Undertaking Systematic Review of Research on Effectiveness. *CRD Report Number 4* 2001; **2nd Edition**.
- 54 Anon. Remicade for Crohn's Disease. *Clinical Trial Information* 2000; <http://www.remicade-crohns.com/hcp/clinical.html>.
- 55 Baert FJ, D'Haens GR, Peeters M, Hiele MI, Schaible TF, et al. Tumor necrosis factor alfa antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. *Gastroenterology* 1999; **116**:22-28.
- 56 D'Haens G, et al. Endoscopic and histological healing with infliximab anti-tumour necrosis factor antibodies in Crohn's disease. *Gastroenterology* 1999; **116**:1029-1034.
- 57 Derkx B, Taminiou J, Tadema S, Stonkhorst A, Wortel C, et al. Tumour-necrosis-factor antibody treatment in Crohn's disease. *Lancet* 1993; **342(8864)**:173-174.
- 58 Heller T, James SP, Drachenberg C, Hernandez C, Darwin PE. Treatment of severe esophageal Crohn's disease with infliximab. *Inflammatory Bowel Diseases* 1999; **5(4)**:279-282.
- 59 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. *Gastroenterology* 1995; **108**:A838.
- 60 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. *Thrombosis & haemostasis* 1995; **73**:946.
- 61 Hommes DW, van Dullemen HM, Levi M, van der Ende A, Woody J, 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; **27**:269-277.
- 62 Kammerer W. Infliximab gegen fisteln bie morbus Crohn. *Pharm Ztg* 1999; **33(144)**:32.
- 63 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. *Gastroenterology* 2000; **110(4)**:Abs A962.

- 64 Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, et al. Infliximab for the treatment of fistulas in patients with Crohn's Disease. *New England Journal of Medicine* 1999; **340**:1398-1405.
- 65 Present DH. Review article: the efficacy of infliximab in Crohn's disease - healing of fistulae. *Aliment Pharmacol Ther* 1999; **13 (Suppl.4)**:23-28.
- 66 Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, et al. Infliximab for fistulas: a hole in one? *Inflammatory Bowel Diseases* 2000; **6(1)**:62-63.
- 67 Rasmussen SN, Petersen JA. Behandling af morbus Crohn med anti-tumornekrosis-faktor-alfa. *Ugeskrift for Laeger* 1999; **1761**:4026-4029.
- 68 Rutgeerts P, D'Haens G, Targan S, Vasiliaskas E, Hanauer SB, et al. Efficacy and Safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's Disease. *Gastroenterology* 1999; **117**:761-769.
- 69 Stack WA, Mann SD, Heath RAJ, Sopwith M, Freeman J, et al. A controlled trial of anti-tumor necrosis factor alfa antibody for crohn's disease. *Gastroenterology* 1997; **113(3)**:1042-1043.
- 70 Targan S. A short term study of chimeric monoclonal antibody cA2 to tumour necrosis factor alpha for Crohn's disease. *New England Journal of Medicine* 1997; **337(15)**:1029-1035.
- 71 van Dullemen HM, van Deventer SJH, Hommes DW, Bijl HA, Jansen J, et al. Treatment of Crohn's Disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). *Gastroenterology* 1995; **109**:129-135.
- 72 Van den Bosch F, Kruithof E, De Vos M, De Keyser F, Veys EM, et al. Crohn's disease with spondyloarthritis: Effect of tumor necrosis factor-alfa blockade (infliximab) on articular symptoms. *Rheumatology & Gastroenterology* 2000.
- 73 Lofberg R. Treatment of fistulas in Crohn's disease with infliximab (comments). *Gut* 1999; **45**:642-643.
- 74 Bourreille A. TNF-alfa et interleukine 1 beta dans les rechutes de maladie de Crohn. *Hepato-Gastro* 1999; **3(6)**:232-233.
- 75 McCabe R.P, et al. A multicentre trial of cA2 anti TNF chimeric monoclonal antibody in patients with active Crohn's disease. *Gastroenterology* 1996; **110**:A962.
- 76 Anon. ACCENT I: A Crohn's disease clinical trial evaluating infliximab in a new long term treatment regimen. *Presented at Digestive Disease Week* 2001; **Atlanta**.
- 77 Centocor B.V. Infliximab (T16 trial). *Application for Marketing Authorization Part IV* 1998; **27**.
- 78 Centocor B.V. A Randomized double-blind, placebo-controlled trial of anti-TNF alfa chimeric monoclonal antibody (infliximab, Remicade) in the long-term treatment of patients with moderately to severely active Crohn's disease (ACCENT I). *Protocol* 1998; **C0168T21**:1-64.
- 79 Dept of Health & Human Services. Statistical Review: Chimeric monoclonal antibody (cA2) to tumor necrosis factor for inflammatory bowel disease (Crohn's Disease). *Food & Drug Administration Memorandum* 1998.
- 80 Anon. Remicade (infliximab) for IV injection. *Physicians Desk Reference* 2000.
- 81 Centocor B.V. Infliximab (T20 trial). *Application for Marketing Authorization Part IV* 1998; **33**.
- 82 Schering-Plough Ltd Remicade in the treatment of Crohn's disease in the United Kingdom. Submission to the National Institute for Clinical Excellence.
- 83 The European Agency for the Evaluation of Medicinal Products. Reports of tuberculosis infections. *EMEA Public Statement on infliximab (Remicade)* 2000;1-8.
- 84 Centocor B.V. Remicade (infliximab). *Periodic Safety Update Report* 2001;1-222.

- 85 Hanauer SB. Review article: safety of infliximab in clinical trials. *Aliment Pharmacol Ther* 1999; **13 (Suppl.4)**:16-22.
- 86 Farrell M, Shah S, Lodhavia M, Alsahli M, Falchuck K, Michetti P, *et al.* Clinical experience with infliximab therapy in 100 patients with Crohn's disease. *Am J Gastroenterology* 2000; **95**(12):3490-3497.
- 87 Anon. Infliximab (Remicade) and tuberculosis. *CSM current problems & Pharmacovigilance* 2001; **27**:7.
- 88 Menghini VV, Arora AS. Infliximab-associated reversible cholestatic liver disease. *Mayo Clin Proc* 2001; **76**:84-86.
- 89 Bickston SJ, Lichtenstein GR, Arseneau KOCRB, Cominelli F. The relationship between infliximab treatment and lymphoma in Crohn's disease. *Gastroenterology* 1999; **117**:1433-1437.
- 90 Sandborn WJ, Hanauer SB. Antitumor necrosis factor therapy for inflammatory bowel disease: A review of agents, pharmacology, clinical results, and safety. *Inflammatory Bowel Diseases* 1999; **5**(2):119-133.
- 91 Lochs H, Adler G, Beglinger CH, Duchmann R, Emmrich J, *et al.* Anti-TNF antibody in Crohn's disease - status of information, comments and recommendations of an international working group. *Z Gastroenterol* 1999; **37**:509-512.
- 92 Hanauer SB, Sandborn W. Management of Crohn's disease in adults. *Am J Gastroenterology* 2001; **96**(3):635-643.
- 93 Schreiber S, Campieri M, Colombel JF, van Deventer SJH, Feagan B, Fedorak R, *et al.* Use of anti-tumour necrosis factor agents in inflammatory bowel disease. European guidelines for 2001-2003. *Int J Colorectal Dis* 2001; **16**:1-11.
- 94 Nikolaus S, Raedler A, Kuhbacher T, Sfikas N, Folsch UR, *et al.* Mechanisms in failure of infliximab for Crohn's disease. *Lancet* 2000; **356**:1475-1479.

