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A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-α) inhibitors, adalimumab and infliximab, for Crohn's disease

J Dretzke,[1] R Edlin,[2] J Round,[2] M Connock,[1] C Hulme,[2] J Czeczot,[1] A Fry-Smith,[1] C McCabe[2] and C Meads[3]*

[1]Department of Public Health & Epidemiology, University of Birmingham, Birmingham, UK
[2]Institute of Health Sciences, University of Leeds, Leeds, UK
[3]Centre for Health Sciences, Barts and the London School of Medicine and Dentistry, Queen Mary, University of London, London, UK

*Corresponding author

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Abstract

A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-α) inhibitors, adalimumab and infliximab, for Crohn's disease

J Dretzke,[1] R Edlin,[2] J Round,[2] M Connock,[1] C Hulme,[2] J Czeczot,[1] A Fry-Smith,[1] C McCabe[2] and C Meads[3]*

[1]Department of Public Health & Epidemiology, University of Birmingham, Birmingham, UK
[2]Institute of Health Sciences, University of Leeds, Leeds, UK
[3]Centre for Health Sciences, Barts and the London School of Medicine and Dentistry, Queen Mary, University of London, London, UK

*Corresponding author

Background: Crohn's disease (CD) is a severe, lifelong disease characterised by inflammation of the gastrointestinal mucosa. The impact on patients and society is high as ill health can be lifelong and can negatively affect patients' quality of life. Costs to the NHS are high, particularly for patients needing hospitalisation. Conventional treatment pathways are complex. More recently, a group of drugs called tumour necrosis factor (TNF) inhibitors (anti-TNF-α agents) have been evaluated for their effectiveness in CD. One of these, infliximab, is currently recommended by the National Institute for Health and Clinical Excellence (NICE; 2002) for patients with severe, active CD where patients are refractory to or intolerant of conventional treatment.

Objectives: To investigate whether there is evidence for greater clinical effectiveness or cost-effectiveness for either adalimumab or infliximab.

Data sources: Cochrane Library (Cochrane Central Register of Controlled Trials) 2007 Issue 2; MEDLINE (Ovid) 2000 to May/June 2007; MEDLINE In-Process & Other Non-Indexed Citations (Ovid) 4 June and 26 June 2007; EMBASE (Ovid) 2000 to May/June 2007. The European Medicines Agency, the US Food and Drug Administration and other relevant websites.

Review methods: Standard systematic review methods were used for study identification and selection, data extraction and quality assessment. Only randomised controlled trials (RCTs) comparing adalimumab or infliximab with standard treatment (placebo), RCTs comparing adalimumab with infliximab, or RCTs comparing different dosing regimens of either adalimumab or infliximab in adults and children with moderate-to-severe active CD intolerant or resistant to conventional treatment were eligible for inclusion. A systematic review of published studies on the cost and cost-effectiveness of adalimumab and infliximab was undertaken. The economic models of cost-effectiveness submitted by the manufacturers of both drugs were critically appraised and, where appropriate, rerun using parameter inputs based on the evidence identified by the authors of the technology asessment report. A de novo Markov state transition model was constructed to calculate the incremental cost-effectiveness ratio for adalimumab and infliximab therapy compared with standard care.

Results: Based on 11 trials, there was evidence from both induction and maintenance trials that both adalimumab and infliximab therapy were beneficial compared with placebo (standard care) for adults with moderate-to-severe CD and, for infliximab, for adults with fistulising CD; results were statistically significant for some time points. Between 6% and 24% (adalimumab), and 21% and 44% (infliximab) more patients achieved remission with anti-TNF-α antibodies than with placebo in the induction trials. Between 24% and 29% (adalimumab), and 14% and 24% (infliximab) more patients achieved remission with anti-TNF-α antibodies in the two large maintenance trials at reported follow-up. In fistulising CD, between 29% and 42% (induction trial) and 23% (maintenance trial) more patients achieved a >50% reduction in fistulas with infliximab than with placebo at reported follow-up. There was no direct evidence to show that 'responders' were more likely to benefit from treatment than 'non-responders' in the longer term. Few differences were found between treatment and standard care arms for selected adverse events, though high proportions of scheduled crossovers resulted in a lack of a true placebo group in most of the maintenance trials. No published studies on the cost-effectiveness of adalimumab were identified.
The four independently funded studies identified for infliximab suggested high cost-effectiveness ratios [all above £50,000/quality-adjusted life-year (QALY) for non-fistulising disease and all above £100,000/QALY for fistulising disease]. A budget impact assessment suggested that total cost to the NHS in England and Wales for induction in severe disease only could range between £17M and £92M and for maintenance for 1 year between £140M and £200M.
Limitations: Regarding clinical effectiveness, there were concerns about the trial design and lack of clarity, which may have affected interpretation of results. None of the trials matched exactly the licence indications or NICE guidance, which specify the use of these drugs in patients with 'severe' disease. All trials were multicentre, and applicability to UK populations, particularly in terms of standard care being provided and in terms of patients having failed or having become intolerant to conventional treatment, was uncertain.
The published economic models relied heavily on little information and data from small samples.
Conclusions: Anti-TNF therapy with adalimumab or infliximab may have a beneficial effect compared with standard care on outcome measures for induction and maintenance. The findings were that for induction, both adalimumab and infliximab are cost-effective (dominant relative to standard care) in the management of severe CD, and adalimumab (but not infliximab) is cost-effective for moderate CD, according to limits generally accepted by NICE. On the basis of the analysis presented here, neither drug is likely to be cost-effective as maintenance therapy for moderate or severe disease. Perhaps, most importantly, the analysis reflected the fact that a substantial number of patients would achieve remission under standard care and that the incidence of relapse among those in remission was such that maintenance therapy would have to show greater effectiveness than at present and/or be much less costly than it currently is in order to reach the levels of generally accepted cost-effectiveness. Any future trials need to be designed to meet the particular challenges of measuring and quantifying benefit in this patient group.
Funding: The research was funded by the HTA programme on behalf of NICE.

Contents

Glossary

There is some difficulty with using the term 'episodic treatment' because it has several possible definitions, depending on where it is being used. Possible definitions include the following:

1. Giving treatment when patients experience a disease relapse (if signs and symptoms recur) [see previous National Institute for Health and Clinical Excellence (NICE) guidance[1]]. The relapse could occur once in several years or much more frequently, such as every 11 weeks [see Rutgeerts *et al.*'s[2] report of ACCENT (A Crohn's disease Clinical trial Evaluating infliximab in a New long-term Treatment regimen) I – median time interval between episodic infusions].
2. Treatment given to the comparator arm (i.e. placebo arm) of the ACCENT I[2,3] trial (see diagram for the treatment given in *Appendix 9*). This includes patients who were given placebo and patients who were given infliximab, i.e. crossovers. It also does not distinguish between responders and non-responders.
3. Treatment 'as needed with infliximab' (see Rutgeerts *et al.*'s[2] report of ACCENT I).
4. 'Intermittent therapy' or 'induction only/reinitiation therapy' (see Abbott's industry submission response to the West Midlands Health Technology Assessment Collaboration (WMHTAC) Technology Assessment Report (TAR), top of page 2).[4]
5. Three retreatments for those who initially respond but subsequently relapse (see economic model in previous TAR, p. 34).[5]
6. Retreatment with a single dose of infliximab (see Marshall *et al.*[6] model).
7. Retreatment when patients relapse *or do not respond* (see Jaisson-Hot *et al.*[7] model).

There is also some difficulty with the term 'maintenance treatment'. Generally this is thought to mean keeping patients who have initially responded to treatment in continuing response or remission. However, the following definitions have also been used:

1. Any *scheduled* maintenance treatment [see most randomised controlled trial (RCT) reports and Jaisson-Hot *et al.*[7] cost-effectiveness analysis].
2. Any continuing treatment (to distinguish between induction and maintenance therapy) – this treatment can be episodic or scheduled maintenance (see ACCENT I[2,3] trial).
3. Any treatment that includes an induction and a maintenance phase (see Schering-Plough response to WMHTAC TAR, p. 3).

In this report, the term episodic treatment has been used in different places in the clinical effectiveness section, particularly with reference to the ACCENT I trial, but does not specify what was meant by the term. In the critical appraisal of the infliximab industry submission, the term 'infliximab clinical discretion' has been used for clarity because the precise definition of episodic treatment that was being used in the model could not be determined.

List of abbreviations

6MP / met	6-mercaptopurine / metronidazole
ACCENT	A Crohn's disease Clinical trial Evaluating infliximab in a New long-term Treatment regimen
AE	adverse event
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CEAC	cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHARM	Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance
CI	confidence interval
CiC	commercial-in-confidence
CLASSIC	CLinical assessment of Adalimumab Safety and efficacy Studied as Induction therapy in Crohn's disease
CRP	C-reactive protein
DNA	deoxyribonucleic acid
EMEA	European Medicines Agency
e.o.w.	every other week
EQ-5D	EuroQoL-5 Dimensions
FDA	US Food and Drug Administration
GAIN	Gauging Adalimumab efficacy in Infliximab Nonresponders
HBI	Harvey–Bradshaw Index
HRQoL	health-related quality of life
HTA	Health Technology Assessment
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICD	infliximab clinical discretion
ICER	incremental cost-effectiveness ratio
IMT	infliximab maintenance treatment
IND	induction (in Chapter 4 only when referring to the Markov model)
IQR	interquartile range
ITT	intention to treat
i.v.	intravenous
LVCF	last value carried forward
MNT	maintenance (in Chapter 4 only when referring to the Markov model)
NACC	National Association for Colitis and Crohn's Disease
NICE	National Institute for Health and Clinical Excellence
PCDAI	Paediatric Crohn's Disease Activity Index
PDAI	Perianal Disease Activity Index
PSS	public social service
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
REACH	A randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNFα chimeric monoclonal antibody (infliximab, Remicade®) in pediatric subjects with moderate-to-severe Crohn's disease

Rx	active treatment (anti-TNF) group
SC	standard care
SD	standard deviation
SF-36	Short Form (36) Health Survey questionnaire
SPCs	*Summary of Product Characteristics*
TAR	Technology Assessment Report
TNF	tumour necrosis factor
WMHTAC	West Midlands Health Technology Assessment Collaboration

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

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable amount of data that were deemed commercial-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence data removed and replaced by the statement 'commercial-in-confidence information removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Executive summary

Background

Crohn's disease (CD) is a severe, lifelong disease characterised by inflammation of the gastrointestinal mucosa. Main symptoms include chronic diarrhoea, abdominal pain, rectal bleeding and weight loss, and growth failure in children. Common complications are strictures (narrowing of the bowel), fistulas (creation of abnormal passageways between the bowel and other structures) and perianal disease (comprising fissures, fistulas and abscesses). The disease is characterised by recurring flares of variable duration alternating with periods of remission of variable duration. There is no cure and most patients will need to take medication for large periods of their life and many will require surgery. CD manifests itself mainly during late adolescence or early adulthood; prevalence estimates range from 50 to 375 per 100,000. The impact on patients and society is high as ill health can be lifelong and can negatively affect education and employment as well as patients' quality of life. Costs to the NHS are high, particularly for patients needing hospitalisation.

Conventional treatment pathways are complex and include a wide range of drugs (corticosteroids, aminosalicylates, immunosuppressants, antibiotics), nutritional therapy and surgery. More recently, a group of drugs called tumour necrosis factor (TNF) inhibitors (anti-TNF-α agents) have been evaluated for their effectiveness in CD. One of these, infliximab, is currently recommended by the National Institute for Health and Clinical Excellence (NICE; 2002) for patients with severe, active CD where patients are refractory to or intolerant of conventional treatment.

Objectives

The objectives of this Technology Assessment Report (TAR) were:

- To update a previous TAR on the effectiveness and cost-effectiveness of infliximab in adults with moderate-to-severe CD or fistulising CD who are refractory to or intolerant of conventional treatment.
- To review the evidence on the clinical effectiveness and cost-effectiveness of infliximab in children with moderate-to-severe CD who are refractory to or intolerant of conventional treatment.
- To review the evidence on the clinical effectiveness and cost-effectiveness of a further anti-TNF-α antibody, adalimumab, in adults with moderate-to-severe CD who are refractory to or intolerant of conventional treatment.
- To investigate whether there is evidence for greater clinical effectiveness or cost-effectiveness for either adalimumab or infliximab.

Methods

Data sources

Data for the review were sought from the Cochrane Library (Cochrane Central Register of Controlled Trials), MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and EMBASE up to June 2007. The European Medicines Agency, the US Food and Drug Administration and other relevant websites were also searched.

Clinical effectiveness

Standard systematic review methods were used for study identification and selection, data extraction and quality assessment. Only randomised controlled trials (RCTs) comparing adalimumab or infliximab with standard treatment (placebo), RCTs comparing adalimumab with infliximab, or RCTs comparing different dosing regimens of either adalimumab or infliximab in adults and children with moderate-to-severe active CD intolerant or resistant to conventional treatment were eligible for inclusion. Outcomes reported in the trials were based mainly around changes in the Crohn's Disease Activity Index (CDAI), a questionnaire measuring various parameters associated with CD. Results were presented in forest plots, but not pooled because of the existence of either a single trial or clinical heterogeneity where there were two trials that potentially could have been pooled. Formal indirect comparisons were not undertaken owing to clinical heterogeneity of trials. Results are reported for those trial arms where dosing regimens were consistent with the licence indications.

Cost-effectiveness

A systematic review of published studies on the cost and cost-effectiveness of adalimumab and infliximab was undertaken. The economic models of cost-effectiveness submitted by the manufacturers of both drugs were critically appraised and, where appropriate, rerun using parameter inputs based on the evidence identified by the authors of the TAR. A de novo Markov state transition model was constructed to calculate the incremental cost-effectiveness ratio (ICER) for adalimumab and infliximab therapy compared with standard care.

Results

Clinical effectiveness review

Based on 11 trials, there was evidence from both induction and maintenance trials that both adalimumab and infliximab therapy were beneficial compared with placebo (standard care) for adults with moderate-to-severe CD and, for infliximab, for adults with fistulising CD; results were statistically significant for some time points. These results were based on changes to the CDAI and, for fistulising disease, on rates of fistula closure. Results from maintenance trials were almost exclusively based on subgroups of 'responders'. Between 6% and 24% (adalimumab) and 21% and 44% (infliximab) more patients achieved remission with anti-TNF-α antibodies than with placebo in the induction trials. Between 24% and 29% (adalimumab) and 14% and 24% (infliximab) more patients achieved remission with anti-TNF-α antibodies in the two large maintenance trials at reported follow-up. In fistulising CD, between 29% and 42% (induction trial) and 23% (maintenance trial) more patients achieved a > 50% reduction in fistulas with infliximab than with placebo at reported follow-up.

There was no direct evidence to show that 'responders' were more likely to benefit from treatment than 'non-responders' in the longer term. The maintenance trials, in the main, did not inform on persistence of the response (remission) state as point prevalence only was reported. There was likely to be a benefit of infliximab therapy for children, but these results were uncertain as the trials had no placebo (standard care) arm; rates of spontaneous improvement could therefore not be quantified. There was no valid evidence regarding the relative effectiveness of 'episodic' and 'scheduled' infliximab treatment regimens. Few differences were found between treatment and standard care arms for selected adverse events, though high proportions of scheduled crossovers resulted in a lack of a true placebo group in most of the maintenance trials.

Cost-effectiveness review

No published studies on the cost-effectiveness of adalimumab were identified. The four independently funded studies identified for infliximab suggested high cost-effectiveness ratios

[all above £50,000/quality-adjusted life-year (QALY) for non-fistulising disease and all above £100,000/QALY for fistulising disease].

Appraisal of industry submissions

For adalimumab there was a lack of clarity over the source and interpretation of data used in the industry model, and key elements of the model could not be verified. Corrected results for both severe CD and moderate and severe (combined) CD were substantially higher than in the industry submitted model; in the severe subgroup of patients the corrected ICER approached cost-effectiveness (at a threshold of £30,000). For infliximab, errors were identified in the industry model (active CD), some of which could not be corrected. The authors' revision of the model (active CD) suggested that infliximab was cost-effective for episodic (clinician discretion) treatment, although an exact description of this intervention was lacking. The revised model indicated that scheduled maintenance treatment with infliximab was unlikely to be cost-effective. The revised industry model for fistulising CD also suggested that infliximab was unlikely to be cost-effective. The model provided for paediatric CD was non-functional.

De novo economic model

A Markov model was developed from an NHS/Personal Social Services perspective to estimate the incremental cost per QALY for both drugs compared with standard care in (a) induction/episodic therapy (as it was defined for the de novo economic model) for moderate and severe disease; and (b) maintenance therapy for moderate and severe disease. The model had a 1-year time horizon and was constructed and analysed in TREEAGE PRO 2008 (TreeAge Software Inc., Williamstown, MA, USA). The findings were that for induction, both adalimumab and infliximab were cost-effective (dominant relative to standard care) in the management of severe CD and that adalimumab was cost-effective (dominant relative to standard care) for moderate CD, according to limits usually accepted by NICE. Induction therapy with infliximab was not cost-effective for moderate CD (ICER of £94,321). Neither drug was cost-effective as maintenance therapy for moderate or severe disease by these criteria (ICER around £5M for severe disease for both drugs, and around £14M for moderate disease for both drugs). Additional work on severe CD suggested that relapse rates were one important factor in determining cost-effectiveness.

A budget impact assessment suggested that the total cost to the NHS in England and Wales for induction in severe disease only could range between £17M and £92M and for maintenance for 1 year between £140M and £200M. These totals would be less if treatment was directed towards only those CD patients whose condition was refractory to other treatment or who were intolerant or experienced toxicity from these treatments and for whom surgery was inappropriate. It is unclear how many people would be in this category so the precise budget impact if the current NICE guidance is maintained was unclear.

Discussion

Regarding clinical effectiveness, there were concerns about the trial design and lack of clarity, particularly regarding the maintenance trials, which may have affected interpretation of results. These related to the division of patients into subgroups (responders and non-responders) at different time points; the high proportions of scheduled crossovers resulting in a lack of a true placebo group; and uncertainties regarding the handling of missing binary and continuous data. Overall, the trials showed a benefit of both adalimumab and infliximab therapy over standard care, as measured by CDAI-related outcome measures (or fistula closure for patients with fistulising CD). Uncertainties remain over the size of the effect for both drugs, the duration of effect (after 1 year), the best type of treatment regimen (e.g. scheduled or as required) and the type of patient who would benefit most (e.g. in terms of disease severity or being an early

'responder'). There are also uncertainties over whether the CDAI-derived measures were adequate for capturing clinically meaningful changes in disease severity. While trial populations overall may appear homogeneous based on similar CDAI scores, individual patients are likely to vary in their disease manifestations and severity. All of the trials were in patients with 'moderate-to-severe' CD (or fistulising CD) and therefore none matched exactly the licence indications or NICE guidance, which specify the use of these drugs in patients with 'severe' disease. All trials were multicentre and applicability to UK populations, particularly in terms of standard care being provided and in terms of patients having failed or having become intolerant to conventional treatment, was uncertain.

The uncertainties in the clinical data (as outlined above) complicated the economic analyses. The published economic models relied heavily on little information and data from small samples. In such cases, the interpretation of economic models within the published papers was difficult. Assessments of the industry-submitted models were hampered by inconsistent use of data and lack of clarity about the source and interpretation of data. Both manufacturers submitted Monte Carlo simulation Markov models, but unfortunately some of the models had serious errors. Also, Markov models assume zero memory; how long a patient has been in a health state and how they got there may impact on resources and could be important in a CD patient group. Both the published cost-effectiveness studies and the industry submission models lacked input of long-term clinical data.

Conclusions

Anti-TNF therapy with adalimumab or infliximab may have a beneficial effect compared with standard care on CDAI-related outcome measures for induction and maintenance. Formal comparisons between the two drugs were not possible owing to clinical heterogeneity between trials. Uncertainty remains regarding the size and duration of the effect of the two drugs and over the type of patient that is likely to benefit more or less from treatment. The findings were that for induction, both adalimumab and infliximab are cost-effective (dominant relative to standard care) in the management of severe CD, and adalimumab (but not infliximab) is cost-effective for moderate CD, according to limits generally accepted by NICE. On the basis of the analysis presented here, neither drug is likely to be cost-effective as maintenance therapy for moderate or severe disease. Perhaps, most importantly, the analysis reflected the fact that a substantial number of patients would achieve remission under standard care and that the incidence of relapse among those in remission was such that maintenance therapy would have to show greater effectiveness than at present and/or be much less costly than it currently is in order to reach the levels of generally accepted cost-effectiveness.

Any future trials need to be designed to meet the particular challenges of measuring and quantifying benefit in this patient group. For example, trials should be conducted in the whole eligible CD population and not be limited to 'responders', for whom no particular benefit has been shown. 'Scheduled crossovers' should be avoided as these result in a lack of a true placebo arm, and results become difficult to interpret. The length of trials should also be sufficient to account for natural periods or remission and relapse. Finally, different treatment strategies (e.g. episodic vs scheduled) need to be evaluated in appropriately designed trials.

Funding

The research was funded by the HTA programme on behalf of NICE.

Chapter 1

Background

Description of health problem

Description of Crohn's disease

Inflammatory bowel disease (IBD) refers to a group of chronic intestinal diseases characterised by inflammation of the gastrointestinal mucosa. The most common types of IBD are ulcerative colitis and Crohn's disease (CD). CD can affect any part of the gastrointestinal tract, from mouth to anus, but most commonly the terminal ileum (35%) or the ileocaecal region (40%) are affected.[8]

The main symptoms of CD are dependent on disease location and include chronic or nocturnal diarrhoea, abdominal pain, anal lesions, rectal bleeding and weight loss. Clinical signs include pallor, cachexia, abdominal mass or tenderness, perianal fissures, fistulas or abscesses. Systemic symptoms include malaise, anorexia or fever.[8–10] Extraintestinal symptoms related to intestinal inflammation include spondyloarthritis, cutaneous manifestations or ocular inflammation.[10] In children, growth failure may be the primary manifestation of CD.[11]

CD can be defined using the Vienna classification (see *Disease classification*), i.e. by location, disease behaviour (inflammatory, stricturing, penetrating) and age at diagnosis.[12] Stricturing disease refers to the narrowing of the bowel which can lead to bowel obstruction, while penetrating (or fistulising) disease refers to the creation of abnormal passageways (fistulas) between the bowel and other structures such as the skin. Inflammatory disease (non-stricturing, non-penetrating) causes inflammation without any strictures or fistulas.

Approximately 40%–50% of patients present with ileocolonic disease at the time of diagnosis, approximately 30% have isolated small bowel disease and approximately another 30% have pure colonic disease. It is estimated that only 10%–15% of patients have a change in disease localisation in the 10 years after diagnosis.[13] Disease behaviour at diagnosis is inflammatory (non-stricturing and non-penetrating) in 70% of patients, stricturing in 17% and penetrating (fistulas, abscesses or both) in 13% of patients.[14]

Where the ileum and colon are affected, this is usually complicated by intestinal obstruction, inflammatory mass or abscess. Where disease is limited to the colon, patients commonly present with rectal bleeding, perianal complications and extraintestinal complications involving the skin or joints. Gastric and duodenal manifestations include nausea and vomiting, epigastric pain or gastric outlet obstruction.[15]

Common complications are strictures, fistulas and perianal disease. Fistulas can develop between loops of bowel adjacent to the bladder, vagina or skin. Perianal disease comprises fissures, fistulas and abscesses, and perianal manifestations may precede the onset of bowel symptoms.[8,15] Symptomatic perianal disease requiring therapy occurs in around 35% of CD patients.[16] CD may also be complicated by sequelae related to malabsorption such as anaemia or metabolic bone disease.[15] Rare complications include acute dilatation, perforation and massive haemorrhage, especially when the disease affects the colon.

CD is characterised by recurring flares alternating with periods of remission. Most patients take medication for a large period of their life because if they stop they might experience a disease flare, but some drugs are tapered off during periods of remission, then if a patient experiences a flare he or she then returns to therapy.[13]

Aetiology

The aetiology of CD remains unknown. It is generally accepted that the disease is a response to environmental triggers (infection, drugs or other agents) in genetically susceptible individuals.[9] Smoking has been shown to be a risk factor in CD, with suggestions that smokers are more than twice as likely to develop the disease.[17] Areas under investigation to identify pathogenic mechanisms include epidemiology (e.g. diet, drugs, water supply), the gut–environmental interface (e.g. work on luminal bacteria), the inflammatory process (e.g. cell signalling pathways) and genetics (e.g. studies on gene expression).[9] Exacerbating factors include intercurrent infections, smoking and the use of non-steroidal anti-inflammatory drugs, while the issue of stress initiating or exacerbating CD remains controversial.[15]

Diagnosis

Recent efforts have focused on discovery of biomarkers that may eventually lead to the development of specific diagnostic tests for CD,[18] but as yet no definitive diagnostic test exists for CD. Overlapping features with other IBDs, a potentially insidious onset, and the heterogeneity of manifestations and/or presentation without gastrointestinal symptoms can make diagnosis difficult.[15] Diseases with symptoms in common with CD include infectious diarrhoea, small bowel lymphoma, ulcerative colitis, appendicitis, coeliac disease and irritable bowel syndrome. A detailed clinical history, a physical examination, laboratory tests and endoscopic evaluation are necessary to make an accurate diagnosis. A diagnosis of IBD should be contemplated in patients presenting with chronic (bloody or non-bloody) diarrhoea, particularly nocturnal diarrhoea and/or weight loss, abdominal pain, fever or extraintestinal manifestations. Family history of the disease should be considered. Signs of volume depletion, ulceration of the oral mucosa, perianal lesions or abdominal tenderness may be observed on physical examination. Laboratory tests should rule out infection and look for markers of IBD such as low serum albumin level or vitamin B_{12} deficiency. Imaging studies of the bowel may be helpful; abdominal radiography may reveal mucosal oedema or dilated loops of small bowel or colon consistent with either inflammation or obstruction. On endoscopy, CD is characterised by deep, linear ulcerations that can occur as segmental areas of mucosal involvement separated by areas of normal intervening mucosa ('skip lesions'). Biopsy findings usually demonstrate transmural inflammation.[19]

CD may be unsuspected and incorrectly diagnosed in the elderly, with as many as 60% of patients being misdiagnosed initially compared with a misdiagnosis rate of only 15% in younger people. The delay in diagnosis has been calculated as 6.4 years after onset of symptoms in older patients compared with 2.4 years in younger individuals.[20]

Disease classification

CD is a heterogeneous condition with a variety of clinical manifestations and presentations. The 'Vienna classification' introduced a schema to categorise the disease according to three important elements: age at diagnosis (A), location of the disease (L) and disease behaviour (B). The Vienna classification, summarised in *Table 1*, was revised in 2005 and this modified version, termed the Montreal classification,[21] expanded the number of categories within each of the three elements as shown in *Table 1*.

The categorisation of CD using these classification systems has allowed descriptions of the progression/natural history of the disease and raised the possibility of identifying genes or environmental factors (including treatments) that may be associated with particular features of

TABLE 1 Vienna and Montreal classificatory schema for CD

Classification element	Vienna	Montreal	
AGE at diagnosis (years) (A)	A1 < 40	A1 < 16	
	A2 > 40	A2 17–40	
		A3 > 40	
LOCATION of disease (L)	L1 Terminal ileum	L1 Terminal ileum	L1 + L4 Terminal ileum + upper GI
	L2 Colon	L2 Colon	L2 + L4 Colon + upper GI
	L3 Ileocolon	L3 Ileocolon	L3 + L4 Ileocolon + upper GI
	L4 Upper GI	L4 Upper GI	
BEHAVIOUR of disease (B)	B1 Non-stricturing non-penetrating	B1 Non-stricturing non-penetrating	B1p Non-stricturing non-penetrating + perianal
	B2 Stricturing	B2 Stricturing	B2p Stricturing + perianal
	B3 Penetrating	B3 Penetrating	B3p Penetrating + perianal

GI, gastrointestinal.

the disease or with the rapidity of progression from one category to another. For example, using the Vienna classification and retrospective analysis of case notes for a cohort of 290 patients with up to 25 years of follow-up, Louis *et al.*[22] found that location of disease was relatively stable with only 15.9% of patients exhibiting a change over a decade while disease behaviour was more labile, changing for 45.9% of patients in a decade. Similarly Cosnes *et al.*[23] reported that over 20 years most patients progressed to penetrating or stricturing disease, that initial location of disease was a determinant of disease behaviour, and that year-by-year disease activity was poorly influenced by previous behaviour of the CD.

Natural history

The disease location of CD is fairly stable; however, the behaviour of the disease can vary substantially during its course. The disease changes from non-stricturing to either stricturing (in 27% of patients) or penetrating disease (in 29% of patients).[14] After the first year of diagnosis, 10%–30% of patients have an exacerbation, 15%–25% have low activity and 55%–65% are in remission; 13%–20% have a chronic active course of disease activity, 67%–73% have a chronic intermittent course and only 10%–13% remain in remission for several years.[14] Most patients with CD will require surgery within 20 years.[14] The lifetime risk for developing fistulas has been reported to be between 20% and 40%. Perianal fistulas are most common, followed by entero-enteric, with many patients developing a fistula at or before diagnosis of CD.[24] CD is associated with an increased risk of colonic carcinoma and the overall mortality is slightly higher than that of the overall population.[9]

A Danish study[25] of an inception cohort of 373 CD patients found the following disease activity distributions: 80% of patients had high activity at diagnosis, decreasing to an almost stable value of 30% in the following 25 years; a constant 15% of patients overall had low activity; and around 55% could expect to be in remission each year. Individual patients however changed from year to year between relapse and remission. The study further found that over a 10-year period 20%–30% of patients could expect to go into remission each year. There was a slight indication of the disease 'burning out', as late in the disease course (more than 15 years post diagnosis) slightly more patients (29%) changed from activity to remission than the 14% who changed from remission to activity. A separate analysis of 171 patients followed for at least 7 years after diagnosis found that, between years 3 and 7, 25% of patients had active disease every year, 22% were in remission and 53% changed between years in remission and years with relapse.[25] This disease course was independent of initial treatment, age, sex, localisation and symptoms

at diagnosis or time from onset to diagnosis. With regard to hospital admissions, 83% were admitted during the year of diagnosis; this decreased during the following 5 years to a constant 20% each year.

A US modelling study[26] examined a retrospective cohort and estimated a future life expectancy of 46.4 years for a representative CD patient aged 28.1 years at the time of diagnosis. The projected clinical course consisted of 11.1 years in remission (with no medication), 0.51 years of requiring surgery, 18.9 years in post-surgery remission (no medication), 12.7 years of receiving aminosalicylate or a similar medication, and disease severe enough to require corticosteroids or immunosuppressives lasted 3.2 years. This was based on a sample of 174 patients and on treatment practices used between 1970 and 1993, which may have changed over the course of the study.

A Norwegian study[12] which followed up 221 CD patients prospectively for 5 years found that during the observation period 28% had undergone surgery. At the time of the 5-year visit 54% used sulfasalazine and 5-aminosalicylic acid, 25% used oral glucocorticosteroids and 13% used azathioprine. There were 16% who had symptoms that interfered with everyday activities and 72% had taken oral glucocorticosteroids at some point during the 5 years.

These cohort studies and the models based on them indicate that the clinical course estimates will vary depending on a variety of characteristics of the patients within the cohort.

Incidence and prevalence

CD can occur at any age, but manifests itself mainly during late adolescence or early adulthood. Peak onset is between 15 and 30 years of age.[27,28] The incidence in younger years is higher in women than in men.[27,29] There is some inconsistency regarding differences in prevalence between women and men overall, with some studies finding a higher prevalence in women, and some finding no difference.[29] There is an increased prevalence among first- and second-degree relatives, suggesting the involvement of genetic factors.[28] CD may also present later in life (sixth and seventh decades) when there tends to be more colonic involvement and disease manifestations may be less severe.[20]

The extent of CD varies across the world and is most common in developed countries, with the UK having one of the highest rates. It was previously thought that IBD occurred less frequently among ethnic minorities. However, studies of migrant populations have shown that ethnic and racial differences are more likely to be attributable to lifestyle and environmental influences than true genetic differences. Similar rates of IBD have been found in African-Caribbean and white children and adults in the UK.[17] No association between CD and social class was found in a UK prevalence study; it has been suggested that this is attributable to exposure to risk factors becoming more similar across social classes.[29]

In regions with a high prevalence of CD, the incidence increased between the 1950s and 1980s, and stabilised after that, which can be explained by an increased availability of gastroenterology units and increased awareness of the disease.[28,30] Some studies suggest that there is still an upward trend, which may be due to continued variations in environmental risk factors.[29] Increases in less developed countries have recently been noted, and it has been suggested that this is a result of changes in lifestyle (e.g. more exposure to smoking, changes in diet).[28]

Table 2 shows the incidence and prevalence of CD in the UK, taken from studies published from 2000 onwards. The incidence ranges from 3.8 to 10 per 100,000 per year and the prevalence ranges from 50 to 375 per 100,000. For children, the British Paediatric Surveillance Unit found an estimated incidence of 5.3 per 100,000 per year.[11] Differences in incidence and prevalence

estimates may result from the way data are gathered, changes in disease awareness and diagnosis over time, or changes in disease risk factors. There is no national CD database that could be used to determine numbers of CD patients.

Impact of health problem

Significance for patients in terms of ill health

The impact on patients and society is high, as patients are often diagnosed at a young age and ill health may be lifelong. Medical treatments can cause secondary health problems and surgery can result in complications such as impotence or intestinal failure. Patients can find symptoms embarrassing and humiliating, and may have difficulties in gaining employment or insurance. Younger people in particular may have psychological problems and growth failure or retarded sexual development. Approximately 75% of patients are fully capable of work 1 year after diagnosis and 15% of patients are unable to work after 5–10 years of disease.[9] Similarly, a Danish study[25] found that, except for the year of diagnosis, 75%–80% of patients were fully capable of work each year, 9%–16% were incapable and 9%–11% only partly capable; after 15 years, 15% of patients obtained a disablement pension. The National Association of Colitis and Crohn's Disease (NACC) website[35] states that most sufferers can be maintained in remission for most of the time and are able to lead a full working life; however, some with severe disease do not achieve their educational and career potential.

Information sheets produced by the NACC[35] relating to the most frequently asked questions to the NACC helpline cover the following issues: difficulties finding insurance companies that

TABLE 2 Incidence and prevalence of CD in the UK

Study	Population/sample	Incidence CD (adults)	Prevalence CD (adults)
Carter *et al.*, 2004[9]	Review by the British Society of Gastroenterology (based on several studies, no details on sample size)	5–10/100,000 per year	50–100/100,000
Ehlin *et al.*, 2003[29]	The 1970 British Cohort study and the 1958 National Child Development Study (1-week national birth cohorts); total sample population of 22,680 (70% of target population)	NR	1970 cohort at age 30 years: 375/100,000 (95% CI 262 to 488) 1958 cohort at age 30 years: 211/100,000 (95% CI 127 to 295) 1958 cohort at age 42 years: 325/100,000 (95% CI 221 to 430)
Rubin *et al.*, 2000[30]	Systematic search of GP records in North England (based on a population of 135,723)	8.3/100,000 per year (95% CI 7.5 to 20.3)	144.8/100,000 (95% CI 124.8 to 168.8)
NACC[31]	UK (no details on sample)	5–10/100,000 per year	100/100,000
Shivananda *et al.*, 1996[32]	Multicentre study of 20 centres across Europe during 1991–3, one of these in Leicester (total sample size unclear)	Non-immigrants: 3.8/100,000 per year (95% CI 0.7 to 6.9) Immigrants: 5.6/100,000 per year (95% CI 0.0 to 12.5) All aged 15–64 years	NR
Stone *et al.*, 2003[33]	Fifteen general practices recruited through the Trent Focus Collaborative Research Network, UK (based on a population of 86,801)	NR	130/100,000 (95% CI 107 to 157)
Yapp *et al.*, 2000[34]	Information from clinical records, the department of pathology database and a questionnaire sent to local family practitioners in the city of Cardiff (total sample size unclear)	5.6/100,000 per year (95% CI 4.4 to 6.8)	NR

CI, confidence interval; NACC, National Association for Colitis and Crohn's Disease; NR, not reported.

will provide life cover, mortgage protection, or travel, critical illness or health insurance (when offered, insurance can be more expensive than if they did not have CD); managing bloating and wind; managing diarrhoea; concerns for young people (particularly focusing on emotional aspects such as embarrassment, body image, anxiety); and supporting someone with CD.

A prospective cohort study[36] of health-related quality of life (HRQoL) in 231 patients with CD found that patients' main worries (in decreasing order of magnitude of concern) related to 'having an ostomy bag', 'uncertain nature of disease', 'energy level', 'having surgery', 'pain and suffering', 'eating normally', 'feelings about my body' and 'effects of medication'. Other concerns related to loss of bowel control, career/finances, sexual relationships, body/self-image, being a burden to others, developing cancer or dying early. Quality of life (QoL), as measured in this study by the Short Form (36) Health Survey questionnaire (SF-36), was lower for CD patients than for the general population (the SF-36 measures various aspects of physical and mental functioning). Factors having a negative impact on QoL were active disease, hospitalisation, receiving steroids, having colonic disease and surgery.

A discussion with a patient representative, who has also worked for the NACC helpline, highlighted the following issues of particular concern to patients who contact the helpline (Denise Cann, NACC, 2007, personal communication):

- difficulty in coping with unpredictability of disease (particularly where patients have been in remission) and a lack of control over it
- difficulty in gaining employment or staying employed
- difficulty in finding insurance
- impact on family and social life
- impact on relationships, sexual activity and pregnancy
- embarrassing nature of disease, e.g. flatulence, need to frequently use toilets because of diarrhoea, incontinence
- distressing symptoms such as rectovaginal fistulas where faeces can be passed through the vagina
- coping with the general tiredness, malaise and lack of energy
- coping with side effects of treatments
- fear that (new) treatment may not work
- coping with depression
- difficulty particularly for children and teenagers to cope emotionally
- costs: drug and continence prescription charges, cost of many sets of clothing/linen, trips to hospital, loss of earnings.

Significance for NHS

A UK study from 2004[37] calculated the cost of CD. The setting was an NHS university hospital with a target population of around 330,000. *Table 3* lists the costs for different patient groups.

Costs comprised all secondary care costs, including drugs, tests (e.g. endoscopy, laboratory tests), in- and outpatient services and surgery. Cost estimates also included all associated costs such as staff salaries, pharmacy services and other miscellaneous costs. Costs did not include visits to a GP, but these were estimated separately and amounted to < £30 per patient per 6 months. The median number of days lost from household and recreational activities in 6 months were 20 [interquartile range (IQR) 9–60]. Fifty per cent of employed patients had some loss of employment days, with a median loss of earnings of £299 (IQR £119–597). Mean out-of-pocket expenses were £66 (range £0–750) and included travel and over-the-counter medication. No patient in this cohort received infliximab or another tumour necrosis factor (TNF) inhibitor (anti-TNF-α antibody).

TABLE 3 Cost of CD

Patient group	Mean cost for 6 months[a]
All CD patients (with complete 6-month follow-up 'prevalent' cases)	£1652 (95% CI £1221 to £2239)
Ambulatory group	£516 (95% CI £452 to £618)
Patients hospitalised during study period	£6923 (95% CI £5415 to £8919)[b]
Quiescent disease	£275 (95% CI £235 to £319)
Ambulatory patients suffering disease exacerbation ('flare')	£578 (95% CI £431 to £701)
Hospitalised patients	£5444 (95% CI £3894 to £9242)[b]
New 'incident' cases	£2662 (95% CI £1006 to £5866)

a To include costs of primary care visits, add approximately £30 per patient per 6 months.
b We were unable to resolve the discrepancy between these two figures; a reply from the author was not received.

The contribution of different items and services to the overall cost of CD in all patients was as follows (estimated from Figure 1 in Bassi *et al.*[37]): 37% surgery, 24% inpatient costs, 11% outpatient costs, 11% tests (laboratory tests, X-ray, endoscopy) and 17% drugs.

Six-month resource use in ambulatory and hospitalised CD patients is shown in *Table 4* (adapted from Table 2 in Bassi *et al.*[37]). There were a total of 260 bed-days for CD within the 6-month period, 196 surgical bed-days and 12 days of intensive care bed occupancy.

Measurement of disease severity in adults

Working definitions of disease severity have been developed by the Practice Parameters Committee of the American College of Gastroenterology,[10] and are:

- Mild–moderate disease:
  Mild-moderate Crohn's disease applies to ambulatory patients able to tolerate oral alimentation without manifestations of dehydration, toxicity (high fevers, rigors, prostration), abdominal tenderness, painful mass, obstruction, or > 10% weight loss.

- Moderate–severe disease:
  Moderate–severe disease applies to patients who have failed to respond to treatment for mild–moderate disease or those with more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anaemia.

- Severe–fulminant disease:
  Severe–fulminant disease refers to patients with persisting symptoms despite the introduction of steroids as outpatients, or individuals presenting with high fever, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess.

- Remission:
  Remission refers to patients who are asymptomatic or without inflammatory sequelae and includes patients who have responded to acute medical intervention or have undergone surgical resection without gross evidence of residual disease. Patients requiring steroids to maintain well-being are considered to be 'steroid dependent' and are usually not considered to be 'in remission'.

TABLE 4 Resource use in hospitalised and ambulatory CD patients

Parameter (per 6 months)	Ambulatory CD patients ($n=130$) Mean (range)	Hospitalised CD patients ($n=28$) Mean (range)
Outpatient services (visits)		
IBD related	2.2 (0–7)	2.9 (0–8)
Extraintestinal	1.25 (1–3)	–
Dietitian	0.07 (0–3)	0.1 (0–1)
Stoma nurse	–	0.03 (0–1)
Laboratory tests[a]	7.6 (0–28)	35.3 (9–66)
Radiology		
Plain X-ray	0.07 (0–1)	1.4 (0–4)
Barium enema	0.01 (0–1)	0.07 (0–1)
Barium follow-through	0.1 (0–1)	0.30 (0–2)
Ultrasound abdomen	0.02 (0–1)	0.18 (0–1)
CT abdomen/pelvis	0.01 (0–1)	0.01 (0–1)
MRI abdomen/pelvis	–	0.07 (0–1)
White blood cell scan	0.01 (0–1)	0.07 (0–1)
DEXA scan	0.07 (0–1)	–
Fistulogram	0.01 (0–1)	–
Endoscopy		
OGD	0.15 (0–1)	0.11 (0–1)
Sigmoidoscopy	0.05 (0–2)	0.18 (0–1)
Colonoscopy	0.1 (0–1)	0.3 (0–3)
Hospital admission	NA	
Number of admissions	–	1.1 (1–2)
Length of each admission (days)	–	14 (4–40)

CT, computerised tomography; DEXA, dual energy X-ray absorptiometry (for measuring bone density); MRI, magnetic resonance imaging; NA, not applicable; OGD, oesophagogastroduodenoscopy.
a Haematology, biochemistry and microbiology.

The severity of CD is difficult to assess, and a global measure encompassing clinical, endoscopic, biochemical and pathological features is not available.[38] The most widely used disease activity measures include the Crohn's Disease Activity Index (CDAI), the Harvey–Bradshaw Index (HBI) or Simple Index, a simplified version of the CDAI, and the Perianal Disease Activity Index (PDAI). A commonly used HRQoL measure is the Inflammatory Bowel Disease Questionnaire (IBDQ). Other measures include the Crohn's Disease Endoscopic Index of Severity (CDEIS).

The CDAI was developed in the 1970s as there was a need for a single index to assess disease severity. Variables measured include number of liquid stools, abdominal pain, general well-being, extraintestinal complications, use of antidiarrhoeal drugs, abdominal mass, haematocrit and body weight. Scores range from 0 to approximately 600, with higher scores corresponding to more severe disease (see *Appendix 1* for full description of the index and the scoring system used). Values of below 150 are suggestive of quiescent disease (remission) and values above 450 are associated with very severe disease.[39] Severe disease is thought to be above 300. Some investigators, however, have arbitrarily labelled CDAI scores of 150–219 as mildly active disease and scores of 220–450 as moderately active disease.[38]

The CDAI has been criticised for having limitations. It does not cover aspects of QoL, such as psychological, social, sexual and occupational functioning. A patient with a low CDAI score may still be severely limited by the disease in those areas.[40] Substantial variability exists when different observers review the same case histories and calculate the CDAI score, although this can be reduced after discussion and education about the terminology. The calculation is based in part on a daily diary kept by the patient for 7 days before the evaluation. In practice, some investigators and study co-ordinators assist the patient to retrospectively complete the diary at the time of an evaluation visit; there is no information on the prevalence of this practice. The CDAI score may be low in patients whose primary symptom is drainage of enterocutaneous fistulas, presumably because the presence of an actively draining fistula contributes only 20 points to the score. The CDAI is therefore not an appropriate instrument for assessing the activity of draining abdominal or perianal enterocutaneous fistulas. The CDAI has been criticised for giving too much weight to 'general well-being' and 'intensity of abdominal pain', as these are relatively subjective items. However, these aspects of disease are important to patients.[41]

Clinical studies have variously defined a clinical response as a decrease in CDAI of 50, 60, 70 or 100 points. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) suggested in 2000 that a clinically meaningful decrease in the CDAI score is a decrease of 100 points.[41]

The HBI is a modified/simplified version of the adult CDAI. It uses a single day's reading for diary entries and excludes three variables (body weight, haematocrit and use of drugs for diarrhoea). Code values are added together rather than summing the products of code values and coefficients (see *Appendix 1*). Scores range from 0 to 20, with higher scores corresponding to worse disease. The CDAI can be predicted reasonably well from the HBI.[42] Other instruments derived from the CDAI are: the Cape Town Index, which includes parameters on subjective symptoms, physician clinical findings and laboratory data; the three-variable version of the CDAI used for survey research; and the van Hees Index, which includes laboratory parameters, sex (male or female) and seven clinical features and excludes subjective, patient-related items such as well-being and pain.[40]

The PDAI was developed to account for the morbidity and impairment of QoL of patients with perianal disease, and to evaluate the effectiveness of perianal disease treatment. Variables include discharge, pain/restriction of activities, restriction of sexual activity, type of perianal disease (including number of fistulas) and degree of induration. Scores range from 0 to 20.[16]

The reliance on traditional disease activity measures (such as the CDAI) to measure treatment effectiveness fails to take into account the impaired QoL experienced by CD patients. The IBDQ is an HRQoL measure. It is a 32-item questionnaire and evaluates general activities of daily living, intestinal function, social performance, personal interactions and emotional status. Four-dimensional scores cluster items under bowel function, emotional function, systemic function and social function. Scores range from 32 to 224.[43]

The CDEIS was developed to take into account endoscopic data, such as lesion severity, when assessing severity of the disease. Variables include the presence or absence of deep or superficial ulceration in various segments of the intestinal tract, the surface involved (in cm), the surface ulcerated (in cm) and presence of ulcerated stenosis. Scores range from 0 to 30.[44]

Measurement of disease severity in children

The paediatric CDAI is a multi-item measure of severity that includes linear growth and places less emphasis on subjectively reported symptoms and more on laboratory parameters of intestinal inflammation than the adult CDAI. It includes 11 variables: weight, height, abdominal

mass, perirectal disease, extraintestinal manifestation, haematocrit, erythrocyte sedimentation rate, albumin, abdominal pain, number of liquid stools and general well-being. Scores range from 0 to 100: ≤10 indicates inactive disease, 11–30 mild disease and >30 moderate-to-severe disease.[45,46]

Current service provision

CD treatment includes nutrition, drugs and surgery. Nutrition includes complete elemental diets and nutritional supplements. Drug treatments can include aminosalicylates (mesalazine and sulfasalazine) and corticosteroids (prednisolone, budesonide, intravenous (i.v.) hydrocortisone and methylprednisolone). Licensed drugs are being used in unlicensed indications for chronically active CD, including immunomodulators (azathioprine, mercaptopurine and methotrexate) and the antibiotic metronidazole.[47] Cytokine modulators (also known as biologics) such as adalimumab and infliximab are licensed for severe active CD. Use of infliximab is subject to the National Institute for Health and Clinical Excellence (NICE) guidance (see below). Adalimumab is discussed in the next section (see *Description of technology under assessment*). Surgery is not curative and is used to manage symptoms. In patients with fistulas, treatment can include use of setons (devices to keep fistulas open and allow drainage) and surgery. At least 50% of CD patients require surgical treatment in the first 10 years of disease and around 70%–80% require surgery within their lifetime.[9]

The NICE guidance on the current use of infliximab in CD is as follows (Technology Appraisal Guidance No. 40):[1]

> 1.1. Infliximab is recommended for the treatment of patients with severe Crohn's disease who fulfil all three of the following criteria:
>
> - Patients who have severe active Crohn's disease. These patients will already be in very poor general health with weight loss and sometimes fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. They may or may not be developing new fistulas or have extra-intestinal manifestations of the disease. This clinical definition normally corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more and a Harvey–Bradshaw Index of 8/9 or above.
> - Patients whose condition has proved to be refractory to treatment with immuno-modulating drugs (e.g. azathioprine or 6-mercaptopurine, methotrexate) and corticosteroids, or who have been intolerant of, or experienced toxicity from, these treatments.
> - Patients for whom surgery is inappropriate (e.g. because of diffuse disease and/or a risk of short bowel syndrome).
>
> 1.2. Treatment can be repeated for those patients who match the above criteria and have responded to the initial treatment course, but then relapsed. A decision about whether or not to re-administer infliximab after the first course or subsequently should be made only after discussion with the patient who has been fully informed of the potential risks and benefits of repeated therapy (episodic treatment).
>
> 1.3. Infliximab should be prescribed by a gastroenterologist experienced in the management of Crohn's disease.
>
> 1.4. Infliximab is not recommended for patients with fistulising Crohn's disease who do not have the other criteria for severe active Crohn's disease as detailed in section 1.1.

For current conventional treatment, the recommendations below are taken from the UK guidelines for the management of IBD in adults from 2004[9] (see *Appendix 2* for full details on medical management of CD). In this guideline, treatment options are complex and depend on the severity of disease, whether first-line treatments have failed, side effects, stage/type of disease (active, in remission, chronic, fistulising). Also, some treatment may be adjunctive.

For patients with active, ileal/ileocolonic/colonic disease, options include aminosalicylates (e.g. mesalazine), corticosteroids (e.g. prednisolone), antibiotics (e.g. metronidazole), immunosuppressants (e.g. azathioprine), nutritional therapy and surgery. Patients with fistulising and perianal disease can be treated with antibiotics or immunosuppressants; infliximab where CD is severe and active, and fistulas are refractory to other treatment; nutritional therapy; and surgery.

The efficacy of treatment for maintenance of remission depends on how remission was achieved (medically or surgically), on risk of relapse and on the site of disease. In addition to smoking cessation (one of the most important factors in maintaining remission), aminosalicylates, immunosuppressants or antimetabolites (e.g. methotrexate) can be used. Infliximab can be used for up to 44 weeks as part of a treatment strategy including immunomodulation. Corticosteroids are not effective for the maintenance of remission, although some patients appear steroid dependent. Immunomodulation should be tried as first-line treatment in steroid-dependent patients; infliximab should be reserved for patients with moderate-to-severe CD who are refractory or intolerant of treatment with steroids, mesalazine, azathioprine/mercaptopurine and methotrexate, and where surgery is considered inappropriate. It has been estimated that around 2% of patients have severe, drug-refractory disease, but this is based on a Markov model rather than on cohort data.[48]

In children, enteral nutrition is used as primary therapy for active CD by the majority of paediatric gastroenterologists in the UK.[11]

An audit[49] carried out in collaboration between the British Society of Gastroenterology, the Royal College of Physicians, the Association of Coloproctology of Great Britain and Ireland and the NACC found marked variation in the resources and quality of care: They found that:

- 44% of sites did not have an IBD nurse specialist
- there was poor provision of dietetic services
- there was a lack of adequate toilet provision in hospitals
- fewer than one-fifth of hospitals were able to refer patients directly for psychological support
- 42% of patients with IBD had a stool sample sent for culture
- 52% of CD patients were weighed
- 37% of CD patients seen by a dietitian
- many patients with CD were receiving inappropriately prolonged course of steroids
- there was inadequate prophylactic bone protection therapy for patients on systemic steroids and inadequate screening for osteoporosis
- there was infrequent participation in clinical research into IBD in the UK.

Description of technology under assessment

Adalimumab and infliximab are TNF inhibitors (anti-TNF-α antibodies). TNF-α is a cytokine, a small protein molecule acting as a cell messenger and involved in inflammatory conditions. It is a key mediator of the inflammation associated with CD and can be detected in diseased areas of the bowel wall, and in blood and faeces of patients with the disease.[50] Both adalimumab and infliximab are manufactured antibodies that bind to and inhibit TNF-α

thus reducing the inflammatory response. They belong to the pharmacotherapeutic group of selective immunosuppressive agents.[51] The term 'biologics' is also applied to these drugs as their production depends on cells that have been genetically engineered to produce a specific protein.

Adalimumab (Humira®, Abbott Laboratories, Abbott Park, IL, USA) is a recombinant, fully human monoclonal antibody expressed in Chinese hamster ovary cells. It binds specifically to TNF and neutralises its biological function. Adalimumab is available as Humira 40 mg solution; each 0.8-ml single-dose vial contains 40 mg of adalimumab. It is administered by subcutaneous injection. Treatment with adalimumab should be initiated and supervised by specialist physicians experienced in the treatment of CD. After training, patients may self-inject with adalimumab, with medical follow-up as necessary. Adalimumab is also licensed for use in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.[52]

The licence indication for CD detailed in the *Summary of Product Characteristics* (SPC)[52] is as follows:

> Humira is indicated for treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. For induction treatment, Humira should be given in combination with cortiocosteroids. Humira can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate.
>
> The recommended Humira induction dose regimen for adult patients with severe Crohn's disease is 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at week 2, can be used with the awareness that the risk for adverse events is higher during induction.
>
> After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped Humira and signs and symptoms of disease recur, Humira may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response may benefit from an increase in dose intensity to 40 mg Humira every week.

Infliximab [Remicade®, Schering-Plough (formerly Schering-Plough Ltd., since 2009 Merck & Co., Kenilworth, NJ, USA)] is a chimaeric human–murine monoclonal antibody manufactured from a recombinant cell line. It binds with high affinity to soluble and transmembrane forms of TNF thus inhibiting the functional activity of TNF. Infliximab is available as Remicade 100 mg powder for concentrate for solution for infusion; each vial contains 100 mg of infliximab. Treatment with infliximab should be initiated and supervised by specialist physicians experienced in the treatment of CD. Infliximab is administered intravenously over a 2-hour period. Infusions should be administered by qualified health-care professionals trained to detect infusion-related issues; patients should be observed for at least 1–2 hours post infusion for acute infusion-related reactions, and emergency equipment (such as adrenaline) must be available. Patients may be pre-treated in order to avoid infusion-related reaction, particularly where these have occurred previously. Infliximab is also licensed for use in rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

The licence indication for CD detailed in the SPC[53] is as follows:

> Adult Crohn's disease: Remicade is indicated for:
>
> - treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies
> - treatment of fistulising, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).
>
> Paediatric Crohn's disease:
>
> Treatment of severe, active Crohn's disease, in paediatric patients aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Remicade has been studied only in combination with conventional immunosuppressive therapy.
>
> Severe, active Crohn's disease:
>
> 5 mg/kg given as an intravenous infusion over a 2-hour period. Available data do not support further infliximab treatment, in patients not responding within 2 weeks to the initial infusion. In responding patients, the alternative strategies for continued treatment are:
>
> - maintenance: additional infusions of 5 mg/kg at 2 and 6 weeks after the initial dose, followed by infusions every 8 weeks or
> - readministration: infusion of 5 mg/kg if signs and symptoms of the disease recur.
>
> Fistulising, active Crohn's disease:
>
> An initial 5 mg/kg infusion given over a 2-hour period is to be followed with additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion. If a patient does not respond after these three doses, no additional treatment with infliximab should be given.
>
> In responding patients, the strategies for continued treatment are:
>
> - additional infusions of 5 mg/kg every 8 weeks or
> - readministration if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks.
>
> In Crohn's disease, experience with readministration if signs and symptoms of disease recur is limited and comparative data on the benefit/risk of the alternative strategies for continued treatment are lacking.
>
> Crohn's disease (6 to 17 years):
>
> 5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient. Available data do not

support further infliximab treatment in paediatric patients not responding within the first 10 weeks of treatment.

As outlined in the licence indications, patients eligible for treatment with anti-TNF therapy are adults or children with *severe*, active (or fistulising CD) who have not responded to and/or are intolerant to conventional treatment. There is no standard definition for what constitutes *severe* CD. NICE guidance defines *severe* as a score of > 300 on the CDAI or 8–9 on the HBI.[1] The group that developed the CDAI defines values of 150 and below as *quiescent* disease and values above 450 as *extremely severe* disease; no intermediate cut-off point is given for *severe* disease.[39] The NICE scope for the current appraisal states that the population of interest consists of patients with *moderate-to-severe* CD; there is no standard definition of what constitutes *moderate-to-severe.* Trials have described patients with a CDAI of 220–400 (or 450) as having moderate-to-severe CD.[57]

Adverse events with anti-TNF treatment

A number of adverse events (AEs) have been associated with anti-TNF therapy and have been reported for infliximab and adalimumab. As the immune response is suppressed, infections may be more likely to occur. These include tuberculosis, other bacterial infections including sepsis and pneumonia, fungal infections and opportunistic infections such as pneumocystosis or cytomegalovirus infection. Cases of reactivation of hepatitis B infection have been observed, as have rare cases of jaundice and hepatitis, optic neuritis and onset or exacerbation of demyelinating disorders including multiple sclerosis. A deficiency of TNF may result in the initiation of an autoimmune process, and the occurrence of lupus-like syndrome has been observed. There is the possibility of an increased risk of lymphoma or other malignancies, worsening of heart failure or of AEs of the haematological system (e.g. cytopenias). Infliximab has been associated with acute, infusion-related reactions (including anaphylactic shock) and delayed hypersensitivity reactions. Injection site reactions are common with adalimumab. Common AEs for both infliximab and adalimumab are upper respiratory infections (such as sinus infections), headache, rash, nausea and stomach pains. The development of anti-TNF antibodies may be associated with a decrease in efficacy and predispose the patient to an additional risk of recurrent delayed or acute allergic reactions.[52–56]

This report will consider the following patient groups (where information is available): adults with moderate-to-severe active CD intolerant or resistant to conventional treatment; children with moderate-to-severe active CD intolerant or resistant to conventional treatment; and adults with fistulising CD intolerant or resistant to conventional treatment. Where possible, patients with severe (rather than moderate-to-severe) CD will be considered as this is in line with the licence indication.

Degree of diffusion

There is no up-to-date evidence available on the degree of diffusion of adalimumab and infliximab for CD treatment in the UK. The only evidence that is available from routinely collected data is for the total number of adalimumab and infliximab prescriptions for all conditions.

Chapter 2

Definition of the decision problem

The main aims of the report were:

- To update a previous Technology Assessment Report (TAR)[5] on the effectiveness and cost-effectiveness of infliximab in adults with moderate-to-severe CD or fistulising CD who are refractory to or intolerant of conventional treatment.
- To review the evidence on the clinical effectiveness and cost-effectiveness of infliximab in children with moderate-to-severe CD who are refractory to or intolerant of conventional treatment.
- To review the evidence on the clinical effectiveness and cost-effectiveness of a further anti-TNF-α antibody, adalimumab, in adults with moderate-to-severe CD who are refractory to or intolerant of conventional treatment.
- To investigate whether there is evidence for greater clinical effectiveness or cost-effectiveness for either adalimumab or infliximab.

Decision problem

Interventions

Adalimumab and infliximab are drugs for use in patients with severe active CD or fistulising active CD (infliximab) who have not responded to conventional treatment or who have experienced toxicity from these treatments. There has been a distinction made between induction treatment and maintenance treatment, but it is unclear where the boundary lies between these for the interventional drugs. Similarly there has been a distinction between 'episodic' treatment, i.e. treatment when a disease flare starts (or at a clinician's discretion), and maintenance treatment, where patients are treated at regular (scheduled) intervals with the intention of keeping them in remission, but it is unclear where the boundary lies between these treatment strategies. It would be useful to know the most effective dosing regimen for each of the drugs.

Comparators

Conventional treatment includes no treatment, dietary intervention, drug treatment with aminosalicylates, methotrexate, corticosteroids (prednisolone, budesonide and hydrocortisone), azathioprine or metronidazole or surgical intervention.

Given that licences for both drugs are for use only when conventional treatment has failed, it is unlikely that randomised controlled trials (RCTs) would compare the drugs to conventional treatment. Instead, the most likely comparator will be no treatment or placebo, but where patients in all trial arms continue to receive elements of conventional therapy. Another relevant comparator may be a different dosing regimen of the same drug.

For comparisons between both drugs under review, head-to-head comparisons within the same trial would be the ideal scenario. It is important to note that, because of earlier licensing, infliximab could be viewed either as the intervention of interest in some of the RCTs or as part of conventional treatment in others. It would also be useful to establish the effectiveness of both drugs compared with non-drug treatments such as surgery or nutrition, particularly in children.

Population and relevant subgroups

Infliximab is licensed for use in adults and children with *severe* active CD or in adults with fistulising disease who are intolerant or resistant to treatment. Adalimumab is licensed for *severe* active CD; current information does not indicate whether this is in adults only.

There is no standard definition for what constitutes *severe* CD. NICE guidance defines *severe* as a score of > 300 on the CDAI or 8–9 on the HBI.[1] The group that developed the CDAI defines values of ≤ 150 as quiescent disease and values > 450 as extremely severe disease; no intermediate cut-off point is given for *severe* disease.[39]

The NICE scope for the current appraisal stated that the population of interest consists of patients with '*moderate-to-severe*' CD. There is no standard definition of what constitutes '*moderate-to-severe*', but RCTs have described patients with a CDAI of 220–400 as having moderate-to-severe CD.[57] Note that this assessment report is therefore investigating treatments outside their licence indications. The main thrust of the work should be to investigate the clinical effectiveness of treatments in patients with a CDAI score of 300 or more. However, it is unlikely that any RCTs have included only these CD patients. Therefore, the options are:

- To look only at subgroups of patients in RCTs with a CDAI score of ≥ 300. This is unlikely to be a valid comparison unless the RCT stratified patients by being more or less than CDAI 300.
- To widen the inclusion criteria of the assessment report to include RCTs where CD patients had lower CDAI scores.[58]

It may be that there is a different effectiveness of the interventions in CD patients with CDAI scores of > 220 compared with > 300.

Most work on measurement of CD has been carried out in adult patients. Where a child has CD, it is unclear how this would be consistently categorised as severe CD or moderate-to-severe CD. Although there is a children's version of CDAI – Paediatric Crohn's Disease Activity Index (PCDAI) – it is unclear how well this measure is validated and how it relates to CDAI cut-off points.

It could be important to look at populations of patients who have failed either infliximab or adalimumab therapy to determine if unresponsiveness to a particular drug is a persistent state and whether unresponsiveness to one drug can be linked to similar unresponsiveness to the other. Finally, it is unclear exactly how resistance to treatment is measured or how long a treatment trial would go on for before a patient would be categorised as being resistant or responsive to treatment.

Outcomes

Key factors are the clinical effectiveness of both drugs particularly in terms of enhancing patient QoL, maintenance of remission, delaying disease progression and prolonging survival. More specifically, outcomes could include overall survival, progression-free survival, HRQoL, disease activity (remission, response, relapse, changes in disease activity indices, number of fistulas for fistulising disease), maintenance of response to treatment over time, need for surgery, need for an ostomy, hospitalisation rates, need for steroid treatment, dropout rates from TNF-α treatment and adverse effects of treatment. It is unclear how outcomes such as mucosal healing would impact on clinical outcomes such as QoL.

Where disease severity and effect of treatment is measured by CDAI or PCDAI scores, it is uncertain how large a change in CDAI score constitutes a clinically significant change and whether this would be the same change for more severe CD as for less severe CD.

Trials in patients with fistulising disease will measure fistula closure but it is uncertain whether this is a good measure of effectiveness as abscesses can form if the fistula is no longer patent; so abscess occurrence may be a better outcome measure. Other clinical outcomes could include abscess formation rates and seton use (if reported).

Overall aims and objectives of assessment

The overall decision problem is 'What is the cost-effectiveness of adalimumab and infliximab in the management of moderate-to-severe CD in the UK NHS?'. Ideally, this analysis would be based on head-to-head comparisons. In the absence of these, this decision problem is operationalised as a number of complementary cost-effectiveness analyses (depending on availability of data):

- What is the expected incremental cost-effectiveness ratio (ICER) for infliximab therapy (induction or episodic/clinician discretion or scheduled maintenance) compared with standard care (SC) in the management of moderate-to-severe CD?
- What is the expected ICER for adalimumab therapy (induction or episodic/clinician discretion or scheduled maintenance) compared with SC in the management of moderate-to-severe CD?
- What is the expected ICER for one dosing regimen of infliximab therapy compared with another dosing regimen of infliximab in the management of moderate-to-severe CD?
- What is the expected ICER for one dosing regimen of adalimumab therapy compared with another dosing regimen of adalimumab therapy in the management of moderate-to-severe CD?
- What is the expected ICER for (different dosing regimens of) infliximab therapy compared with (different dosing regimens of) adalimumab therapy in the management of moderate-to-severe CD?

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

Search strategy

The search strategy was designed to update that undertaken for the previous technology assessment of the clinical effectiveness and cost-effectiveness of infliximab in adults with moderate-to-severe CD[5] and to encompass the new anti-TNF therapies identified for review. A search was undertaken to find existing good quality systematic reviews in order to document the evidence base to date. Searches for primary studies were restricted to RCTs. The following sources were searched for relevant primary studies:

- bibliographic databases: Cochrane Library [Cochrane Central Register of Controlled Trials (CENTRAL)] 2007, Issue 2; MEDLINE (Ovid) 2000 to May/June 2007; MEDLINE In-Process & Other Non-Indexed Citations (Ovid) 4 June 2007 and 26 June 2007; EMBASE (Ovid) 2000 to May/June 2007. Searches were based on index and text words that encompass the condition: CD and the interventions: adalimumab, certolizumab pegol, infliximab and natalizumab. [Natalizumab and certolizumab pegol were originally part of this technology appraisal so were included in the searches. They were subsequently dropped from the report after completion of searches (see *Protocol modification*).] Where it was appropriate, a methodological 'filter' was applied to identify RCTs
- EMEA, FDA and other relevant websites
- citations of relevant studies
- contact with experts
- research registries of ongoing trials including National Research Register 2007, Issue 2, Current Controlled Trials and ClinicalTrials.gov
- submissions from industry
- hand search of conference abstracts in 2006 and 2007: British Society of Gastroenterology, Digestive Disease Week, United European Gastroenterology Meeting, European Crohn's and Colitis Organisation, Federation of Clinical Immunology Societies.

Searches were not limited by language. Full search strategies can be found in *Appendix 3*.

Inclusion and exclusion criteria

Only studies meeting the following inclusion criteria were included:

- Study design: RCTs (study designs other than RCTs were excluded).
- Population: adults (≥ 18 years) and children (6–17 years) with moderate-to-severe, active CD intolerant or resistant to conventional treatment; adults (≥ 18 years) with fistulising CD resistant to conventional treatment. 'Moderate-to-severe' disease includes patients with an average CDAI score of ≥ 220 or those who are described by trial authors as having moderate-to-severe disease.
- Intervention: adalimumab *or* infliximab (any dosage/treatment regimen).
- Comparator: conventional treatment without TNF-α inhibitors including no treatment, placebo, dietary intervention, drug treatment with aminosalicylates, methotrexate, corticosteroids (prednisolone, budesonide and hydrocortisone), azathioprine, metronidazole

or surgical intervention. Adalimumab and infliximab compared with each other. Different dosage or treatment regimens of the same drug.
- Outcomes: at least one of the following: overall survival, progression-free survival, HRQoL, disease activity (remission, response, relapse, changes in disease activity indices, number of fistulas for fistulising disease), need for surgery, hospitalisation rates and adverse effects of treatment.
- Trials that looked at both induction and maintenance of remission were included.

Based on the above inclusion/exclusion criteria, study selection was made independently by two reviewers. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. All discrepancies were resolved in this way.

Data extraction strategy

Information on study characteristics, study quality and results for each trial was extracted by one reviewer and checked by a second reviewer. Four reviewers were involved in data extraction. A standardised data extraction form was used, based on the form designed for the previous TAR on infliximab.[5] The data extraction template can be found in *Appendix 4*. Where necessary the template was adapted to accommodate details relevant to a specific trial. Where required, information was extracted from graphs as follows (see *Appendix 5*): the graph was scanned into a WORD document, overlaid with an appropriate template with graph gridlines, and printed and enlarged to A3 size, and information was extracted using the gridline template. To reduce error in this procedure, extracted information was checked by comparing graph readings with any available values in the report text and/or by redrawing the graph using the extracted data and comparing this with the original (see *Appendix 5* for examples). Data extraction discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. All discrepancies were resolved in this way.

Quality assessment strategy

Quality assessment was based on the published papers only and note was taken that absence of a quality criterion may be due to lack of reporting rather than actual poor methodological quality. Authors were not contacted for further information. Quality assessment was descriptive, a quality scoring system was not used. The quality criteria assessed were based on guidelines suggested by the Cochrane Collaboration, inviting consideration of threats arising from selection, performance, attrition and detection biases. Individual checklist items were: randomisation, concealment, blinding, comparability of groups, follow-up of trial participants, handling of missing data [intention-to-treat (ITT) analysis], power calculation and selective reporting (see *Appendix 4* for checklist). Study quality was assessed by one reviewer and checked by a second. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. All discrepancies were resolved in this way.

Handling of manufacturer and other submissions

The main industry submissions (including appendices) were checked for additional relevant trials and additional clinical effectiveness data for included trials. Because editorial constraints meant the results available in published accounts of the trials were necessarily selective, information in the submitted Clinical Study Reports was sourced as required for purposes of balance and completeness. It was not possible to systematically review all such additional information submitted owing to the volume of the submissions [e.g. more than 38,000 pages for the clinical study report of ACCENT (A Crohn's disease Clinical trial Evaluating inflixmab in a New long-term Treatment regimen) I,[2,3] more than 5000 pages for the Clinical Study Report of Targan *et al.*,[57] both included studies]. No references to specific sections of the clinical study reports were made in the main industry submissions. [Please note that the clinical study

reports for the CLASSIC (CLinical assessment of Adalimumab Safety and efficacy Studied as Induction therapy in Crohn's disease), CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) and GAIN (Gauging Adalimumab efficacy in Infliximab Nonresponders) RCTs that were received from the manufacturers of adalimumab started on section 4 and had no page numbers or tables of contents. Also some of the appendices were missing, particularly ones referred to in the text as having all of the raw results in tables. Therefore it is unclear whether some pages are missing from the middle of these reports or not and potentially the most useful appendices were not supplied.] For details on how the submitted economic models were assessed see *Chapter 4, Critique of the submission on infliximab by Schering-Plough*.

Analysis strategy

The clinical effectiveness section of this report mainly focuses on the results from RCTs and/or RCT trial arms in which the drugs were administered within the limits of their current respective licence indication (see *Appendix 6*). Results of trials are organised and reported in four categories:

- induction trials in adult populations predominantly or wholly constituted of non-fistulising patients
- maintenance trials in adult populations predominantly or wholly constituted of non-fistulising CD patients
- trials in populations wholly constituted of patients with fistulising CD
- trials in paediatric patients.

Results are reported within these four categories on a trial-by-trial basis except with regard to AEs and side effects which were considered simultaneously across all included trials across both drugs. Most outcome results are presented in forest plots so as to provide an overview of the quantitative spread of effect sizes. These are accompanied with brief narrative commentary. In some instances outcome results are tabulated. Both placebo and intervention rates and both risk difference and risk ratio effect sizes are presented for most outcomes in *Tabulation of included studies*. The confidence intervals (CIs) quoted were not adjusted for repeated measures.

The clinical heterogeneity of trials, or the existence of only a single trial, precluded pooling of data in meta-analysis. The feasibility of undertaking indirect comparison analysis was considered in-depth in order to assess the relative effectiveness of different drugs because there were no RCTs directly comparing both drugs included in this technology appraisal. However, indirect comparisons were not done because of the variation in placebo effect sizes in the RCTs (induction trials), the lack of similarity in the apparently common comparator (i.e. placebo arm maintenance trials), and the reporting of subgroup results only at follow-up (i.e. variously defined responders only) in many of the RCTs.

Protocol modification

The protocol originally encompassed assessment of the clinical effectiveness and cost-effectiveness of infliximab, adalimumab, certolizumab pegol and natalizumab within their licensed indications for moderate-to-severe CD. At the time of producing the protocol, certolizumab pegol and natalizumab were not licensed for CD, but imminent licensing was anticipated by the commissioners of this report (NICE). After the start of the review process it became clear that neither drug would achieve a licence within the time frame required for this technology assessment and consequently both drugs were dropped from the review. This occurred after completion of the search strategy. As of November 2010 these drugs remain unlicensed for CD.

Results

Quantity of research available

Eleven relevant trials were identified,[2,3,45,46,57,58,62–67] some supported by multiple publications. *Figure 1* details the trial identification process.

At the time of writing of this report, 11 hard copies of ordered publications were still outstanding or not available; none of these are likely to contain new trial data (see *Appendix 7* for details of publications).

Eleven RCTs were included in total.[2,3,45,46,57,58,62–67] Seven trials meeting the inclusion criteria were identified through the main database searches.[2,3,45,46,58,63,65,67] Two additional studies[57,62] from the previous TAR on infliximab were included,[5] as were two trials from 2007 which had been published after the search cut-off date.[64,66]

Searching through the main industry submissions from both manufacturers did not yield any additional RCTs. The search for conference abstracts yielded no further relevant trials. An abstract of the study by Hommes *et al.*[61] was identified, which is referred to in *Chapter 5, Other relevant factors*. This study did not meet the criterion of a population of CD patients who are resistant or intolerant to conventional treatment.

The search for ongoing trials yielded four potentially relevant RCTs, all of adalimumab (see *Appendix 8*). All were at the recruitment stage (or not yet recruiting) at the time the information

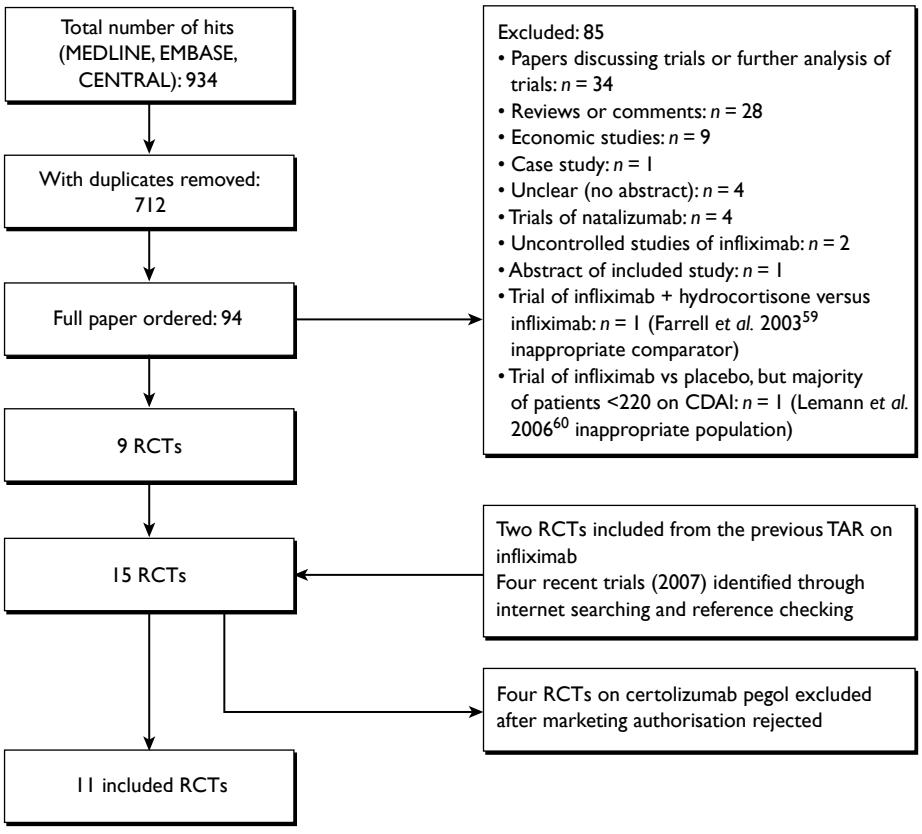

FIGURE 1 Study identification process.

was verified by the respective manufacturers. Two were trials (induction and maintenance) of adalimumab in Japanese patients with moderate-to-severe CD. Two multicentre trials of adalimumab were in patients with moderate-to-severe ileocolonic CD and in children with moderate-to-severe CD respectively. Two ongoing trials of infliximab were identified, but did not meet the inclusion criteria as they compared either infliximab with infliximab plus methotrexate or infliximab with infliximab plus azathioprine. No ongoing trials of head-to-head comparisons of adalimumab and infliximab were identified. No preliminary reports of any of these ongoing trials were identified in the manufacturer submissions.

Tabulation of included studies

All of the included RCTs recruited patients having 'moderate-to-severe CD' defined according to CDAI scores of between 220 and 450, or 220 and 400; it is therefore likely that they do not reflect the intended licensed population of severe active CD (i.e. CDAI score of more than 300).

The included studies encompassed two trial designs, induction therapy and maintenance therapy, in any of three populations: adults predominantly or wholly non-fistulising, fistulising adults and children. *Table 5* gives an overview of the included studies with reference to trial design and recruited patient population.

Of the 11 included RCTs,[2,3,45,46,57,58,62–67] nine compared infliximab or adalimumab with placebo.[2,3,57,58,62–67] Two RCTs compared different doses of infliximab only and these were both in children.[45,46] Two RCTs of infliximab were in patients with fistulising disease.[62,65] Both induction and maintenance trials were identified for both drugs. All RCTs were multicentre studies conducted mainly in North America and Europe. No RCTs of head-to-head comparisons of adalimumab and infliximab were identified. No RCTs of adalimumab in children were identified. Based on the information in the published papers, all RCTs were either industry sponsored or in part industry sponsored, had participants from industry involved in study design or manuscript writing, or had one or more authors with industry involvement.

In the induction trials, patients received short-duration anti-TNF or placebo to see if a favourable clinical response was induced. In the maintenance trials, all patients received short-term induction therapy with anti-TNF and then continued with longer term anti-TNF or placebo.

TABLE 5 Overview of the 11 included trials

		Population		
Type of trial	**Drug**	**Wholly or predominantly non-fistulising adults**	**Fistulising adults**	**Children**
Induction	Infliximab	[a]Targan *et al.*, 1997[57]	Present *et al.*, 1999[62]	Baldassano *et al.*, 2003[46]
	Adalimumab	CLASSIC I Hanauer *et al.*, 2006[63] GAIN Sandborn *et al.*, 2007[64]	No trials identified	No trials identified
Maintenance	Infliximab	Rutgeerts *et al.*, 1999[58] ACCENT I; Rutgeerts *et al.*[2] Hanauer *et al.*, 2002[3]	ACCENT II; Sands *et al.*, 2004[65]	REACH; Hyams *et al.*, 2007[45]
	Adalimumab	CLASSIC II; Sandborn *et al.*, 2007[66] CHARM; Colombel *et al.*, 2007[67]	No trials identified	No trials identified

REACH, A randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNFα chimeric monoclonal antibody (infliximab, Remicade®) in pediatric subjects with moderate-to-severe Crohn's disease.
a D'Haens *et al.*, 1999[68] described a subgroup of patients from Targan *et al.*, 1997.[57]

In the maintenance trials most published results reported only the follow-up of patients who initially responded to the induction therapy, and results for 'non-responders' were generally not provided.

The most widely reported outcomes were based on CDAI scores (see *Appendix 1* for details). Although group mean or median CDAI scores were usually recorded at various times of follow-up, the variance of these scores was incompletely reported and trials emphasised binary outcome measures derived by dichotomising CDAI scores. Three such binary measures were used:

- response 70: defined as a reduction of 70 or more in CDAI score relative to baseline
- response 100: defined as a reduction of 100 or more in CDAI score relative to baseline
- remission: defined as a CDAI score of less than 150.

The definitions of the binary measures given above were often qualified by stipulation of additional criteria usually including no requirement for a change in concomitant medication because of worsening clinical condition and no requirement for surgery.

This section describes the results about the effectiveness of the anti-TNF interventions. The results reviewed were taken mainly from publications. When judged necessary for purposes of completeness and balance, information in the unpublished industry trial reports was also sourced.

There are four sections in the clinical effectiveness results: induction treatment in adults (predominantly non-fistulising), maintenance in adults (predominantly non-fistulising), treatments in adult patients exclusively with fistulising CD, and paediatric CD (≤ 18 years old). Within each section infliximab is reported before adalimumab and the earliest trial publication date first. Each of the four sections are organised for each trial as follows:

- description of intervention used in the trial and other unusual points about the trial design
- report of outcomes organised as A, response 70; B, response 100; C, remission; D, other outcomes; and E, other considerations, in the first two sections, primary and secondary outcomes in the last two sections
- quality assessment
- summary for that trial (in box).

Adverse events and side effects are considered simultaneously across all included trials for both drugs at the end of the clinical effectiveness section (see *Adverse events*), just before the discussion of clinical effectiveness (see *Discussion of results and assessment of effectiveness*).

Induction trials in adult populations (wholly or predominantly non-fistulising)

Induction trials are patients who were not receiving anti-TNF therapy at the time of randomisation. Three trials were identified.[57,63,64] One, Targan *et al.*,[57] compared infliximab with placebo. A further publication, D'Haens *et al.*,[68] reported on a subgroup from Targan *et al.*[57] and so will not be further discussed. Two trials compared adalimumab with placebo (CLASSIC I[63] and GAIN[64]). Apart from the subgroup study the trials recruited patients who had initial CDAI scores between 220 and 450. The outcomes reported are summarised in *Table 6* and trial details are summarised in *Table 7*.

Targan *et al.*, 1997[57] (infliximab)

This RCT had four arms.[57] Patients were randomised to a single i.v. infusion of placebo ($n = 25$) or of infliximab at 5 mg/kg ($n = 27$), 10 mg/kg ($n = 28$) or 20 mg/kg ($n = 28$). Disease status

TABLE 6 Outcomes measured in induction trials with mainly non-fistulising adult populations

	% with remission	% with response 100	% with response 70	CDAI score	IBDQ score	Other outcomes
Infliximab						
Targan *et al.*, 1997[57]	✓	X	✓	✓	✓	CRPc
Adalimumab						
CLASSIC I[63]	✓	✓	✓	✓	✓	CRPc
GAIN[64]	✓	✓	✓	✓	✓	CRPc, improvement in draining fistulas, fistula remission at week 4 (in subgroup)

CRPc, C-reactive protein concentration.

(remission, response 70 and CDAI score) was monitored at baseline and at weeks 2 and 4 after infusion. The 4-week blinded phase was followed by an open-label phase with a further 12 weeks of follow-up. The primary outcome measure was defined as a response 70 at week 4 with no change in any concomitant medication.

A, response 70

Response 70 at week 4 was the primary outcome. Results for response 70 at weeks 2 and 4 are summarised in *Figure 2*. For response 70 at week 4 there was a statistically significant difference in favour of the infliximab groups (combined) compared with placebo ($p < 0.001$). The percentage of placebo patients achieving response 70 was ≤ 16% at both time points and for infliximab groups at week 4, and was between 50% and 81% depending on dose regimen. Point estimates of percentage response were associated with considerable uncertainty. The rate of response 70 at week 4 for the combined infliximab groups was 61% (95% CI 51% to 71%). At week 4 the risk difference (infliximab–placebo) was between 0.34 and 0.65, and risk ratio (infliximab/placebo) was between 3.1 and 5.1 depending on dose. Both risk difference and risk ratio at week 4 reached statistical significance in favour of intervention.

Table 8 summarises the comparison between different dose regimens for response 70 at week 4. The low-dose regimen (5 mg/kg) appeared more effective than the 10 mg/kg regimen ($p = 0.009$). The difference between dose regimens for other comparisons did not reach statistical significance.

B, response 100 was not reported

C, remission

Figure 3 summarises remission rates. At 4 weeks, between 25% and 48% of patients in the infliximab groups were in remission, depending on dose, but only one placebo patient achieved remission.

There was a discrepancy between remission rates published in Targan *et al.*[57] and rates presented in the manufacturer's submission. The latter for the 5 mg/kg group at week 4 were placebo rate 4% (1/24), infliximab rate 0% (0/24). These remission rates generate a negative risk difference (infliximab–placebo) at week 4 (–0.04). CIs for risk ratios (infliximab/placebo) in the manufacturer's submission were described as 'unadjusted', but were unexpectedly narrow compared with those calculated using standard software packages or using the standard error of ln (risk ratio) given by:[69] $([e_i]^{-2} + [e_p]^{-2} - [T_i]^{-2} - [T_p]^{-2})^{0.6}$, where e_i, and e_p, are the number of patients with the outcome in the intervention and placebo arms respectively, and T_i and T_p are

TABLE 7 Main study and population characteristics: induction trials in predominantly or wholly non-fistulising adult populations

Study[a] Drug	Study weeks *n*	Population: severity of CD (baseline CDAI and IBDQ if stated)	Intestinal areas affected	Main concomitant medication, % not on any medication	Previous/concomitant treatment with anti-TNF inhibitors	Intervention and comparator (dosing regimen)
Targan *et al.*, 1997[57] Infliximab	4[b] 108	Moderate-to-severe, CDAI 220–450 Eligible if receiving mesalamine or oral corticosteroids or mercaptopurine or azathioprine Mean baseline CDAI (SD): 288 ± 54) placebo, 312 ±56), 318 ±59), 307 ±50) infliximab groups Mean baseline IBDQ (SD): 128 ±29) placebo, 122 (29), 116 ±23), 118 ±28) infliximab groups	Mainly ileum/ colon, also colon only, some ileum only	Aminosalicylates or corticosteroids, also mercaptopurine or azathioprine % not on medication (if any) not stated	Exclusion criterion: previous treatment with monoclonal antibodies	One 2-hour i.v. infusion of: 5 mg/kg, 10 mg/kg or 20 mg/kg infliximab or of placebo
Hanauer *et al.*, 2006[63] CLASSIC I Adalimumab	4 299	Moderate-to-severe, CDAI 220–450 Mean baseline CDAI (SD): placebo 296 (60); adalimumab groups 299 (57); 301 (61); 295 (52) Median baseline IBDQ (range): placebo, 131 (52–200); adalimumab groups 129 (81–218); 128 (63–200); 127 (37–192).	Mainly ileum and colon	Aminosalicylates, also corticosteroids, immunosuppressives, and few on antibiotics % not on medication (if any) not stated	Exclusion criterion: infliximab or other anti-TNF therapy	Subcutaneous infusion at weeks 0 and 2: 40 mg/20 mg, 80 mg/40 mg or 160 mg/80 mg adalimumab at week 0 and 2 respectively. Placebo at weeks 0 and 2
Sandborn *et al.*, 2007[64] GAIN Adalimumab	4 325	Moderate-to-severe, CDAI 220–450 Mean baseline CDAI (SD): placebo 313 (66); adalimumab 313 (58) Mean baseline IBDQ (SD): 124 (28) placebo, 120 (27) adalimumab	Mainly ileum or colon, some rectum, perianal or anus or gastro-duodenal	Corticosteroids or immunosuppressives, also oral aminosalicylates % not on medication (if any) not stated	Patients must have been treated with infliximab and either lost response or been intolerant; excluded patients with primary non-response to infliximab	Subcutaneous injections 160 mg adalimumab at week 0 and 80 mg at week 2 or placebo at weeks 0 and 2

SD, standard deviation.
a All were multicentre studies conducted in the US, Canada and Europe, and sponsored by industry.
b There was an open-label extension beyond week 4.

TABLE 8 Risk difference between dose regimens in response 70 at week 4 in Targan *et al.*[57]

Dose comparison	Risk difference	Lower CI	Upper CI
5 mg/kg vs 10 mg/kg	0.315	0.079	0.551
5 mg/kg vs 20 mg/kg	0.172	–0.058	0.402
10 mg/kg vs 20 mg/kg	–0.143	–0.399	0.114

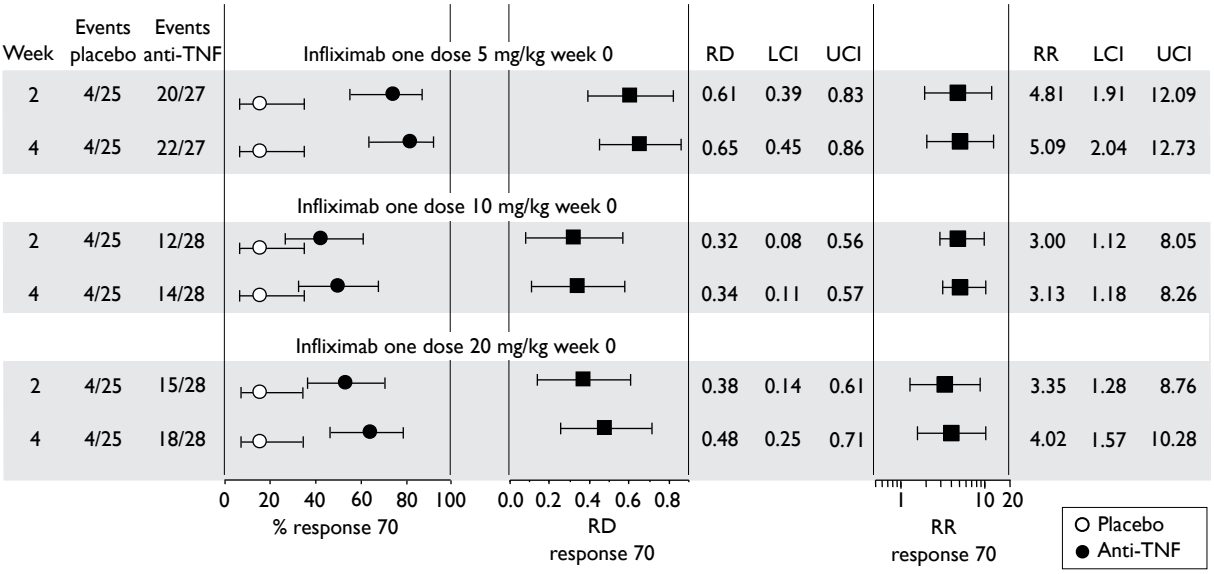

FIGURE 2 Response 70 rates in Targan *et al.*[57] At week 4 risk difference $p < 0.001$, $p = 0.0045$, $p < 0.001$, for 5, 10 and 20 mg/kg dose regimens respectively. At week 4 risk ratio $p < 0.001$, $p = 0.022$, $p < 0.004$ for 5, 10 and 20 mg/kg dose regimens respectively. LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

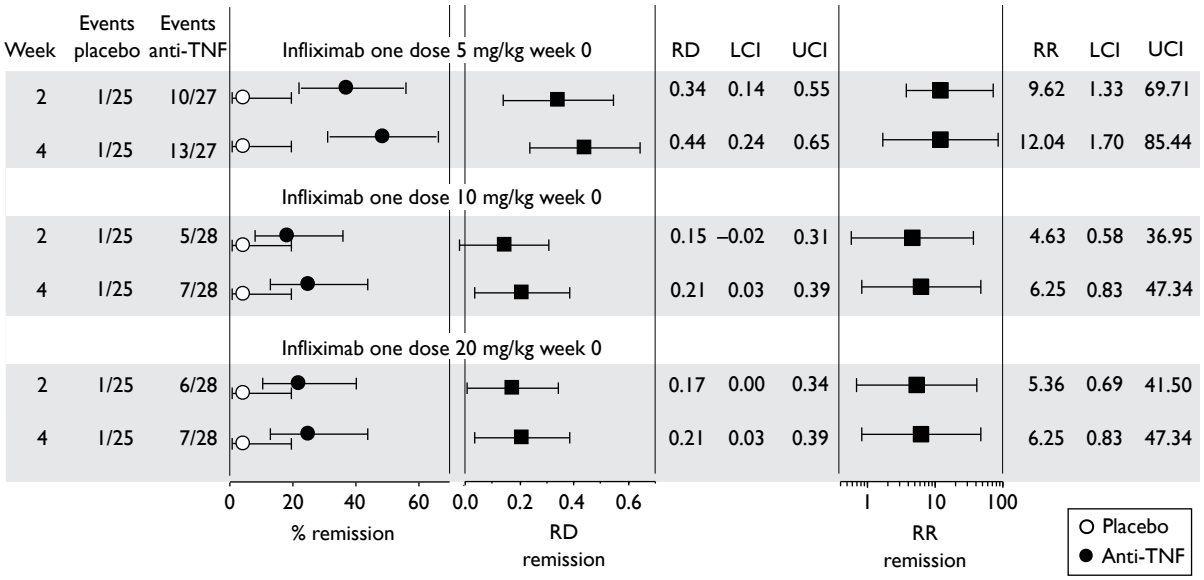

FIGURE 3 Remission rates in Targan *et al.*[57] At week 4 risk difference $p < 0.001$, $p = 0.0206$ and $p = 0.0206$, for 5, 10 and 20 mg/kg dose regimens respectively. At week 4 risk ratio $p = 0.013$, $p = 0.076$ and $p = 0.076$ for 5, 10 and 20 mg/kg dose regimens respectively. LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

total number of patients in the intervention and placebo arms respectively. (This discrepancy in CIs applies to CDAI-based binary risk ratios for all trials in the infliximab industry submission.)

Maintenance of initial response to single infusion At week 4 there were 54/83 (65%) responders (response 70) to infliximab (combined dose groups); by 12 weeks (see *E, open-label phase* below) there were 34 responders (41%). At week 4, 27/83 (33%) patients given infliximab had gained remission and at 12 weeks 20 patients (24%) were in remission.

TABLE 9 Mean (standard deviation) values for CDAI, IBDQ and CRP concentrations at baseline and week 4

	Placebo *n*=25	5 mg/kg *n*=27	10 mg/kg *n*=28	20 mg/kg *n*=28	All infliximab groups *n*=83
Score on CDAI					
Baseline	288 ± 54	312 ± 56	318 ± 59	307 ± 50	312 ± 55
4 weeks	211 ± 82	166 ± 76[a]	226 ± 115[b]	211 ± 107[a]	201 ± 103[a]
Score on IBDQ					
Baseline	128 ± 29	122 ± 29	116 ± 23	118 ± 28	118 ±27
4 weeks	133 ± 28	168 ± 36[a]	146 ± 41[c]	149 ± 35[d]	154 ± 38[e]
CRP (mg/l)[f]					
Baseline	12.8 + 13.9	22.1 + 23.6	23.2 + 34.2	22.4 ± 23.9	22.5 ± 21.4
4 weeks	14.8 ± 18.6	5. 1 ± 9.3[g]	12.1 ± 18.6	6.9 ± 11.6[a]	8.3 ± 1.39[a]

a $p<0.001$.
b $p=0.003$.
c $p=0.02$.
d $p=0.03$.
e $p=0.001$.
f Levels of CRP < 8 mg/l are considered normal.
g $p=0.004$; authors calculated *p*-values for change from baseline comparing placebo with intervention using analysis of variance with the van der Waerden normal scores blocked according to centre. If the treatment effect was significant, the infliximab treatment groups were compared with the placebo group with linear contrasts.

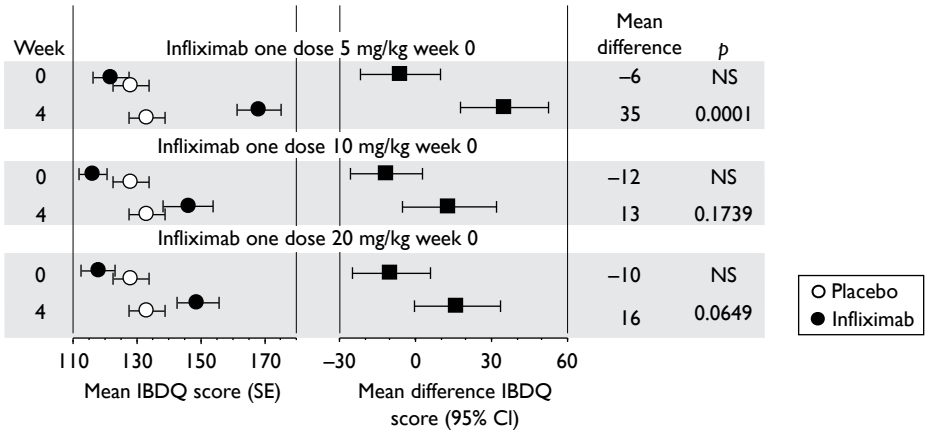

FIGURE 4 Mean IBDQ scores and mean difference at baseline and week 4 of Targan *et al*.[57] NS, not significant.

D, other outcomes

At week 4 favourable responses to treatment were reported for CDAI scores, for QoL scores (IBDQ), and for C-reactive protein (CRP) levels. The results reported are summarised in *Table 9*.

Figure 4 shows the mean difference in IBDQ score (infliximab–placebo) at week 4. Mean difference reached statistical significance only for patients who received the low-dose regimen.

E, other considerations – open-label phase

In the open-label phase of the trial, extending by at least 12 weeks from week 4, non-responder patients at week 4 were eligible for a 10 mg/kg infusion of infliximab. The distribution of this

TABLE 10 Numbers of patients receiving second infusion in open-label phase of Targan *et al*.[57]

Original randomisation group (*n*)	Number receiving and not receiving second infusion (%)		Response 70 at times after second infusion (non-responders at week 4 after first infusion)		
	Did not receive	Received	Week 4	Week 8	Week 12
Placebo (25)	6 (24)	19 (76)	11/19 (58%)	13/19 (68%)	10/19 (53%)
5 mg/kg group (27)	21 (78)	6 (22)	2/6 (33%)	3/6 (50%)	1/6 (17%)
10 mg/kg group (28)	13 (46)	15 (54)	6/15 (40%)	5/15 (33%)	5/15 (33%)
20 mg/kg group (28)	20 (71)	8 (29)	2/8 (25%)	4/8 (50%)	2/8 (25%)
Combined infliximab groups					8/29 (28%)
All groups (108)	60 (56)	48 (44)	21/48 (44%)	25/48 (52%)	18/48 (38%)

second infusion among the patient groups is summarised in *Table 10*. Of the original 25 placebo group patients, 19 non-responders received infliximab; 29 non-responder patients who had received a first dose of infliximab received the second dose. *Table 10* lists the percentage of the patients (not responsive at week 4) in each group who subsequently achieved response 70 at follow-up weeks 4, 8 and 12 after the second infusion.

Of patients unresponsive to the first dose of infliximab, 28% (8/29) responded by week 12 following the second dose, compared with 53% (10/19) of patients whose second infusion was their first exposure to active intervention. During this open-label phase there was a lack of a true placebo control group and the results therefore only suggest that some patients poorly responsive to an initial infusion may respond subsequently on receipt of further infusion. Whether a 10 mg/kg second dose represents the most appropriate dose regimen for this second-dose strategy is unknown.

Quality assessment (based on published report)

Randomisation, allocation concealment, and blinding (up to week 4) were all adequate. Baseline characteristics were similar between groups except for CRP levels and for the proportion of patients with ileal involvement. Placebo CRP level {mean 12.8 [standard deviation (SD) 13.9]} was substantially lower than that for the active intervention groups [mean (SD): 22.1 (23.6), 23.2 (34.2) and 22.4 (23.9) for the 5 mg/kg, 10 mg/kg and 20 mg/kg groups respectively]. The potential impact on results of the imbalanced CRP levels is difficult to determine. Follow-up appeared almost complete. The original study protocol did not specify the use of ITT analysis, but the publication stated that patients were analysed according to assignment. A power calculation was conducted; this assumed a 30% response in the placebo group presumably reflecting the authors' assessment of placebo rates reported in other CD trials. The actual placebo response rate observed was less than half this value (16%) and was low compared with other similar trials. The low placebo rate and imbalance of placebo CRP level may indicate an atypical placebo population possibly stemming from the small sample size of the group ($n = 25$).

CLASSIC I[63] (adalimumab)

In this trial,[63] patients ($n = 299$) were randomised to two subcutaneous injections 2 weeks apart of either placebo ($n = 74$) or adalimumab at dose regimens of 40 mg then 20 mg ($n = 74$), at 80 mg then 40 mg ($n = 75$), or at 160 mg then 80 mg ($n = 76$). Patients were excluded if they had previously received any anti-TNF treatment. At baseline 11% of patients had fistulas. Outcomes were monitored at weeks 1, 2 and 4 after the first injection. The primary outcome was defined as the proportion of patients in remission at week 4 in the two high-dose adalimumab groups versus the placebo group (tested using chi-squared test).

Targan *et al.*, 1997.[57] Summary of effectiveness evidence

A single i.v. infusion of infliximab (5, 10 or 20 mg/kg) was more effective than placebo at delivering a clinical response (a reduction of ≥70 points in CDAI score) at week 4 of follow-up ($p < 0.005$ for risk differences and $p < 0.022$ for risk ratios). Estimates of the percentage of patients responding to infliximab were associated with considerable uncertainty, and at 4 weeks ranged between 50% and 80% depending on dose. Of the dose regimens used, the lowest appeared to be the most effective, suggesting the possibility that the most appropriate dose could be less than the lowest used in the trial (5 mg/kg). A proportion of patients (~30%) not responsive at week 4 did respond subsequently when given a second dose of infliximab (10 mg/kg); although it is likely this 'second-dose' response required active intervention, this was not properly demonstrated because the trial lacked a true placebo comparator after week 4. The most effective dose regimen for a 'second-dose' response was uncertain. After week 4 nearly all trial participants had received active intervention, and inferences about the relation of outcomes to infliximab were obscured. The Targan *et al*.[57] trial was completed more than a decade ago and no further induction trial of infliximab in this population has been conducted, so the uncertainties described above remain to be addressed.

A, response 70

At week 4 for the less robust measure of a clinical improvement by more than 70 points in CDAI score from baseline (response 70), a statistically significant result was observed for both risk difference and risk ratio for all three dose regimens (results are summarised in *Figure 5*).

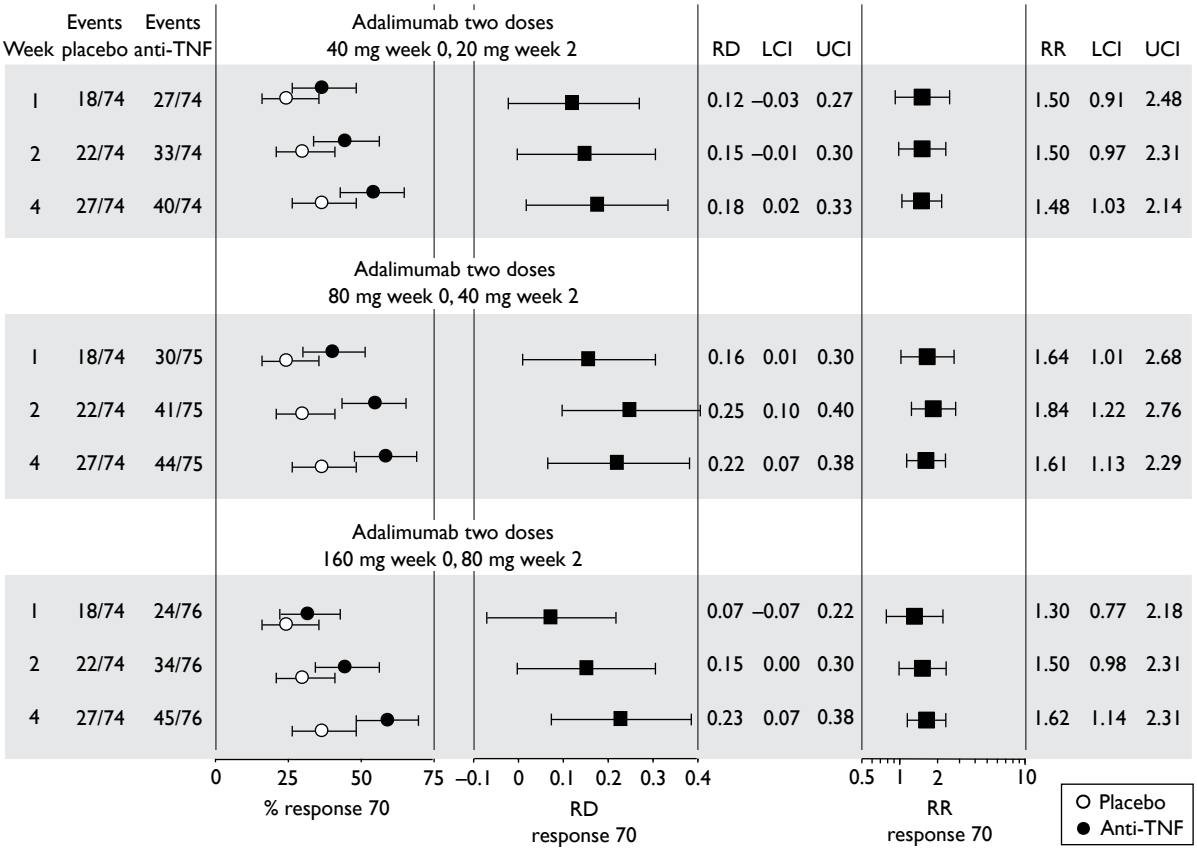

FIGURE 5 Rates of response 70 in CLASSIC I.[63] At week 4 for risk difference $p = 0.029$, $p = 0.005$ and $p = 0.004$ for 40/20, 80/40 and 160/80 dose regimens, At week 4 for risk ratio $p = 0.0357$, $p = 0.0088$ and $p = 0.0073$ for 40/20, 80/40 and 160/80 dose regimens. LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

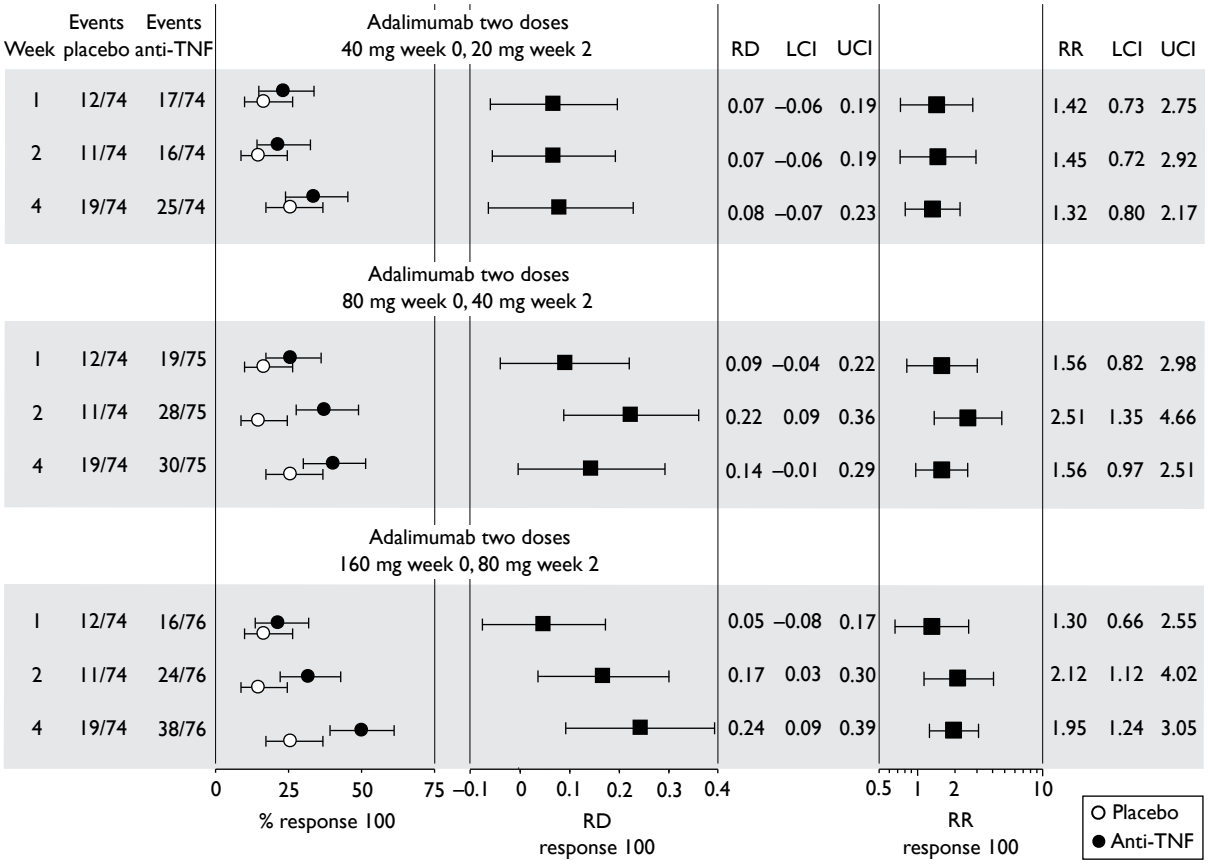

FIGURE 6 Rates of response 100 in CLASSIC I.[63] At week 4 for risk difference $p = 0.279$, $p = 0.060$ and $p = 0.0015$ for 40/20, 80/40 and 160/80 dose regimens respectively. At week 4 for risk ratio $p = 0.284$, $p = 0.0682$ and $p = 0.0036$ for 40/20, 80/40 and 160/80 dose regimens respectively. LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

B, response 100

At week 4 the risk difference for response 100 (intervention–placebo) reached statistical significance only for the highest dose regimen while risk ratio (intervention/placebo) reached statistical significance for the two higher dose regimen groups. The results for response 100 are summarised in *Figure 6*.

C, remission rates

Remission rates were the primary outcome in this RCT. For remission rates there was a statistically significant difference in favour of the two high-dose adalimumab regimens relative to placebo for the proportion of patients in remission at (45/151 vs 9/74; $p = 0.004$). At week 4 the risk difference (intervention–placebo) and risk ratio (intervention/placebo) reached statistical significance only in the highest dose regimen group. Remission rates are summarised in *Figure 7*.

For each of the three CDAI-based binary outcome measures there was an apparent linear dose response trend with greater effectiveness for higher dose.

D, other outcomes

At week 4, favourable responses to treatment were reported for CDAI scores, for QOL scores (IBDQ), and for CRP levels. The results reported are summarised in *Table 11*.

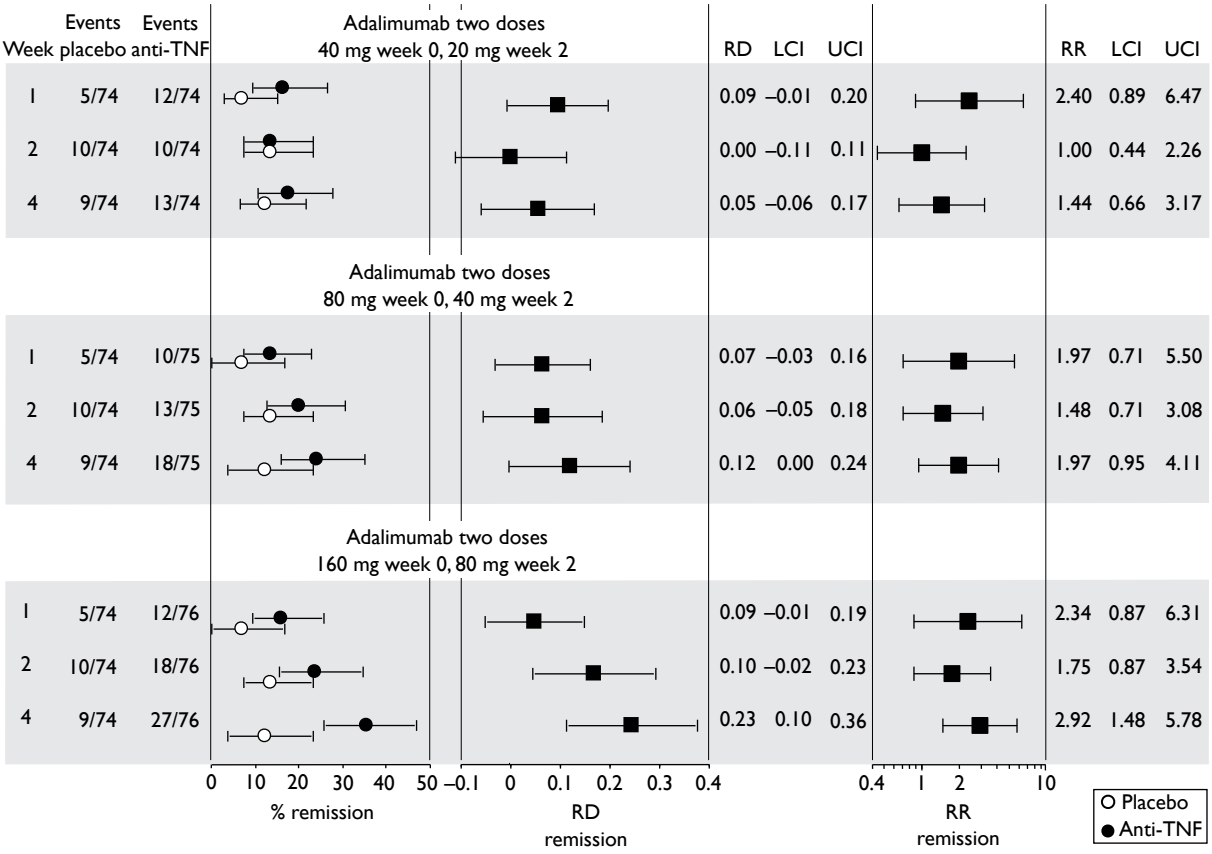

FIGURE 7 CLASSIC I remission rates.[63] At week 4 risk difference $p = 0.354$, $p = 0.057$ and $p = 0.0005$ for 40/20, 80/40 and 160/80 dose regimens. At week 4 risk ratio $p = 0.359$, $p = 0.0691$ and $p = 0.0021$ for 40/20, 80/40 and 160/80 dose regimens respectively. LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

TABLE 11 Mean (SD) values for CDAI, IBDQ and CRP concentrations at baseline and week 4

	Placebo ($n=74$)	40/20 ($n=74$)	80/40 ($n=75$)	160/80 ($n=76$)
Score on CDAI: mean (SD)				
Baseline	296 (60)	299 (57)	301 (61)	295 (52)
4 weeks	240 (NR)	228 (NR)	210 (NR)[a]	193 (NR)[b]
Score on IBDQ median (range)				
Baseline	131 (52–200)	129 (81–218)	128 (63–200)	127 (37–192)
4 weeks	147 (NR)	147 (NR)	158 (NR)[c]	158 (NR)[c]
CRP (mg/l) median (range)[d]				
Baseline	0.9 (0–17.3)	0.9 (0–11.3)	0.9 (0–14.9)	0.7 (0–9.3)
4 weeks	0.8 (0–9.3)	0.3 (0–8.6)[e]	0.4 (0–34.0)[f]	0.2 (0–4.6)[g]

NR, not reported.
Comparisons vs placebo:
a $p < 0.01$.
b $p < 0.001$.
c $p < 0.05$.
d Levels of CRP < 8 mg/l are considered normal.
e $p = 0.032$.
f $p = 0.0002$.
g $p = 0.0001$.

E, other considerations – subgroup analyses

Logistic regression failed to show a relationship between baseline CRP levels or concomitant immunosuppressive therapy and remission rates at week 4 with placebo or adalimumab.

For the small subgroup of patients with fistulas (11%), no significant differences were observed between placebo and intervention with regard to fistula improvement or remission.

Quality assessment (based on published report)

Randomisation, allocation concealment and blinding were adequate. Baseline characteristics were reasonably well balanced between groups. There were no losses to follow-up, and withdrawals were limited to 5%. Efficacy estimates appear to have been calculated using ITT analysis, but this was not stated explicitly. A power calculation was conducted; this assumed 20% and 45% remission rates in the placebo and intervention arms respectively (the observed placebo rate in the trial was about 12%). Last observation carried forward was used for analysis of IBDQ scores, but the number of missing data was not stated.

CLASSIC I.[63] Summary of effectiveness evidence

Two subcutaneous injections of adalimumab given 2 weeks apart at 40 mg then 20 mg, at 80 mg then 40 mg, or at 160 mg then 80 mg, were more effective than placebo at achieving remission (CDAI score < 150) at week 4 after the first injection ($p = 0.004$ for the two high-dose regimens combined vs placebo). The percentage of placebo-treated patients gaining remission at week 4 was ~12% compared with between ~18% and ~36% for adalimumab-treated patients depending on dose regimen received. Point estimates of response 70 rates, response 100 rates and remission rates were associated with considerable uncertainty, but for all three outcome measures a trend was evident for higher doses to be more effective. At week 4 of follow-up, risk differences (intervention–placebo) and risk ratios (intervention/placebo) for the highest dose regimen reached statistical significance in favour of adalimumab for all three outcomes. Subgroup analyses failed to identify any baseline characteristics associated with a better response to active intervention relative to placebo.

GAIN[64] (adalimumab)

In this trial,[64] 325 patients were randomised to two subcutaneous injections 2 weeks apart of either placebo ($n = 166$) or adalimumab at a dose regimen of 160 mg then 80 mg ($n = 159$). To be included patients had to have been previously exposed to infliximab treatment and found to be intolerant ($n = 190$), unresponsive ($n = 164$), or intolerant and unresponsive ($n = 40$). The primary response was defined as the proportion of patients in remission at week 4 after the first injection.

A, response 70; B, response 100; and C, remission

The primary outcome was remission rates. The remission rate at week 4 was 7% in the placebo group and 21% in the adalimumab group ($p < 0.001$). This result and those for the secondary outcomes as reported are summarised in *Table 12*. The CDAI-based binary response outcome measures reported are summarised graphically in *Figure 8*. At weeks 2 and 4, risk differences (adalimumab–placebo) and risk ratios (adalimumab/placebo) were in favour of the intervention and reached statistical significance.

D, other outcomes

Results for these are also shown in *Table 12*. Mean CDAI scores reduced from baseline to a greater extent with adalimumab than with placebo (at week 4, $p < 0.001$ for mean change from baseline). At week 4 the improvements from baseline in IBDQ scores were 30 and 15 for the

TABLE 12 Outcome measures reported in the GAIN trial[64]

	Placebo ($n=159$)	Adalimumab 160/80 ($n=164$)	Difference (95% CI) (adalimumab–placebo)	p[a]
Remission (rate; %)[b]				
Week 1	4%	6%	2.7% (–2.0 to 7.4)	(CiC information has been removed)
Week 2	6%	21%	14.7% (7.2 to 22)	(CiC information has been removed)
Week 4	7%	21%	14.2% (6.7 to 21.6)	(CiC information has been removed)
Response 70 (rate; %)				
Week 1	21%	35%	14.1% (4.5 to 23.7)	0.004
Week 2	33%	52%	19.7% (9.1 to 30.1)	(CiC information has been removed)
Week 4	34%	52%	17.8% (7.3 to 28.4)	(CiC information has been removed)
Response 100 (rate; %)				
Week 1	12%	20%	7.4% (–0.5 to 15.4)	(CiC information has been removed)
Week 2	18%	37%	18.4% (8.9 to 27.9)	(CiC information has been removed)
Week 4	25%	38%	13.7% (3.7 to 23.7)	(CiC information has been removed)
CDAI: mean (SD)				
Baseline	313 (66)	313 (58)	0	
Week 1	287 (NR)	264 (NR)	–23	
Week 2	281 (NR)	232 (NR)	–49	
Week 4	264 (NR)	226 (NR)	–38	
IBDQ score: mean (SD)				
Baseline	124 (28)	120 (27)	+4	
Week 4	139 (NR)	150 (NR)	+11	<0.001
CRP: median (range) mg/l[d]				
Baseline	7.0 (0–235)	9.0 (0–115)	+2	
Week 4	7.0	5.0	–2	
Change from baseline	0	4	4	Significant

CiC, commercial-in-confidence; NR, not reported.
a Comparisons adalimumab vs placebo.
b Primary outcome % remission at week 4.
c Chi-squared test.
d Levels of CRP < 8 mg/l are considered normal.

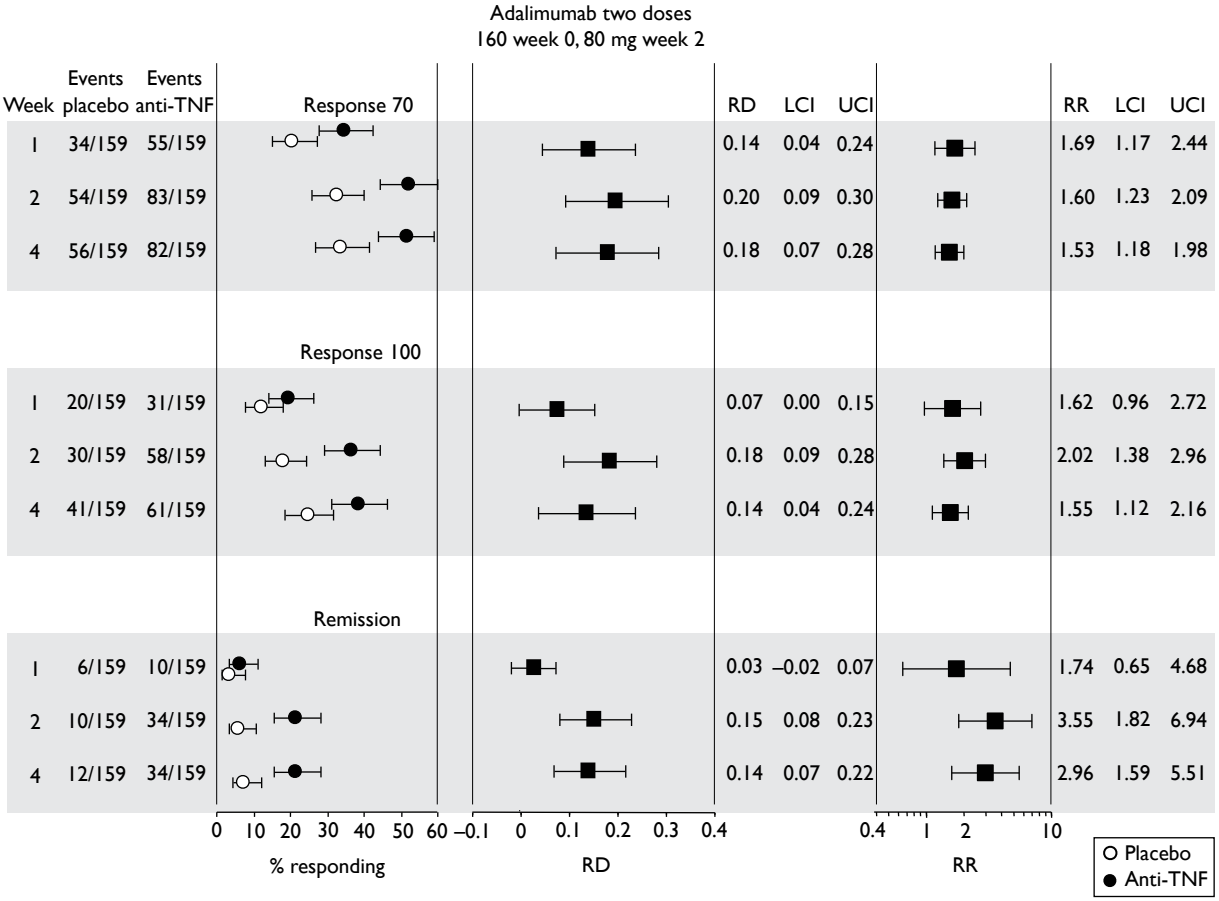

FIGURE 8 Response 70, response 100 and remission rates reported in GAIN.[64] At week 4 risk difference $p = 0.001$, $p = 0.007$ and $p = 0.0002$ for response 70, response 100 and remission respectively. At week 4 risk ratio $p = 0.0014$, $p = 0.009$ and $p = 0.0006$ for response 70, response 100 and remission respectively. LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

adalimumab and the placebo groups respectively. CRP levels at week 4 relative to baseline were more normalised in the intervention than in the placebo group. The change from baseline comparing adalimumab with placebo reached statistical significance in favour of adalimumab.

E, other considerations – subgroup analyses

The primary outcome (remission at week 4) was reported for subgroups of patients defined according to: previous response or intolerance to infliximab; receiving or not receiving immunosuppressive agents at baseline; receiving or not receiving corticosteroids at baseline; or having a negative or positive test for antibodies to infliximab. Risk difference was in favour of adalimumab relative to placebo for all subgroups.

A small proportion of patients (14%, $n = 45$) had draining fistulas or perianal fistulas at baseline. Rates of fistula improvement and remission were similar between placebo and adalimumab groups.

Quality assessment (based on published report)

Randomisation, allocation concealment and blinding were adequate. Baseline characteristics were well balanced between groups. There were no losses to follow-up, and withdrawals were limited to 4%. Efficacy estimates appear to have been calculated using ITT analysis for remission

and response outcomes. For continuous variables such as IBDQ, last observation was carried forward; the number of missing data for IBDQ was small (eight patients). A power calculation was conducted; this assumed 20% and 35% remission rates in the placebo and intervention arms respectively (the observed rates at week 4 in the trial were 7% and 21% respectively).

GAIN.[64] Summary of effectiveness evidence

Two subcutaneous injections of 160 mg and then 80 mg of adalimumab given 2 weeks apart were more effective than injections of placebo at achieving remission (CDAI score < 150) at week 4 after the first injection ($p < 0.001$). The percentage of placebo-treated patients gaining remission at week 4 was 7% (95% CI 4% to 12%) compared with 21% (95% CI 14% to 27%) for adalimumab-treated patients. At weeks 2 and 4 of follow-up, risk differences (intervention–placebo) and risk ratios (intervention/placebo) reached statistical significance in favour of adalimumab for remission, response 70 and response 100. A statistically significant difference in favour of adalimumab versus placebo was observed for change in IBDQ score at week 4 relative to baseline.

Pooling and indirect comparison

The two adalimumab trials differed with respect to their populations: CLASSIC I[63] excluded patients if they had previously received any anti-TNF treatment while the GAIN[64] trial recruited only patients who had previously experienced infliximab treatment but had proved intolerant or unresponsive; because of these clear population differences results from the two trials were not pooled. The existence of only a single induction trial for infliximab in this population precluded pooling.

No head-to-head induction trial of infliximab versus adalimumab has been conducted. A possible approach to compare effectiveness of the two drugs is by indirect comparison using trials with a 'common' comparator (e.g. placebo). The Targan *et al.* population,[57] in contrast to that in GAIN,[64] was naive to anti-TNF therapy and therefore indirect comparison between these trials was not judged productive. The placebo rates for remission and response 70 in Targan *et al.*[57] were low compared with those in the adalimumab trials and are indicative of likely differences between the potentially 'common' comparator groups possibly stemming from the very small sample size of the placebo group in the Targan *et al.*[57] trial. Because of the likely difference in target placebo populations, indirect comparison was judged more likely to be misleading than informative. It is relevant that neither industry submission undertook an indirect comparison between these induction trials. One way clinical heterogeneity may be expressed is in different response rates in placebo groups. Although CDAI scores at baseline may be similar between trials, this could mask considerable clinical heterogeneity because CDAI is a summary score and patients can achieve the same score yet may have problems with quite different aspects of their disease.

Maintenance trials in adults (wholly or predominantly non-fistulising)

These are trials in which all patients receive short-term induction therapy with anti-TNF and then proceed to longer term treatment with either placebo or anti-TNF. The predominant aim of these trials was to investigate whether anti-TNF was superior to placebo in maintaining any favourable clinical response observed from induction therapy. As no true placebo comparator existed during the induction therapy it is not possible to determine how much of the favourable clinical response seen from induction was actually attributable to active intervention. This complicates interpretation of results.

Four trials were identified, two with infliximab [Rutgeerts *et al.*[58] and ACCENT I (Hanauer *et al.*[3] and Rutgeerts *et al.*[2])] and two with adalimumab [CLASSIC II (Sandborn *et al.*[66]) and CHARM

(Colombel *et al.*[67])]. These studies were characterised by distinct differences in induction regimens.

The Rutgeerts *et al.*[58] trial was an extension of the Targan *et al.*[57] infliximab induction trial. Patients eligible had received variably one or two previous infusions of placebo or of infliximab at doses of 5, 10 or 20 mg/kg. Patients with a response 70 were then eligible for the trial. The induction regimen of participants in this trial was variable and not clearly defined, making it difficult to identify the precise target population involved.

Similarly to Rutgeerts *et al.*,[58] the CLASSIC II[66] trial was an extension of a previously conducted induction trial, namely the CLASSIC I[63] study of adalimumab. Patients eligible for CLASSIC II were required to be in remission (CDAI < 150) at week 4 of CLASSIC I and also 4 weeks later. These patients may have received two subcutaneous injections 2 weeks apart of various doses of adalimumab (40 mg then 20 mg, 80 mg then 40 mg, or 160 mg then 80 mg) or of placebo.

The ACCENT I[2,3] (infliximab) and CHARM[67] (adalimumab) trials were free-standing maintenance trials with more straight forward induction regimens. In ACCENT I patients received a single induction infusion of 5 mg/kg infliximab. In CHARM patients received subcutaneous induction injections of 160 mg of adalimumab and of 80 mg of adalimumab 2 weeks apart.

The main study and population characteristics are shown in *Table 13*. The main outcome measures described in the published reports of the four trials are summarised in *Table 14*.

Rutgeerts *et al.*, 1999[58] (infliximab)

The Rutgeerts *et al.*[58] trial was an extension of the Targan *et al.*[57] infliximab induction trial and included 73 of the original 108 patients. Targan *et al.*[57] consisted of a 4-week comparison between placebo and one dose of infliximab in three arms (5 mg/kg, 10 mg/kg or 20 mg/kg). This was followed after a maximum of 2 weeks by an open-label phase with 12 weeks of follow-up that started with the option of a 10 mg/kg dose of infliximab for week 4 non-responder patients. To be eligible to enrol in Rutgeerts *et al.*[58] the Targan *et al.* week 4 responder patients needed to achieve a response 70 at week 8, and the week 4 non-responder patients needed to achieve a response 70 at week 8 after the open-label option of a 10 mg/kg infusion of infliximab. Four weeks after qualifying (week 8 after induction infliximab or 8 weeks after open-label infliximab) the eligible patients were randomised to i.v. infusion of placebo or 10 mg/kg infliximab (designated week 12 of maintenance phase) and a further three infusions at 8-week intervals (a total of four infusions after becoming eligible to participate; administered weeks 12, 20, 28 and 36). Follow-up continued to week 48.

The induction regimen in this study was variable between patients in duration and in exposure to infliximab. In consequence, induction was ill-defined and the distinction between the induction regimen and maintenance regimen was also unclear. The eligible patients could have received any of the following possible infusions of infliximab: no infliximab (placebo), one 5 mg/kg infusion, one 10 mg/kg infusion or one 20 mg/kg infusion; a second infusion of 10 mg/kg could be given (to any patients) at week 4 if there was no response. Four patients received no infliximab (placebo and no second 10 mg/kg dose as a response was achieved). How closely the trial induction phase corresponds to the licence indication is uncertain.

A, response 70

No primary outcome measure was identified. The response 70 results presented (summarised in *Figure 9*) referred to point prevalence at assessment time points and do not necessarily indicate maintenance of individual patient response. At week 8 > 90% of patients had a response 70

TABLE 13 Main study and population characteristics: maintenance trials in adults predominantly or wholly non-fistulising

Study[a] Drug	Weeks *n*	Population: severity of CD Baseline CDAI and IBDQ if stated	Areas affected	Main concomitant medication[b]	Previous anti-TNF therapy	Intervention and comparator (dosing regimen)
[c]Rutgeerts *et al.*, 1999[58] Infliximab	48 73	Moderate-to-severe, CDAI 220–400 'treatment resistant' Median CDAI: placebo 305; infliximab 310 Median IBDQ: placebo 121; infliximab 111	Mainly ileum and colon or colon only, some ileum only	Corticosteroids or immunosuppressive agents 'allowed', non-responders to aminosalicylates 'eligible'	Excluded if had received monoclonal antibodies prior to Targan *et al.* study[57]	Variable treatment with infliximab or placebo in previous RCT then re-randomisation to placebo or infliximab (10 mg/kg/kg i.v.) at 8-week intervals
Hanauer *et al.*, 2002[3] and Rutgeerts *et al.*, 2004[2] – ACCENT I[2,3] Infliximab	54 573	Moderate-to-severe, CDAI 220–450 CDAI median (IQR): placebo 292 (256–341); infliximab 303 (268–346) and 297 (256–346) IBDQ median (IQR): placebo 126 (110–144); infliximab 126 (109–146) and 131 (109–152)	Mainly ileum/ colon, also colon only or ileum only; some gastroduodenum	Corticosteroids, immunosuppressives, oral aminosalicylates	Excluded if previously treated with any anti-TNF agent	All receive 5 mg/kg infliximab i.v.; then seven additional infusions (weeks 2, 6, then every 8 weeks) of either placebo or infliximab (5 mg/kg or 10 mg/kg) (Note both infliximab groups received 5 mg/kg at weeks 2 and 6)
Sandborn *et al.*, 2007[66] – [d]CLASSIC II[66] Adalimumab	56 55	All patients in remission week 0 (week 4 CLASSIC I[63]) Baseline corresponds to CLASSIC I[63] week 4 CDAI mean (SD): Placebo 107 (62); adalimumab 106 (33) and 88 (50) IBDQ median (range): placebo 191 (138–224); adalimumab 188 (128–213) and 200 (138–216)	No further details As CLASSIC I[63]	Mainly oral aminosalicylates or corticosteroids, some immunosuppressive agents	Unclear if all previously received adalimumab or if patients in remission after placebo were included	Subcutaneous infusion 40-mg adalimumab from weeks 4–55, weekly or e.o.w. Not stated if placebo weekly or e.o.w.
Colombel *et al.*, 2007[67] – CHARM[67] Adalimumab	56 778	Moderately-to-severely active CD, CDAI 220–450 CDAI mean (SD)[e]: 313.1 (62.0) IBDQ median (range)[e]: 122.0 (44–205)	Mainly ileum or colon, few gastroduodenal or other (not stated)	Corticosteroids, immunosuppressive agents, oral aminosalicylates	424 (49.6%) previously exposed to anti-TNF (must *not* have exhibited an initial non-response)	All received adalimumab 80 mg subcutaneously, then 40 mg at week 2; randomisation at week 4, then 40-mg adalimumab, weekly or e.o.w. Not stated if placebo weekly or e.o.w.

e.o.w., every other week.

a All were industry sponsored multicentre studies mostly conducted in the USA, Canada and Europe; CHARM centres in Australia and South Africa also participated.

b Percentage 'not on any medication' was not stated in any study.

c An extension of the Targan *et al.*[57] trial.

d An extension of the CLASSIC I[63] trial.

e Whole group, includes patients who withdrew before randomisation.

TABLE 14 Outcomes measured in maintenance trials with mainly non-fistulising adult populations

	% of patients in remission (CDAI score <150)	% achieving 100-point response on CDAI	% achieving 70-point response on CDAI	CDAI score (mean or median)	IBDQ score (mean or median)	Additional outcomes
Infliximab						
Rutgeerts *et al.*, 1999[58]	✓	X	✓	✓	✓	Median CRPc. Time to loss of response
ACCENT I[2,3]	✓	X	✓	✓	✓	Patients with CD-related intra-abdominal surgery; CD-related hospitalisations; patients discontinuing and remaining free from corticosteroids; mucosal healing (subgroup)
Adalimumab						
CLASSIC II[66]	✓	✓	✓	X	✓	Median CRPc, % of patients discontinuing steroids without loss of remission
CHARM[67]	✓	✓	✓	✓	✓	% of patients in remission at week 4 who were also in remission at week 56; median time in remission; corticosteroid free remission; fistula response

CRPc, C-reactive protein concentration.

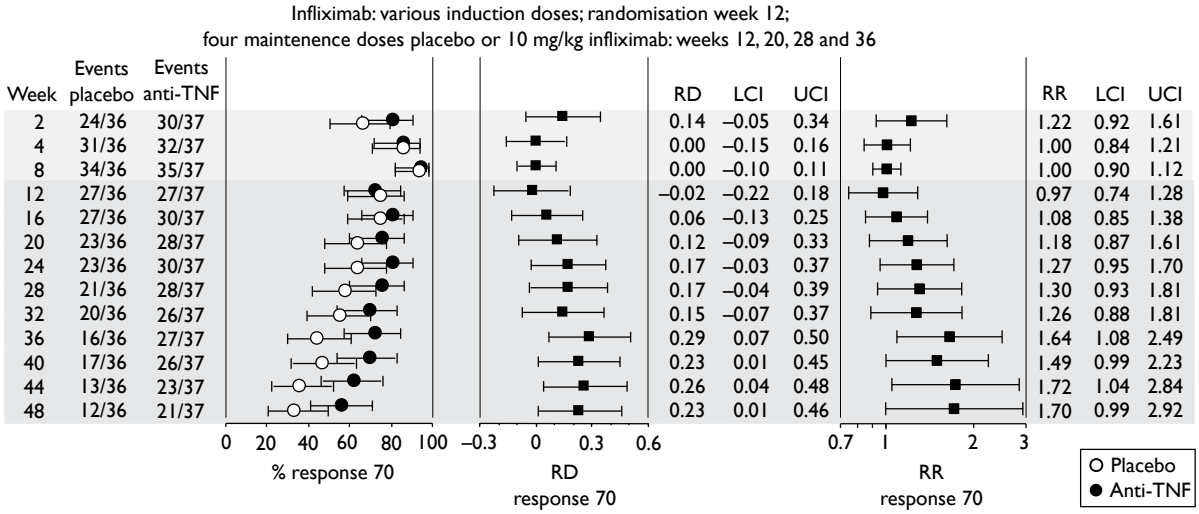

FIGURE 9 Response 70 rates in Rutgeerts *et al.*[58] At weeks 24 and 48 risk difference $p = 0.094$ and $p = 0.038$ respectively. At weeks 24 and 48 risk ratio $p = 0.108$ and $p = 0.054$ respectively. LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

(CDAI reduced by > 70 points relative to baseline in Targan *et al.*[57]). At week 12 (randomisation week) this had diminished to about 75% and by week 48 had further diminished to 33% in the placebo group and 57% in the infliximab group ($p = 0.038$ for risk difference and $p = 0.054$ for risk ratio). Point estimates were associated with considerable uncertainty. The authors stated that of patients with response 70 at the last infusion (week 36), 62% of the infliximab group and 37% of the placebo group maintained their response for the 8 weeks to week 44 ($p = 0.16$).

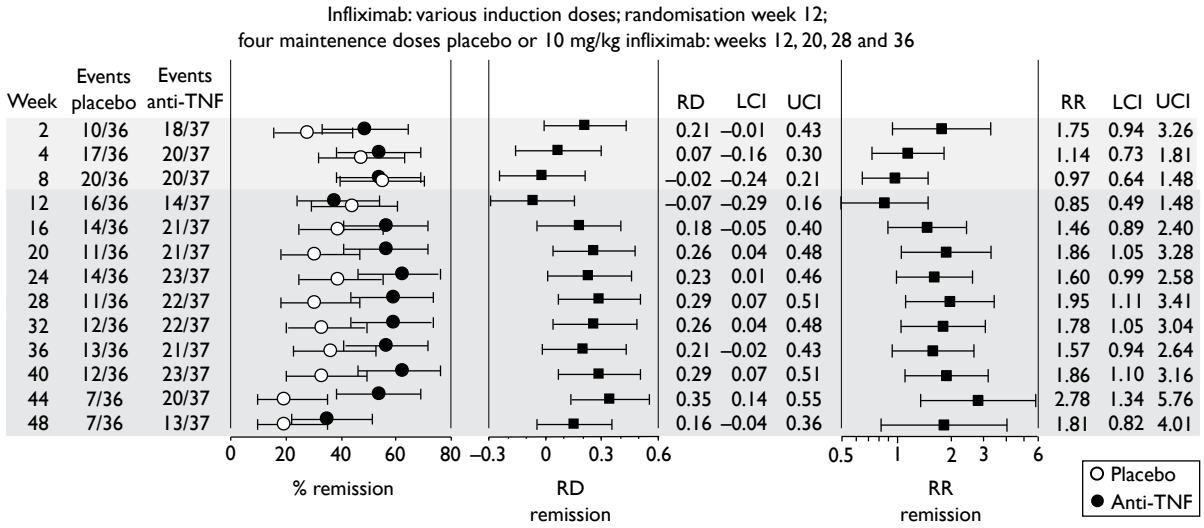

FIGURE 10 Remission rates in Rutgeerts *et al*.[58] LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

B, response 100

This outcome was not reported.

C, remission

The point prevalence of remission at different follow-up weeks was reported (results are summarised in *Figure 10*). Point estimates were associated with considerable uncertainty. At randomisation (week 12) ~38% of patients were in remission in the infliximab group; this increased to ~ 60% during weeks 16–40. The corresponding values for the placebo group were ~ 44% (week 12) and 35% (weeks 16–40). Risk difference (infliximab–placebo) and risk ratio (infliximab/placebo) just reached statistical significance ($p < 0.05$) at most time points for weeks 16–40.

D, other outcomes

Time to loss of response for patients achieving a response at '*any time*' during follow-up after randomisation was reported. The criteria for loss of response were not explicit. Over 48 weeks it is possible for a patient to enter a response state on several occasions. The publication did not make clear which occasion(s) were used in the analysis, or how and if double counting was avoided. The log rank test for difference between placebo and infliximab groups just failed to reach statistical significance ($p = 0.057$).

Median CDAI score, median IBDQ score and median CRP concentrations were reported, but range of values and statistical analyses for these outcomes were not presented. The results were in favour of infliximab relative to placebo with greater reduction in CDAI scores, larger increases in IBDQ scores and more 'normalisation' of CRP concentrations. The results published are summarised in *Figure 11*.

Quality assessment (based on published report)

Randomisation, allocation concealment and blinding were adequate. Baseline values for those characteristics reported were evenly balanced, but values for CRP, which was not balanced in the original Targan *et al*. trial,[57] were unclear. Analysis of response 70 and remission rates was by ITT; the results presented were point prevalence values at various follow-up times, and they therefore represent maintenance of response at the group level only and not maintenance by individual

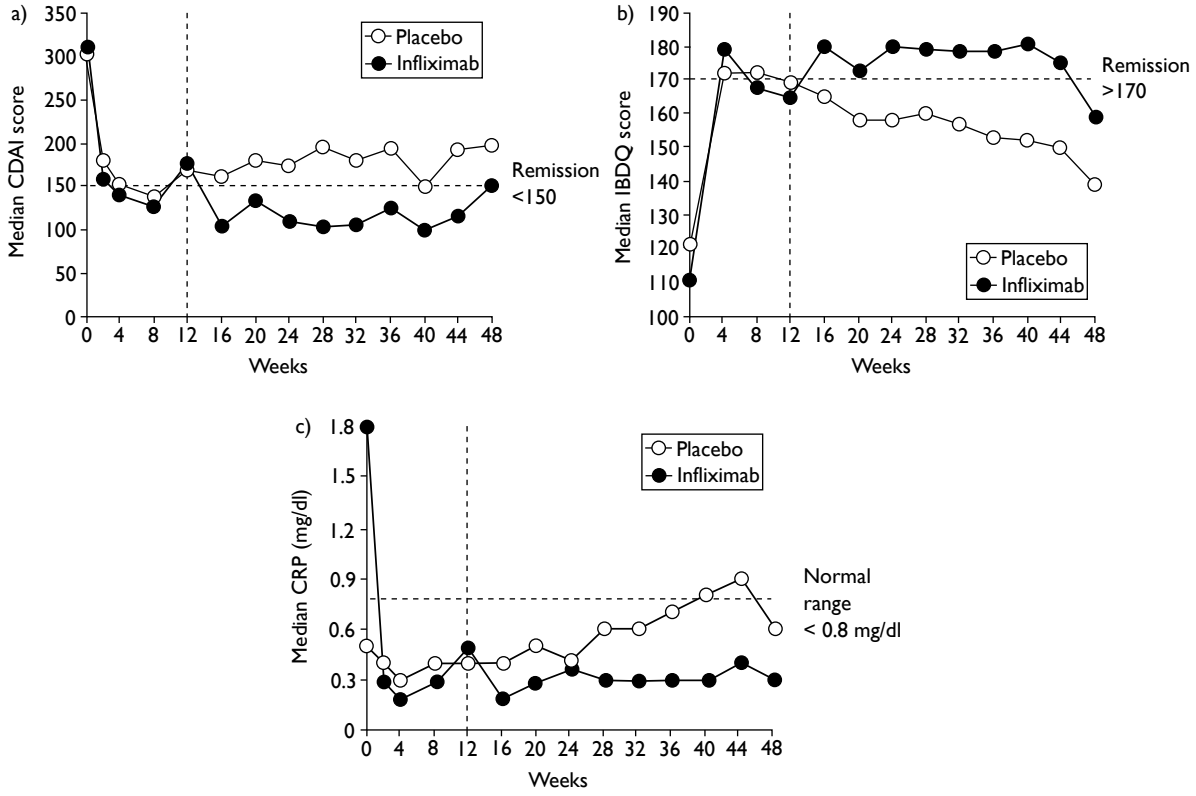

FIGURE 11 Median CDAI, IBDQ and CRP levels reported in Rutgeerts *et al*.[58] Data taken from published graphs and redrawn. Where necessary the authors carried last observation forward.

patients. For continuous outcomes, last observation was carried forward where necessary, but the number of missing data was not reported. No primary outcome was identified and no power calculation was described; the combined trials appear to have been powered only for the induction analysis of Targan *et al*.[57] (at week 4 of that study). The maintenance part of the study was probably underpowered. About 33% of patients withdrew.

Rutgeerts *et al*., 1999.[58] Summary of effectiveness evidence

The study recruited patients from among responders (CDAI score reduced by 70 points) following on from the Targan *et al*. trial[57] and the resulting induction phase varied between patients in both duration and dose regimen. Subsequent maintenance treatment with infliximab (four infusions of 10 mg/kg at 8-week intervals) generated a greater proportion of patients with a response 70 and with remission than did treatment with placebo. Point prevalence estimates for these outcomes were associated with considerable uncertainty. The trial left unanswered how well a clinical response is sustained at the individual patient level.

ACCENT I[2,3] (infliximab)

This was a free-standing maintenance trial (i.e. newly started).[2,3] There were 580 eligible patients (CDAI range 220–400), of whom 573 received a single induction infusion of 5 mg/kg infliximab. Two weeks later patients were randomised to placebo, to 5 mg/kg infliximab at weeks 2 and 6 and then every 8 weeks to week 54, or to 5 mg/kg at weeks 2 and 6 and then 10 mg/kg infliximab every 8 weeks to week 54 (these groups are here termed 5 mg/kg and 10 mg/kg groups respectively).

At week 2 (randomisation week) patients were classified as responders (335/573, 58.5%) or non-responders (238/573, 41.5%) depending on whether they achieved a response 70 (a reduction of > 70 points in CDAI score at week 2 relative to baseline). At week 14 patients who initially responded but then worsened were eligible to cross over to treatment with increased dosage of infliximab; this crossover treatment for the placebo group was termed 'episodic treatment'. The results for responders were published in 2002 (Hanauer *et al.*[3]) and patients who crossed over to increased dosage after week 14 for most of these analyses were considered as treatment failures.

Effectiveness results published for responders only in 2002 (Hanauer *et al.*[3]) are reviewed below, and results for all patients, irrespective of responder status at week 2 and published in 2004 (Rutgeerts *et al.*[2]), are considered in the following section.

ACCENT I: results for responders

Of the 335 responders (58.5% of those who had received an induction dose of 5 mg/kg infliximab), 110 were randomised to placebo, 113 to the 5 mg/kg infliximab group and 112 to the 10 mg/kg infliximab group.

A, response 70

The published results for responders[3] included graphical presentation of point prevalence of response 70 at weeks 30 and 54. These results are summarised in *Table 15*. A statistically significant difference in rates in favour of infliximab versus placebo was reported for both infliximab groups at weeks 30 and 54. The manufacturer's submission provided point prevalence rates for response 70 for all assessment visit weeks from 2 to 54. These results are summarised in *Figure 12*.

Point estimates were associated with appreciable uncertainty. Week 2 response rates of ~90% had diminished in all groups by week 54 to 15% in the placebo group and 38% and 47% in the 5-mgkg and 10 mg/kg infliximab groups respectively. Risk differences (infliximab–placebo) remained fairly constant from week 14 onwards. Risk differences and risk ratios (infliximab/placebo) reached statistical significance in favour of infliximab at all visit times from week 10 to week 54. It is unclear why week 2 response rates were less than 100%; it is possible some patients with a 70-point CDAI reduction from baseline nevertheless required surgery or a change in concomitant medication for worsening of clinical condition. After week 2, decline of response occurred in both placebo and intervention groups, then after week 10 risk differences remained similar [e.g. for the 5 mg/kg arm risk differences (infliximab–placebo) remained similar after week 14 as follows: at weeks 10, 14, 22, 30, 38, 46 and 54 risk differences were 0.14, 0.23, 0.26, 0.24, 0.21, 0.23 and 0.23 respectively]. This suggested that most benefit of infliximab was delivered in the first 10–12 weeks of the trial.

TABLE 15 Published response 70[a] rates for responders at weeks 30 and 54 in ACCENT I[2,3]

	Week 30[b]		Week 54[b]	
Dose regimen (*n*)	Response 70 (%)[b]	*p*[c]	Response 70 (%)[b]	*p*[c]
Placebo (110)	27%	NA	16%	NA
5 mg/kg group (113)	51%	0.0002	38%	0.0001
10 mg/kg group (112)	58%	< 0.0001	47%	0.0001

NA, not applicable.
a Response 70 defined as reduction of ≥ 70 CDAI points from baseline and no requirement for medication change or for surgery.
b Data read from published graph in Hanauer *et al.*[3]
c Intervention vs placebo.

B, response 100

This outcome was not reported.

C, remission rates

Remission was a coprimary outcome. The results published for remission at week 30 and week 54 are summarised in *Table 16*. For this outcome patients who worsened and crossed over to 'episodic treatment' (allowed from week 14 onwards) were counted as treatment failures (i.e. as no longer in remission). The results reported measured the point prevalence of remission for each group at week 30 and did not require maintenance of response from week 2 to week 30 at the patient level. A statistically significant greater proportion of patients were in remission at weeks 30 and 54 in the infliximab groups than in the placebo group. At week 30 the risk differences (infliximab–placebo) were 18% and 25% for the 5 mg/kg and 10 mg/kg groups respectively and the corresponding numbers needed to treat (NNT) (30 weeks) were 5.66 and 4. Note this NNT

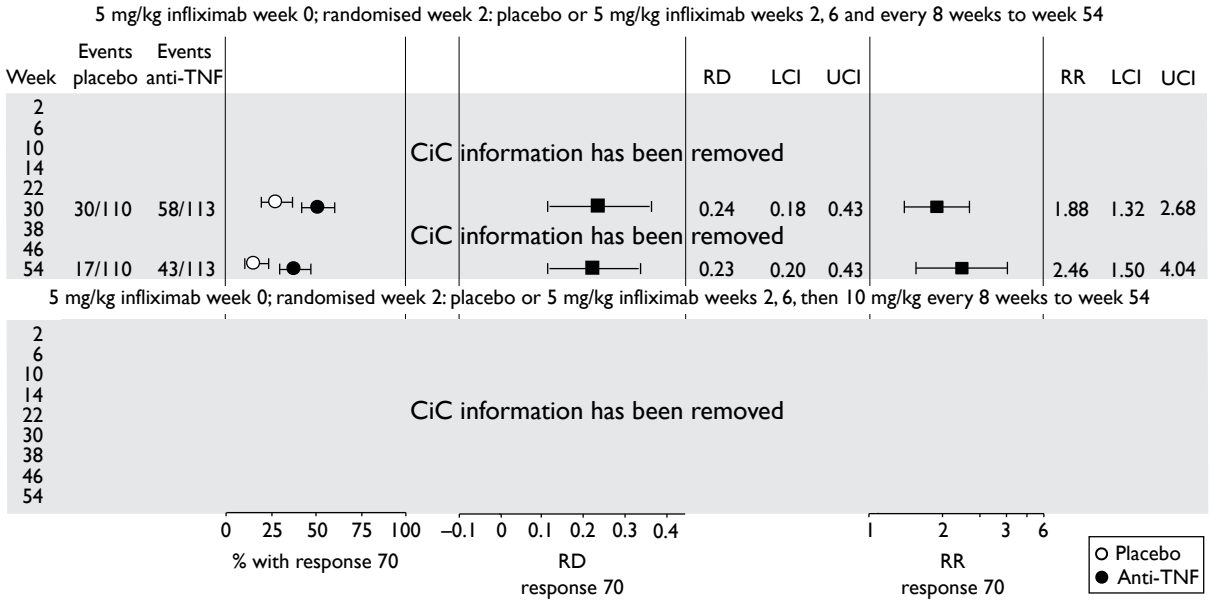

FIGURE 12 Response 70 rates for responders throughout follow-up in ACCENT I.[2,3] CIC, commercial-in-confidence; LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

TABLE 16 Remission[a] rates for responders reported at weeks 30 and 54 in ACCENT I[2,3]

	Week 30			Week 54	
Dose regimen (*n*)	Remission: % (95% CI[b]) (number)	Odds ratio (95% CI) intervention/placebo	*p*[c]	Remission (%)[d]	*p*[c]
Placebo (110)	21% (14% to 29%) (23)	NR	NA	14%	NA
5 mg/kg group (113)	39% (30% to 48%) (44)	NR	0.003	28%	0.007
10 mg/kg group (112)	45% (36% to 55%) (50)	NR	0.002	38%	< 0.0001
5 mg/kg and 10 mg/kg groups combined (225)	42% (36% to 48%) (94)	2.7 (1.6 to 4.6)	NR	33%	

NA, not applicable; NR, not reported.
a Remission defined as a CDAI < 150 and no requirement for change in medication or for surgery.
b Calculated from published values.
c Intervention vs placebo.
d Data read from published graph in Hanaeur *et al.*[3]

estimate does not include non-responders who had been administered induction infliximab. The point prevalence of remission had diminished somewhat by week 54.

The unpublished Industry Trial Report for ACCENT I[2,3] provided information regarding the maintenance of remission at the individual patient level for weeks 14–54. The percentages were slightly discrepant with those in the published report as indicated in *Table 17*.

The manufacturer's submission and the Industry Trial Report provided commercial-in-confidence (CiC) point prevalence rates for remission for all assessment visits from weeks 2 to 54. These results are summarised in *Figure 13*.

Point estimates were associated with appreciable uncertainty (CiC information has been removed). From week 10, remission rates diminished in all groups and risk difference (infliximab–placebo) diminished or remained fairly constant; risk differences and risk ratios (infliximab/placebo) reached statistical significance at all visit times from week 10 onwards. It is evident that loss of remission was continuous after weeks 6–10 of follow-up and that the advantage of intervention over placebo was mostly gained by about weeks 6–10, the phase of the study during which dose frequency was greatest. Thereafter decline of response was about the same for both placebo and intervention groups despite continued infliximab every 8 weeks in the

TABLE 17 Patient level maintenance of remission reported in ACCENT I[2,3]

	% in remission at all visits from weeks 14 to 54		
	Placebo	**5 mg/kg group**	**10 mg/kg group**
Published report	11%	25%	33%
Trial report	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)

(CiC information has been removed.)

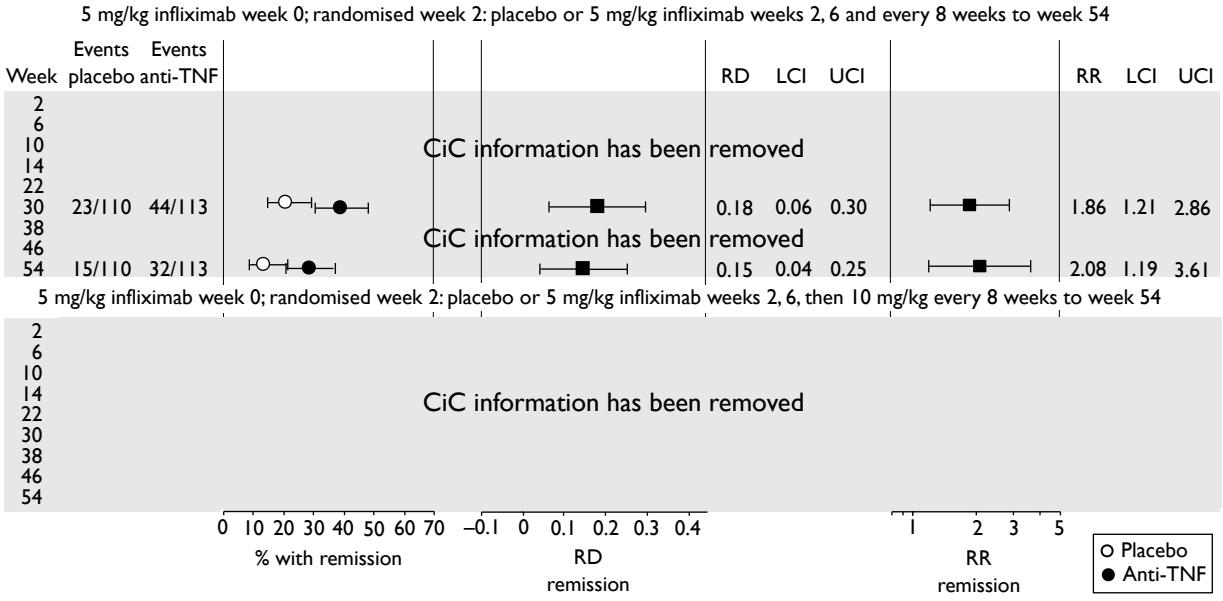

FIGURE 13 Remission rates for responders throughout follow-up in ACCENT I.[2,3] At week 30 risk difference $p = 0.0027$ and $p < 0.0001$ for 5 mg/kg and 10 mg/kg groups respectively. At week 30 risk ratio $p = 0.0047$ and $p = 0.00025$ for 5 mg/kg and 10 mg/kg groups respectively. LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

treatment arms; for example, for the 5 mg/kg arm risk differences (infliximab–placebo) remained similar after week 14 as follows: at weeks 10, 14, 22, 30, 38, 46 and 54 risk differences were 0.15, 0.21, 0.20, 0.18, 0.15, 0.15 and 0.15 respectively.

D, other outcomes

The primary outcome in ACCENT I[2,3] was identified as time to loss of response. (Note: a protocol amendment added the proportion of responder patients in remission at week 30 as a coprimary outcome, which has been reported above.) Loss of response was defined as a CDAI of ≥ 175, a CDAI increased by ≥ 35% and a CDAI increased by ≥ 70 points relative to the qualifying value for a response on at least two consecutive assessments, or requirement for change in medication or requirement for surgery. Assessments were scheduled at weeks 0, 2, 6, 10, 14 and then every 8 weeks to week 54. With this definition of loss of response, it is possible for an individual responder to no longer qualify as achieving a response 70 status, but counter-intuitively nevertheless to not have lost response. (For example, an individual with a CDAI of 221 at enrolment would qualify as a responder at week 2 with a CDAI score reduced by 71 points to 150. If this patient's CDAI subsequently rose to 170 he or she would no longer be in a response 70 but would nevertheless not have lost response because the increase in score from week 2 was < 70 points, < 35% of week 2 score and below a score of 175.) For this primary outcome, patients in the active intervention arms had significantly longer time to loss of response than patients given placebo ($p = 0.0002$, log rank test). The median times to loss of response are summarised in *Table 18*.

Published effectiveness results for responders included median CDAI scores and median IBDQ scores. These are summarised in *Table 19*. For missing values of CDAI and IBDQ, the nearest observation was carried forward. CDAI scores and IBDQ scores diminished and increased respectively to a greater extent in the infliximab groups than in the placebo group. The IQRs for median values during follow-up were not reported.

The manufacturer's submission provided information about QoL measures (SF-36). The SF-36 scores were reported separately for mental and physical components for weeks 30 and 54 of the trial, and mean improvement from baseline was reported. SDs of values were provided. The results are summarised in *Table 20*. Change from baseline for SF-36 physical component reached statistical significance in favour of infliximab at both weeks 30 and 54.

Median daily steroid dose was reduced by week 14 in all groups and then remained constant. The reduction in the infliximab groups was greater than that for the placebo group. The odds ratio for discontinuation of steroid use (infliximab/placebo) at week 54 was 4.2 (95% CI 1.5 to 11.5).

E, other considerations – subgroup analysis of remission rate in severe CD patients

The manufacturer's submission for infliximab provided CiC information about the proportion of responder patients who initially had severe disease (defined as a baseline CDAI score > 300) and who achieved remission status during follow-up. Results presented referred to patients classified as having severe disease who were randomised to the 5 mg/kg infliximab group [$n = 63/113$ (56%)] and placebo group [$n = 48/110$ (44%)]. No information was provided regarding patients with severe disease among non-responders. The remission rates in placebo and 5 mg/kg infliximab arms and the risk difference for this subgroup of patients are shown in *Figure 14*. Remission rates were slightly poorer in this more severe CDAI group than for all responders, but a similar pattern was shown during follow-up, in that most of the advantage from the intervention was achieved with the first three doses (early phase). Thereafter, remission decayed at approximately similar rates in the two arms even though patients in the intervention arm received further doses of infliximab and risk differences decreased from week 14 onwards.

TABLE 18 Median time to loss of response in responders in ACCENT I[2,3]

Dose regimen (*n*)	Median time (weeks) to loss of response	IQR (weeks)
Placebo (110)	19	10 to 45
5 mg/kg group (113)	38	15 to > 54
10 mg/kg group (112)	> 54	21 to > 54
5 mg/kg and 10 mg/kg groups combined (225)	46	17 to > 54

The upper range is given as > 54, as 54 weeks is the longest follow-up time; the upper end of the range is not actually known.

TABLE 19 Median CDAI and IBDQ scores for responders during follow-up in ACCENT I[2,3]

	CDAI: median[a]				IBDQ: median[a]			
Week	Placebo (*n* = 110)	5 mg/kg (*n* = 113)	10 mg/kg (*n* = 112)	*p*	Placebo (*n* = 110)	5 mg/kg (*n* = 113)	10 mg/kg (*n* = 112)	*p*
0	290	305	305	NS[b,c]	129	128	130	NS[b,c]
2	157	155	152	0.01[b] 0.04[c]	173	169	173	NR
6	159	138	140	< 0.0001[b] < 0.002[c]	165	174	161	NR
10	165	131	127	< 0.0001[b,c]	160	170	169	NS[b,c]
14	197	145	125	< 0.0001[b,c]	155	167	172	0.05[b] 0.0076[c]
22	217	163	135	< 0.0001[b,c]	142	164	169	0.013[b] < 0.0001 [c]
30	225	172	150	< 0.0001[b,c]	144	162	167	0.015[b] 0.001[c]
38	238	214	140	< 0.0001[b,c]	137	151	170	0.015[b] < 0.0001 [c]
46	235	200	142	< 0.0001[b,c]	135	144	169	0.06[b] < 0.0001[c]
54	238	192	152	< 0.0001[b,c]	136	150	167	0.015[b] < 0.0001 [c]

NR, not reported; NS, not significant.
a Data read from graph in Hanauer *et al.*[3]
b Comparison: 5 mg/kg group vs placebo.
c Comparison: 10 mg/kg group vs placebo.
Tests for significance were done by analysis of variance.

TABLE 20 SF-36 results reported for responders in ACCENT I[2,3]

SF-36 component	Group	SF-36 score			Mean improvement from baseline	
		Baseline	Week 30	Week 54	Week 30	Week 54
Physical Component	Infliximab	33.0 ± 8.5	40.4 ± 11.3	39.2 ± 11.9	7.3 ± 10.3	6.1 ± 10.8
	Placebo	33.9 ± 8.8	37.2 ± 11.3	36.5 ± 11.0	3.1 ± 9.5	2.5 ± 9.0
					p = 0.002	*p* = 0.014
Mental Component	Infliximab	38.8 ± 11.3	43.2 ± 11.4	43.9 ± 12.2	4.6 ± 12.7	5.1 ± 12.8
	Placebo	39.8 ± 11.3	42.8 ± 12.0	42.1 ± 12.0	2.9 ± 11.2	2.0 ± 10.9
					p = 0.348	*p* = 0.072

The results for infliximab refer to the 5 mg/kg group only. *p*-values refer to comparison between infliximab and placebo groups.

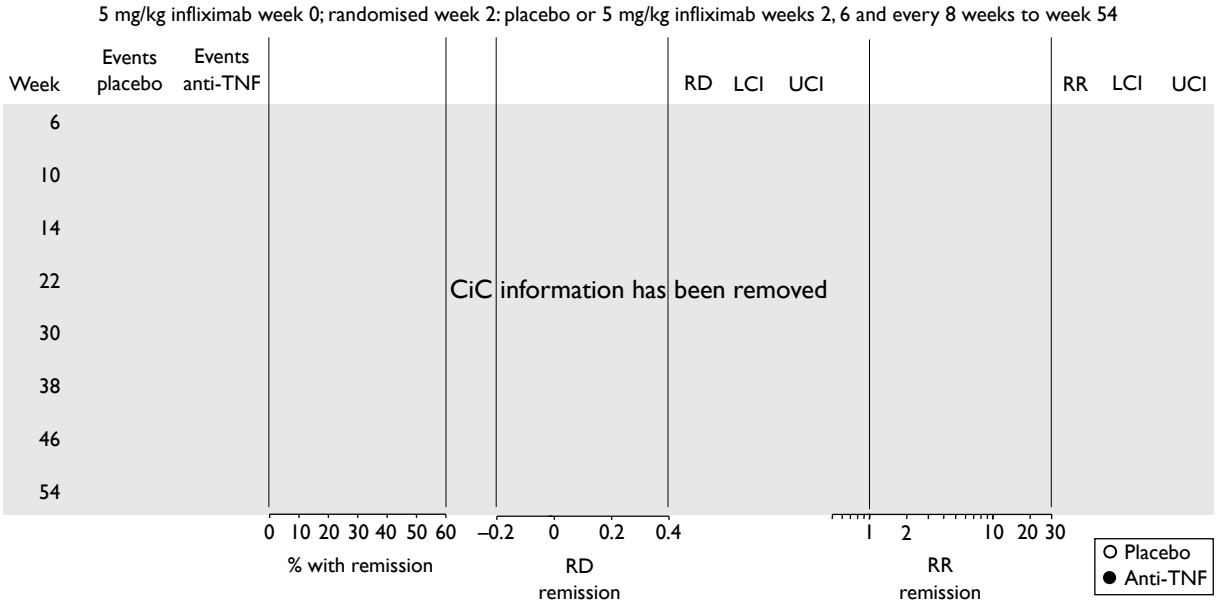

FIGURE 14 Remission rates, risk difference and risk ratio (severe disease responders ACCENT I[2,3]). LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

ACCENT I[2,3] (responders): quality assessment (based on published report of Hanauer et al.*[3])*

Randomisation, allocation concealment and blinding were adequate. Baseline characteristics were only reported for all patients (i.e. for all responders and for all non-responders). It was therefore not possible to judge if baseline characteristics were evenly balanced between the three arms of responders that were analysed for effectiveness outcomes. Similarly the number of patients who withdrew was reported for all enrolled patients and it was not possible to determine how many responders discontinued their randomised treatment. Where necessary, the nearest or last observation was carried forward for continuous outcomes but the number of missing data was not reported. A power calculation was conducted and based on the primary outcome of loss of response. The definition of loss of response was complex and did not correspond to a failure to maintain a response 70 status, and its clinical meaning was difficult to gauge.

ACCENT I: results for all patients (Rutgeerts *et al.*[2]) (infliximab)

The results for all 573 patients who received an induction dose in ACCENT I[2,3] were presented by Rutgeerts *et al.*[2] in a paper published 2 years after that, describing results for responders only. Separate results for non-responders have not been published. The 573 patients were 335 responders and 238 non-responders (defined according to whether a 70-point reduction in CDAI score was attained by week 2 after the induction infusion).

Randomisation at week 2 resulted in allocation of 188 patients to the placebo group, 192 to the 5 mg/kg group and 193 to the 10 mg/kg group.

The authors stated 'the primary objective of the analysis was to examine the difference in efficacy between episodic and scheduled treatment strategies with infliximab under conditions that simulate clinical practice'. For this purpose the patients in the original placebo group were designated as receiving 'episodic strategy', and those in the infliximab groups as receiving a '5 mg/kg scheduled strategy' and a '10 mg/kg scheduled strategy' respectively. From week 14 onwards patients who had shown a response to infliximab therapy at any time but then worsened were eligible to cross over to 'active episodic treatment as needed with infliximab 5,

ACCENT I.[2,3] Summary of effectiveness evidence for responders

Of the 573 patients (with baseline CDAI 220–400), 58.5% (335) achieved response 70 2 weeks after a single induction infusion of 5 mg/kg infliximab. These patients were designated 'responders'. It is unclear if the three trial arms of randomised responders were well balanced at baseline. Of responders, (CiC information has been removed)% were in remission (CDAI < 150) at week 2. This represented (CiC information has been removed)% of the original 573 patients. The proportion of responders with remission had declined by week 30 to 23% (95% CI 14% to 29%) for those who only received placebo after induction and to 39% (95% CI 30.% to 48%) for those who received four infusions of 5 mg/kg infliximab (at weeks 2, 6, 14 and 22) and to 42% (95% CI 36% to 55%) for those who received four infusions consisting of 5 mg/kg at weeks 2 and 6 and 10 mg/kg at weeks 14 and 22. Risk differences (infliximab–placebo) and risk ratios (infliximab/placebo) for remission at week 30 reached statistical significance in favour of infliximab for both infliximab groups. By week 54 the percentage of patients in remission had diminished further in all three groups. Most of the advantage of intervention relative to placebo was achieved by weeks 10–14; thereafter risk differences remained fairly stable. A similar pattern of results was observed for response 70. Published information regarding maintenance of remission at the patient level (as distinct from group level) was meagre. Between weeks 14 and 54, 11% of placebo patients retained remission at all six study visits; the corresponding values were 25% and 33% respectively for 5 mg/kg and 10 mg/kg infliximab groups. Somewhat lower values of (CiC information has been removed)%, (CiC information has been removed)% and (CiC information has been removed)% respectively were quoted in the Industry Trial Report. Results favouring infliximab over placebo were reported for several other outcomes including median CDAI scores and median IBDQ scores. These measures required last or nearest observation carried forward in order to allow for missing data.

10, and 15 mg/kg for patients originally assigned to episodic, 5 mg/kg scheduled, and 10 mg/kg scheduled treatment strategies respectively'. This description is confusing as it clearly states that active episodic treatment is given in both episodic and scheduled strategies, which renders a comparison of episodic and scheduled strategies problematic. The publication designates the start of episodic treatment to be week 14 (see *Appendix 9* for patient flow through the trial).

The treatment regimens received before week 14 in each of the randomised groups were as follows:

- placebo/'episodic group': 5 mg/kg infliximab week 0, placebo weeks 2 and 6
- 5 mg/kg group 'scheduled strategy': 5 mg/kg infliximab weeks 0, 2 and 6
- 10 mg/kg group 'scheduled strategy': 5 mg/kg infliximab weeks 0, 2 and 6.

Treatment to week 14 was therefore similar for the two infliximab 'scheduled strategy' groups and was determined according to randomisation. From week 14, crossover to an increase in infliximab dosage was allowed in all three trial arms for patients whose CD worsened. The criteria for worsening were 'an increase CDAI of ≥ 70 points from the qualifying score with a total score of at least 175, an increase in CDAI of 35% or more from baseline value, or the introduction of new treatment for active Crohn's disease'. From week 14 onwards it was possible for patients in different arms to be receiving identical infliximab treatment; for example, a placebo patient might cross over at week 14 to receive 5 mg/kg and this corresponds to treatment received by a 5 mg/kg 'scheduled strategy' patient who did not cross over. This complicates the interpretation of any comparisons between groups.

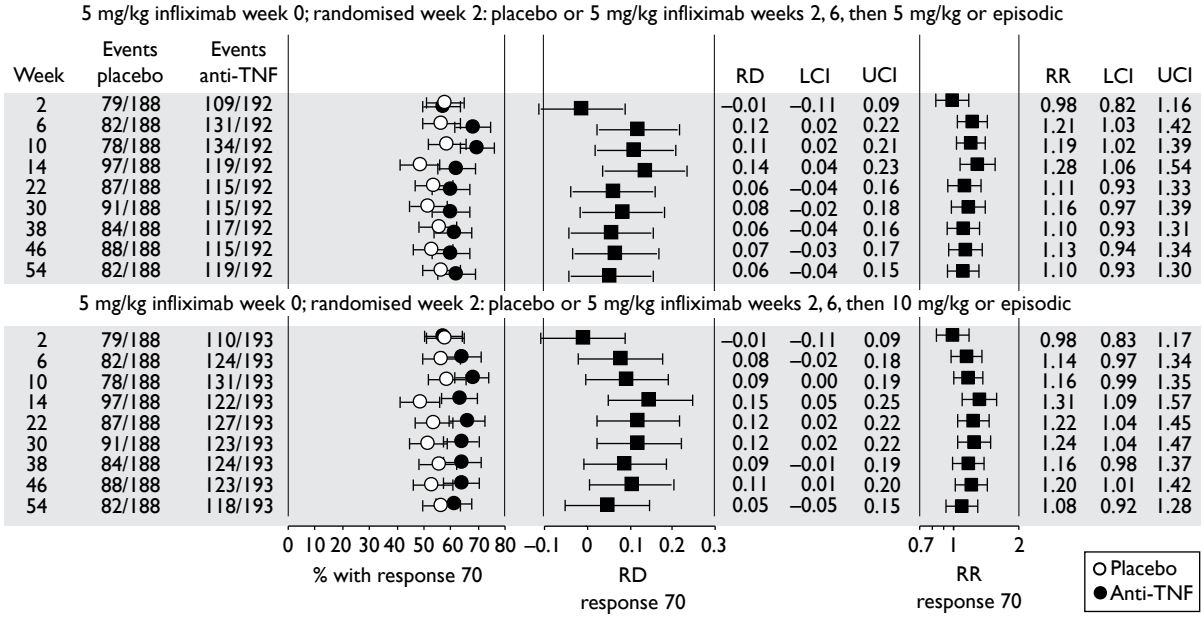

FIGURE 15 Response 70 rates for all patients in ACCENT I.[2,3] LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

A, response 70

No primary outcome was identified. Analyses were according to randomised group irrespective of crossover after week 14 to different treatment regimen, and comparisons were drawn between the 'episodic group' and the two 'scheduled strategy' groups. The results for response 70 for all patients in ACCENT I are summarised in *Figure 15*. By week 14, statistically significant differences in CD status were evident between placebo group and intervention groups (*p*-values for risk differences and risk ratios are shown in *Table 21*). Risk differences and risk ratios for comparison between 'episodic' and 'scheduled' strategies after week 14 were in favour of 'scheduled strategies' but failed to reach statistical significance at most time points. Interpretation of these differences is problematic.

B, response 100

This outcome was not reported.

C, remission rates

Figure 16 summarises the published results for rates of remission at clinic visits to end of follow-up (week 54). Week 14 remission rates were greater in the two 'scheduled treatment' arms (37.5% in the 5 mg/kg group and 43% in the 10 mg/kg group) than in the 'episodic' group (25.5%). *p*-values for week 14 comparisons between placebo and intervention groups are shown in *Table 22*.

Treatment regimens up to week 14 were strictly pre-specified and designed to examine effectiveness for maintenance of the induced response. After week 14 treatment regimens became variable (termed 'episodic' by the authors). It is clear that by week 14 the CD status of patients in the placebo/'episodic' arm had departed from that of patients in the two 'scheduled strategy' arms; this means that at baseline (week 14) for the comparison of 'episodic' with 'scheduled strategies', the groups were imbalanced. Comparisons between 'episodic' and 'scheduled' strategies after week 14 are not randomised comparisons. For a randomised comparison of the two strategies patients should have been rerandomised at week 14. Such rerandomisation

TABLE 21 *p*-values for comparison of response 70 rates at week 14 for all patients in ACCENT I[2,3]

	Risk difference (placebo–active intervention)		Risk ratio (placebo/active intervention)	
	vs 5 mg/kg group	vs 10 mg/kg group	vs 5 mg/kg group	vs 10 mg/kg group
p	0.00725	0.00326	0.00865	0.00418

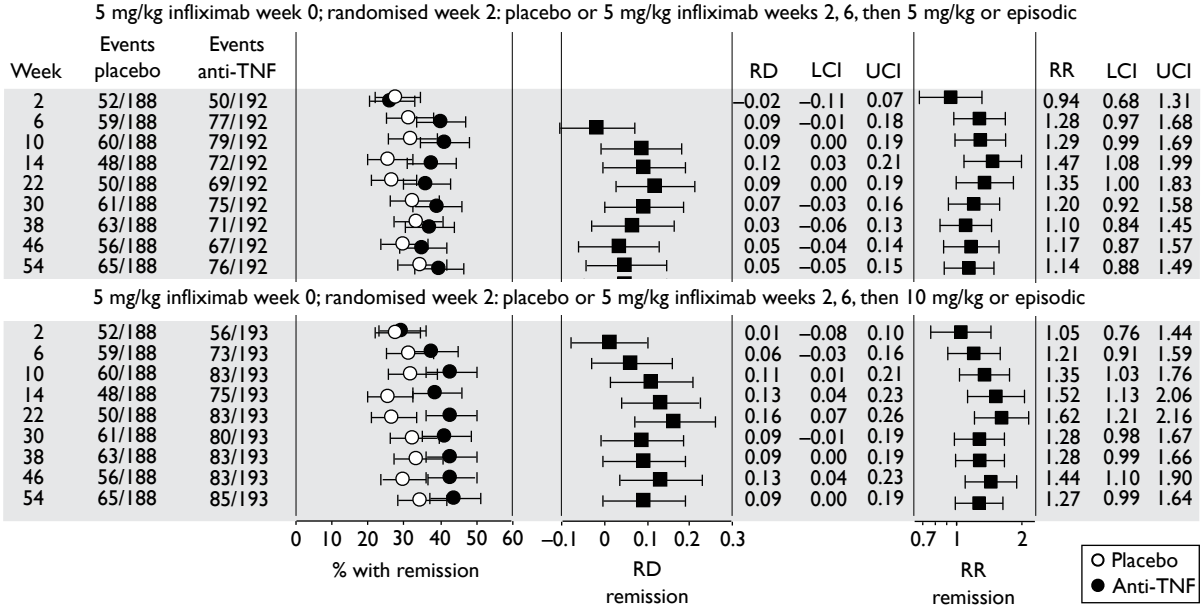

FIGURE 16 Remission rates for all patients in ACCENT I.[2,3] LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

TABLE 22 *p*-values for comparison of remission rates at week 14 for all patients in ACCENT I[2,3]

	Risk difference (placebo–active intervention)		Risk ratio (placebo/active intervention)	
	vs 5 mg/kg group	vs 10 mg/kg group	vs 5 mg/kg group	vs 10 mg/kg group
p	0.0113	0.0049	0.0135	0.0063

was precisely the study design adopted by Menter *et al.*[70] when comparing continuous with intermittent treatment strategies with infliximab in psoriasis.

Risk differences and risk ratios for comparison between 'episodic' and 'scheduled' strategies after week 14 were in favour of 'scheduled strategies', but failed to reach statistical significance at nearly all time points. Interpretation of these differences is problematic because, as described above, the comparisons are not between properly randomised groups and because patients in all groups were allowed the option of 'episodic' treatment.

D, other outcomes

Median CDAI score and the proportion of patients with IBDQ score > 170 were reported and are summarised in *Table 23* and presented graphically in *Appendix 10*. By week 14, statistically significant differences in CDAI median scores were evident between the placebo group and the intervention groups. Differences were less pronounced after week 14, especially for the placebo versus 5 mg/kg comparison. The percentage of patients with IBDQ score > 170 did not differ

TABLE 23 CDAI and IBDQ results for all patients in ACCENT I[2,3]

	CDAI: median[a]				% patients with IBDQ score > 170[a]			
Week	Placebo (*n* = 188)	5 mg/kg (*n* = 193)	10 mg/kg (*n* = 192)	*p*	Placebo (*n* = 188)	5 mg/kg (*n* = 193)	10 mg/kg (*n* = 192)	*p*
0	292	303	297	NS[b,c]	4.8	5.2	8.3	NS[b,c]
2	197.5	205	195	NS[b,c]	35.6	32.3	35.8	NS[b,c]
6	205	180	180	NS[b,c]	33.5	41.7	38.3	NS[b,c]
10	187.5	170	167.5	< 0.05[b,c]	35.1	41.7	39.9	NS[b,c]
14	225	185	182.5	< 0.05[b,c]	29.8	38.0	40.9	NS[b] < 0.05[c]
22	212.5	185	167.5	< 0.05[b,c]	29.3	37.0	44.0	NS[b] < 0.05[c]
30	212.5	180	177.5	NS[b] < 0.05[c]	33.5	39.6	44.0	NS[b] < 0.05[c]
38	200	187.5	170	NS[b] < 0.05[c]	35.1	34.9	47.7	NS[b] < 0.05[c]
46	205	190	175	NS[b] < 0.05[c]	33.5	35.4	48.7	NS[b] < 0.05[c]
54	205	185	170	NS[b] < 0.05[c]	35.1	37.5	46.1	NS[b] < 0.05[c]

NS, not significant.
a Data read from graph in Rutgeerts *et al.*[2]
b Comparison: 5 mg/kg group vs placebo.
c Comparison: 10 mg/kg group vs placebo.
There was no adjustment for repeated measures in the comparisons.

TABLE 24 Endoscopy, hospitalisation and abdominal surgery results: all patients in ACCENT I[2,3]

	Endoscopy		Hospitalisations[a]		Abdominal surgery	
	Mucosal healing at week 54	*p*[b]	*n*/*N* (%)	Relative risk (95% CI)	*n*/*N*	Relative risk (95% CI)
Placebo	4/22	NA	71/188 (38%)	NA	14/188	NA
5 mg/kg group	8/19	0.093			5/193	0.348[c] (0.128 to 0.947)
10 mg/kg group	8/17	0.053			6/192	
Combined 5- and 10 mg/kg groups	16/36	0.041	86/305 (23%)	0.591[b,c] (0.455 to 0.768)	11/385	0.373 (0.173 to 0.806)

NA, not applicable.
a The hospitalisation rates were presented differently to other rates as number per 100 patients, rather than number per total at risk. We have calculated the number of hospitalisations based on the reported percentage and the known total numbers of patients.
b Comparison for placebo vs infliximab.
c Values presented in industry submission for hospitalisation were 0.6 (0.5 to 0.7) and for abdominal surgery were 0.3 (0.2 to 0.6).

significantly between placebo and 5 mg/kg groups, but after week 14 favoured the 10 mg/kg group relative to placebo.

The manufacturer's submission provided information regarding CD-related hospitalisation rates and rates for intra-abdominal surgery. These rates and the relative risk for the 5 mg/kg 'scheduled maintenance' group relative to the 'episodic' are summarised in *Table 24*. The results for mucosal healing observed for a small subgroup of patients ($n = 58$) at European study centres who underwent endoscopy examination are also tabulated. The interpretation of the comparisons is problematical for the reasons already described, in particular after week 14. The extent to which avoidance of hospitalisation and abdominal surgery might depend on the administration of active intervention is not measurable because no true control (placebo) group existed after that time.

Quality assessment of ACCENT I[2,3] (all patients): (based on published report of Rutgeerts et al.*[2])*

Randomisation, allocation concealment and blinding were adequate. Baseline characteristics at week 0 were well balanced. Where necessary, the nearest or last observation was carried forward for continuous outcomes but the number of missing data was not reported. No power calculation was conducted for the analysis of all patients. The number of patients who withdrew was reported except for patients who crossed over to a 15 mg/kg dose regimen from a 10 mg/kg regimen. The proportion of patients who withdrew before the end of the trial was substantial.

Trial design, withdrawals, crossovers and validity of comparisons It must be questionable whether the 'episodic' (placebo) arm did 'simulate clinical practice' as stated to be an objective of the study. Patients in this arm of the study received one dose of 5 mg/kg infliximab at week 0, followed by an interim period of > 3 months with no active infliximab therapy before the 'episodic' use of infliximab according to worsening disease (for patients 'who had responded at any time to infliximab therapy'). There is little evidence to support the idea that this resembles clinical practice. The scheduled strategy is difficult to define as it did not follow a prescribed programme of treatment as might be anticipated by the term 'scheduled strategy', but encompassed 'episodic' treatment in the same manner as the 'episodic' arm.

Because of the large numbers of patients who withdrew from treatment and crossed over to dose escalations, the actual treatments received in the three different trial arms are difficult to define. *Figure 17* summarises the progression of patients through the trial with respect to withdrawal from treatment and crossover to increased dose of infliximab.

Over a period of 1 year, about a quarter of patients withdrew from treatment, and of those allocated active intervention at randomisation only about half completed the trial receiving the treatment regimen to which they had been allocated at randomisation.

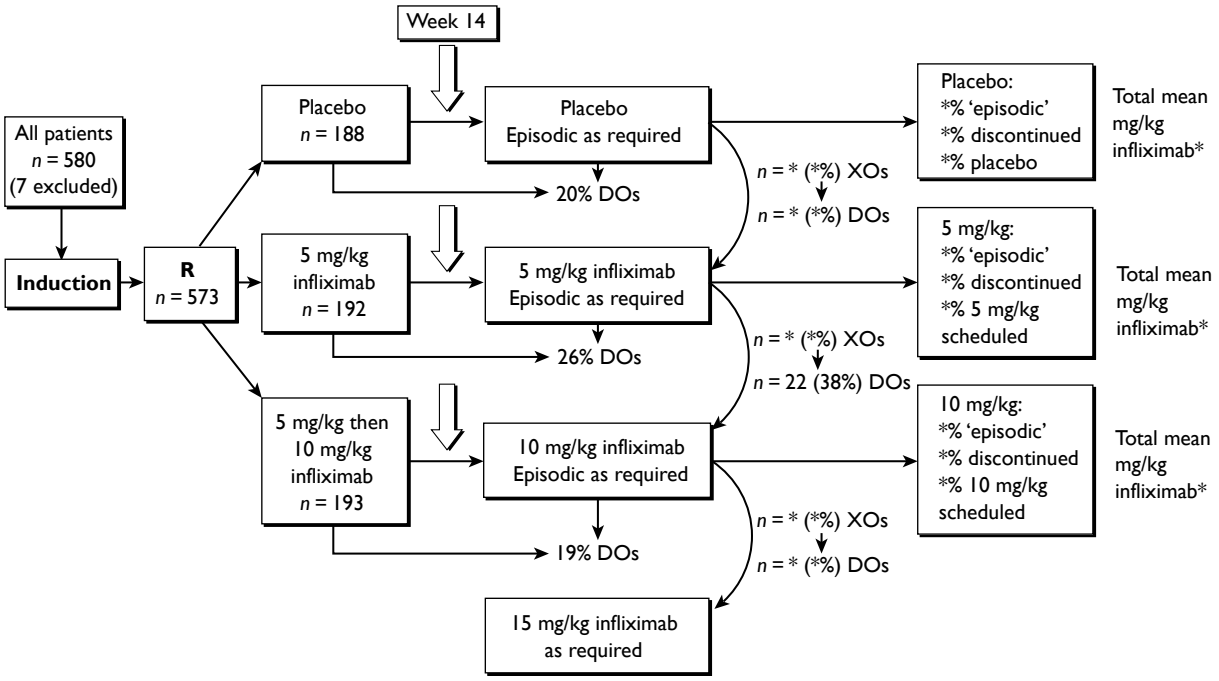

FIGURE 17 Withdrawals and crossovers in ACCENT I.[2,3] *(CiC information has been removed). R, randomisation. Note: Dropouts (DOs) and week 14 or later crossovers (XOs) allowed 'as required'.

The authors' stated primary objective '…was to examine the difference in efficacy between episodic and scheduled treatment strategies with infliximab'.[2] They concluded that the scheduled treatment strategy was superior to episodic treatment. Unfortunately, the comparisons were compromised by strong biases introduced as a result of the study design. These biases are explained below:

(a) Crossover to increased infliximab was allowed for patients 'who had responded at any time to infliximab therapy' and subsequently worsened. In the placebo group ('episodic strategy'), 78 of 188 patients (41%) were classified at week 2 as non-responders and received no further infliximab to week 14; these patients were unlikely to become responsive and therefore to qualify for crossover to active intervention. In contrast to this group the week 2 non-responders in the 'scheduled strategy' arms received additional doses of infliximab (5 mg/kg) at both weeks 2 and 6, boosting their opportunity to 'respond at any time' to infliximab. The greater opportunity to respond at any time in the 'scheduled strategy' arms represents a strong bias in their favour in any subsequent comparison with the episodic arm. Relative to the scheduled strategy this resulted in a substantial proportion of patients in the episodic arm being denied access to active therapy. This is reflected in the very large difference between arms in their exposure to infliximab stated to be 3 and 5 times greater in the two scheduled strategy arms than in the episodic arm.
(b) Episodic treatment was introduced at week 14 of the trial, but by this time the CD status of patients in the placebo 'episodic' arm was significantly inferior to that in the scheduled strategy arms in terms of several efficacy measures. This advantage for the scheduled strategy arms is reflected in increases not seen in the placebo group from week 2 in the response 70 rates and at weeks 6 and 10 in the remission rates. The result is a bias in favour of scheduled strategy for any comparison between strategies at times after week 14. Essentially, the compared arms were unbalanced at the start of the compared strategies (week 14).

ACCENT I.[2,3] Summary of effectiveness evidence for all patients

Two infusions of 5 mg/kg infliximab at weeks 2 and 6 after a single induction infusion of 5 mg/kg were better than placebo infusions at generating remission and response 70. At week 14, risk differences (infliximab–placebo) and risk ratios (infliximab/placebo) were in favour of infliximab and reached statistical significance ($p < 0.02$ for remission, $p < 0.01$ for response 70).

At week 14, 'episodic' treatment was introduced and subsequent comparisons were made between the original placebo arm (designated 'episodic treatment strategy') and original infliximab arms (termed 'scheduled treatment strategies'). Because of bias strongly in favour of scheduled strategy groups, the post 14-week comparisons were not valid estimates of the relative effectiveness of strategies. Biases identified arose from: (a) reduced opportunity for crossover to active therapy for patients in the episodic group compared with the scheduled groups; and (b) gross imbalance in disease status at the start of the strategies (week 14).

Difficulties in interpreting post 14-week comparisons between groups were compounded by the very high rate of withdrawal from treatment and the use of 'episodic' treatment in all three arms of the trial so that the distinction between episodic and scheduled strategies was obscured except for the fact that the original infliximab groups were allowed larger dosages of active intervention.

CLASSIC II[66] (adalimumab)

The CLASSIC II[66] trial was an extension of the previously conducted adalimumab induction trial, CLASSIC I,[63] which had enrolled 299 patients. To be eligible for CLASSIC II, patients were required to be in remission (CDAI < 150) at week 4 of CLASSIC I and also 4 weeks later (equivalent to week 8 of CLASSIC I and designated week 4 of CLASSIC II). These patients may

have received two subcutaneous injections 2 weeks apart of various doses of adalimumab (40 mg then 20 mg, 80 mg then 40 mg, or 160 mg then 80 mg) or two injections of placebo. Fifty-five eligible patients entered CLASSIC II, this means about 12 patients did not retain remission from weeks 4–8 of CLASSIC I or declined to participate. The 55 patients were randomised at week 4 of CLASSIC II to receive placebo ($n = 18$) or 40 mg of adalimumab every other week (e.o.w.) ($n = 19$) or 40 mg of adalimumab weekly ($n = 18$) from weeks 4 to 54. Thus CLASSIC II analysed only strong responders from the CLASSIC I trial.

For the purposes of the 'primary efficacy analysis', patients who had continued non-response defined as 'a decrease in CDAI $\leq$70 points vs. Week-0 value in CLASSIC I' were considered treatment failures and became eligible for open-label treatment. This means patients in remission at start of CLASSIC II became treatment failures if they ceased to qualify as response 70 responders relative to their baseline CDAI score in CLASSIC I. In addition, patients who flared during CLASSIC II follow-up were also counted as treatment failures and were eligible for open-label treatment. CD flare was defined as an increase of $\geq$70 points above the week 4 CLASSIC II value (which by definition was < 150) AND a CDAI score > 150 (no longer in remission). Thus a patient in remission at week 4 (CLASSIC II) with a CDAI score of 149 would need to move to a CDAI of at least 219 to be classified as having experienced flare. For this patient a score of 218 would not count as a flare but could count as treatment failure if his or her week 0 CLASSIC I CDAI score had been < 288 (for reference the mean baseline CDAI score at week 0 for 299 CLASSIC I patients was 298).

A, response 70 and B, response 100

Response 100 and response 70 rates throughout follow-up were among the secondary outcome measures of efficacy. Results reported for responses 100 and 70 are summarised in *Figure 18*. The placebo rates were high for these less rigorous measures of effectiveness, and the risk differences (adalimumab–placebo) and risk ratios (adalimumab/placebo) failed to reach statistical significance at most time points.

C, remission

The primary outcome was the proportion of patients in remission at week 56 in each arm of the randomised cohort. Remission throughout follow-up was among the secondary outcome measures of efficacy. For the primary outcome, 10 patients (18%) withdrew before week 56 (five from placebo and five from adalimumab). These were counted as remission failures for the primary analysis. Remission rates at week 56 are summarised in *Table 25*. Remission rates during the trial are summarised in *Figure 19*.

Point estimates of remission rate during the trial were associated with considerable uncertainty, reflecting the small number of patients in the trial. The fact that rates rose and fell during follow-up indicated the values reported referred to point prevalence. Nearly half of patients in the placebo group were in remission at week 56 despite not receiving active intervention from 2 weeks prior to randomisation onwards. Risk differences (intervention–placebo) and risk ratios (intervention/placebo) were in favour of intervention at all follow-up times and reached statistical significance at several time points.

D, other outcomes

The results published for continuous measures are summarised in *Table 26*. These measures involved last observation carried forward to allow for missing values. The amount of missing values was not published but was available (CiC) in the unpublished Industry Trial Report. For week 56 changes in favour of adalimumab relative to placebo were reported for mean IBDQ and CDAI scores.

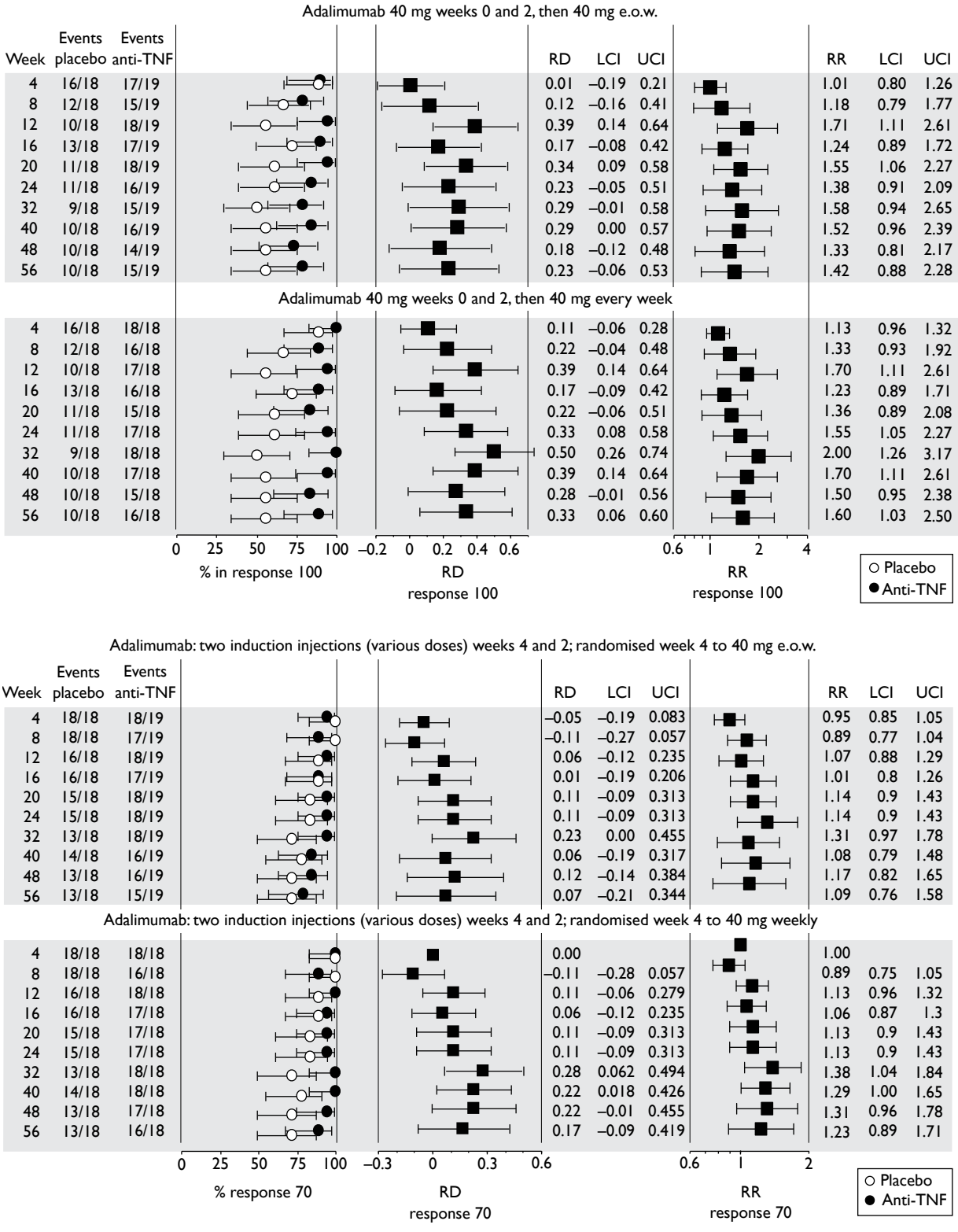

FIGURE 18 Response 100 (upper panel) and response 70 (lower panel) rates in CLASSIC II.[66] LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

TABLE 25 Remission rates at week 56 in CLASSIC II[66] (primary outcome)

Dose regimen (*n*)	Number in remission (%; 95% CI)	*p*[a]
Placebo (18)	8 (44%; 25 to 66)	NA
40-mg adalimumab e.o.w. (19)	15 (79%; 57 to 91)	< 0.05
40-mg adalimumab weekly (18)	15 (83%; 61 to 94)	< 0.05
Open-label [(CiC information has been removed)[b]]	(CiC information has been removed)[c] [(CiC information has been removed)%]	

NA, not applicable.
a Adalimumab vs placebo.
b 60 patients increased regimen from e.o.w. to weekly.
c Trial report data; publication states 94.

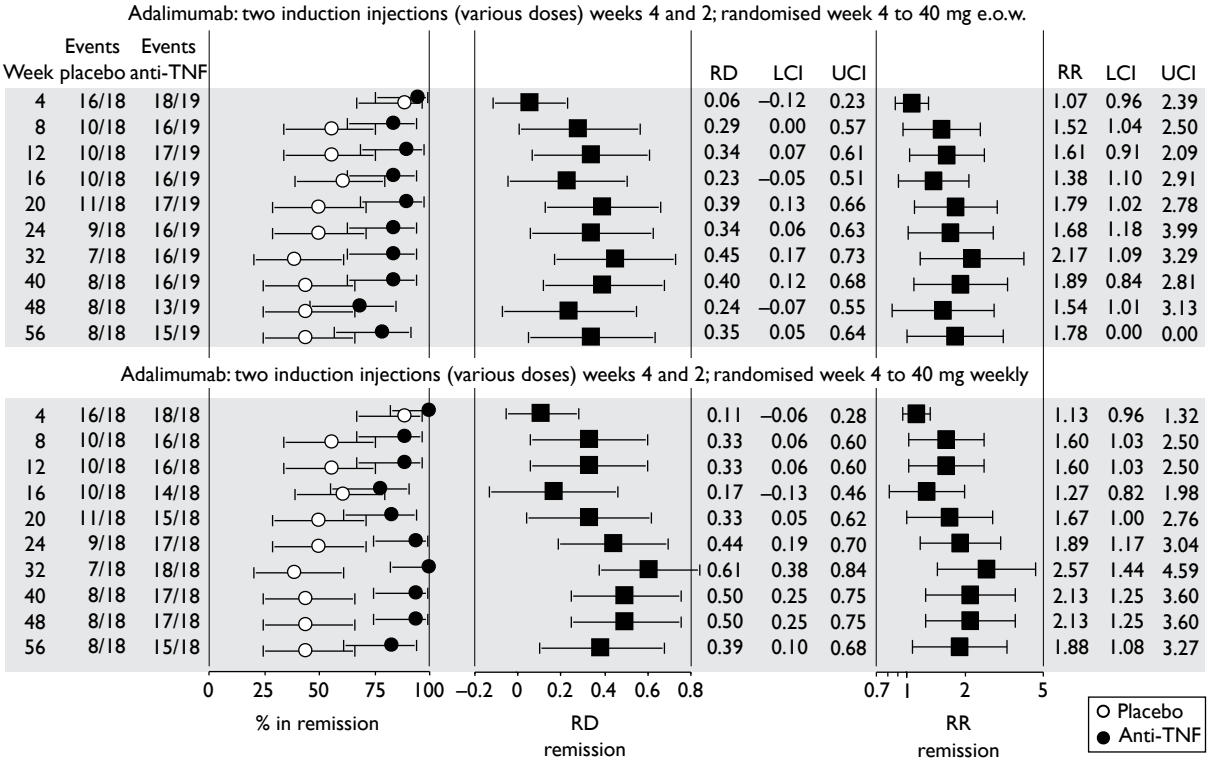

FIGURE 19 Remission rates in CLASSIC II.[66] LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

At the start of CLASSIC II,[66] 49% of patients were receiving systemic steroids or budesonide; seven of the placebo group, seven of the e.o.w. adalimumab group, and eight of the weekly adalimumab group. Using the last observation carried forward it was reported that by week 56 the number who had discontinued steroids was four in both the placebo and e.o.w. adalimumab groups, and seven in the weekly adalimumab group.

E, other considerations – open-label study

Most patients from CLASSIC I[63] who did not qualify for CLASSIC II[66] participated in an open-label study in parallel with CLASSIC II. The results reported were not randomised comparisons and are outwith the inclusion criteria for this report.

TABLE 26 IBDQ scores, CDAI scores and CRP concentrations reported in CLASSIC II[66]

	Placebo ($n=18$)	Adalimumab 40 mg e.o.w. ($n=19$)	Adalimumab 40 mg weekly ($n=18$)	p
Mean IBDQ score[a]				
Week 0[b]	187.5	181	191.5	
Week 4	188.5	187	191	
Week 8	178	181	187	
Week 12	170.5	182.5	189	
Week 16	172.5	181	182	
Week 20	170.5	177	186.5	
Week 24	167.6	176.3	192.2	<0.005[c,d]
Week 32	166.5	182	192	<0.05[c] <0.005[d]
Week 40	167	179	188	<0.005[c,d]
Week 48	163.5	178	183.5	
Week 56	162.4	178.4	185.6	
CDAI: mean change (95% CI) from baseline in CLASSIC I[e]				
Week 56	–119.6 (–74 to –65.1)	–158 (–202 to –99.8)	–197.7 (–248 to –147)	<0.005[c,d]
CRP concentration mg/dl: median (range) [levels of CRP < 0.88 mg/dl are considered normal]				
24	0.5 (0 to 1.2)	0.4 (0 to 1.9)	0.1 (0 to 1.6)	NR
56	0.4 (0 to 0.9)	0.3 (0 to 2.8)	0.3 (0 to 1.2)	NR

NR, not reported.

a Data read from graph except for weeks 24 and 56; last observation carried forward; the number observations at weeks 24 and 56 (CiC information has been removed) for the placebo, e.o.w. and weekly groups respectively.

b Week 4 of CLASSIC I.

c Comparison e.o.w. adalimumab vs placebo.

d Comparison weekly adalimumab vs placebo.

e Last observation carried forward number of observations (CiC information has been removed) for placebo, e.o.w. and weekly groups respectively; CLASSIC I baseline mean (95% CI) CDAI scores for these patients (not published) were (CiC information has been removed) for placebo, adalimumab e.o.w. and adalimumab weekly groups respectively.

Quality assessment (based on published report)

Randomisation, allocation concealment and blinding were adequate. Baseline characteristics at week 0 were well balanced. The study was powered for the primary outcome (remission at week 4) of CLASSIC I, and no further power calculation was conducted for CLASSIC II. The number of patients who withdrew was reported; 5 of 18 placebo patients withdrew and 5 of 37 patients given adalimumab withdrew. There were 32 patients (58%) who completed to 56 weeks of double-blind follow-up. The last observation was carried forward as necessary for continuous outcomes, but the number of missing data was not reported.

CLASSIC II.[66] Summary of effectiveness evidence

The trial population ($n=55$) was recruited from responders in the previous CLASSIC I[63] adalimumab induction trial ($n=299$). Only responders with a strong response (remission for at least a month) were selected; they had received various induction dose regimens.

Maintenance injections of 40 mg of adalimumab administered weekly or e.o.w. generated a statistically significant greater proportion of patients in remission at week 56 than did placebo (frequency of administration not published). About half of the placebo group and 81% of those who received infliximab were in remission at week 56. Point estimates of response rates were associated with considerable uncertainty due to the small size of the trial. There were no statistically significant differences in effectiveness between e.o.w. and weekly adalimumab regimens.

CHARM[67] (adalimumab)

This was a free-standing maintenance trial (i.e. newly started).[67] There were 854 enrolled patients (CDAI range 220–400), of whom 130 (15.2%) had fistulas at screening and baseline. An induction regimen consisting of an 80-mg injection of adalimumab at week 0 and a 40-mg injection 2 weeks later was followed by randomisation of 778 patients at week 4 to one of three arms as follows: placebo to week 56 ($n = 261$), 40 mg adalimumab e.o.w. to week 56 ($n = 260$) and 40 mg adalimumab weekly to week 56 ($n = 257$). There were 76 (8.9%) withdrawals prior to randomisation. Assessment visits were planned for weeks 0, 2, 4, 6, 8, 12, 16, 20, 26, 32, 40, 48, 56 and 60.

At week 4 patients were classified as responders or non-responders. Responders had to have a reduction of ≥70 CDAI points relative to baseline. Of the 854 patients given the induction regimen, 499 (58%) were categorised as responders and were the focus of the published effectiveness results. This population was different to that followed up in the other adalimumab maintenance trial, CLASSIC II,[66] in that the latter were on average better responders, having achieved remission from induction. The numbers of responders randomised to the three trial arms of CHARM were 170 to placebo, 172 to adalimumab e.o.w. and 157 to adalimumab weekly.

The coprimary outcome measures were designated: the percentage of week 4 responders who achieved remission at weeks 26 and 56. Pre-specified secondary outcomes included (1) percentage achieving response 70 and response 100 at weeks 26 and 56; (2) change in IBDQ score from baseline at weeks 26 and 56; (3) percentage achieving clinical remission at weeks 26 and 56 who were able to discontinue corticosteroid use; (4) percentage achieving clinical remission at weeks 26 and 56 who were able to discontinue steroids for ≥90 days; (5) percentage of patients with fistula remission (closure of all fistulas that were draining at screening and baseline visits); and (6) median time in clinical remission among randomised responders achieving remission. Post hoc analyses examined subgroup responses and sustainability of response.

At or after week 12, patients with disease flare (an increase of ≥70 CDAI points from the score at week 4 and a CDAI score >220) or sustained non-response (CDAI score not reduced by ≥70 points from week 0) were eligible to cross over to 40-mg adalimumab e.o.w. which could be escalated to 40-mg weekly for patients with continued non-response or recurrent flare. For the primary effectiveness outcome (responders), any patients who crossed over were counted as remission failures.

A, response 70 and B, response 100

The published response 70 and response 100 rates at weeks 26 and 56 are summarised in *Table 27*. Rates reached statistical significance in favour of adalimumab for both dose regimens at both time points.

The unpublished Industry Trial Report for CHARM provided (CiC) values for response 70 at time points for all assessment visits. These are summarised in *Figure 20*. (CiC information has been removed.)

Similar CiC results were observed for response 100 and are summarised in *Figure 21*. From week 8 onwards (CiC information has been removed).

C, remission

The primary outcome was the proportion of patients in remission at weeks 26 and 56. The results are summarised in *Table 28*. The difference between adalimumab groups and placebo reached statistical significance in favour of adalimumab for both dose regimens.

TABLE 27 Reported response 100 and response 70 rates in CHARM[67]

	Number with response 100 (%; 95% CI)		
Dose regimen (*n*)	**Week 26**	**Week 56**	***p*[a]**
Placebo (170)	45 (26.5%; 20 to 34)	28 (16.5%; 12 to 23)	NA
40-mg adalimumab e.o.w. (172)	89 (52%; 44 to59)	71 (41%; 34 to 49)	< 0.001
40-mg adalimumab weekly (157)	82 (52%; 44 to 60)	75 (48%; 40 to 56)	< 0.001
	Number with response 70 (%; 95% CI)		
	Week 26	**Week 56**	
Placebo (170)	48 (28%; 22 to 35)	30 (18%; 13 to 24)	NA
40-mg adalimumab e.o.w. (172)	93 (54%; 47 to 61)	74 (43%; 36 to 50)	< 0.001
40-mg adalimumab weekly (157)	88 (56%; 48 to 63)	77 (49%; 41 to 57)	< 0.001

NA, not applicable.
a Adalimumab vs placebo; chi-squared test.

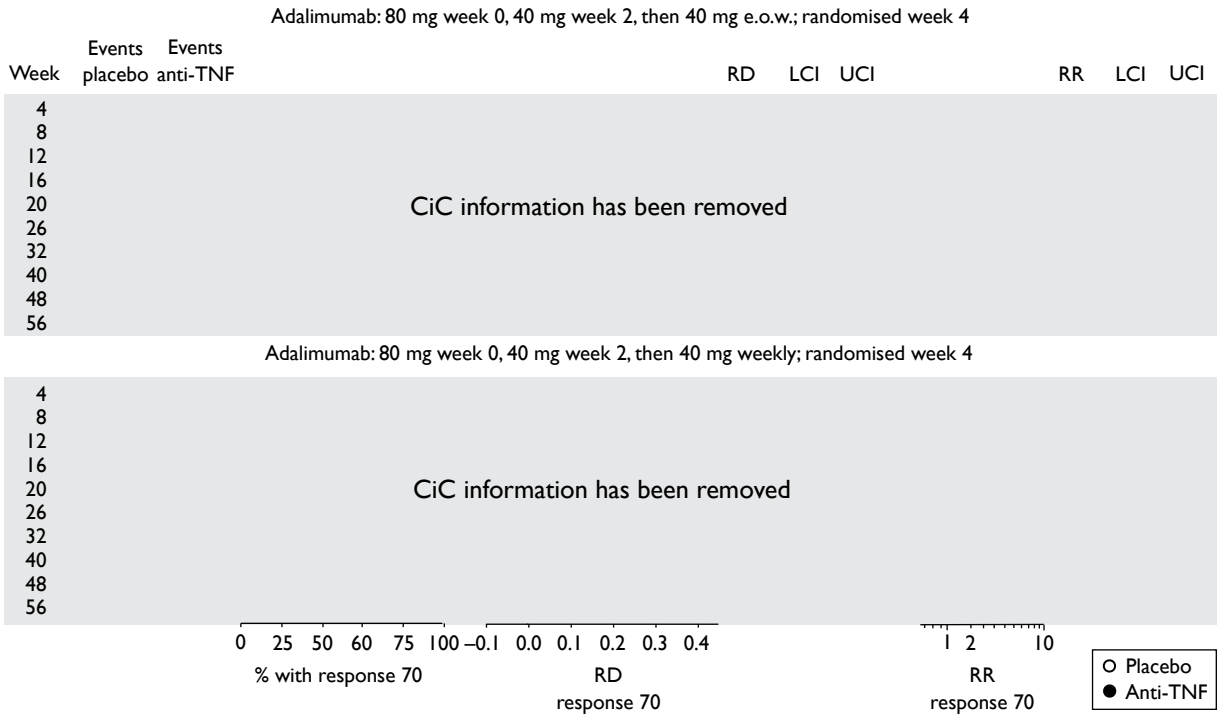

FIGURE 20 Response 70 rates among responders in CHARM.[67] LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

The secondary outcomes of remission rates for each follow-up visit to week 56 are summarised in *Figure 22*. Risk differences (adalimumab–placebo) and risk ratios (adalimumab/placebo) reached statistical significance in favour of adalimumab at all time points after week 6. Rates of remission in the adalimumab e.o.w. arm diminished through follow-up. From weeks 12–16 onwards, risk differences remained stable so that most benefit of the intervention appeared to be delivered in the first quarter of the trial. The rates reported were group point prevalence values and do not reflect maintenance of remission at the patient level. The difference in rates between the two adalimumab regimens at week 56 was not significant (risk difference $p = 0.32$, risk ratio $p = 0.32$).

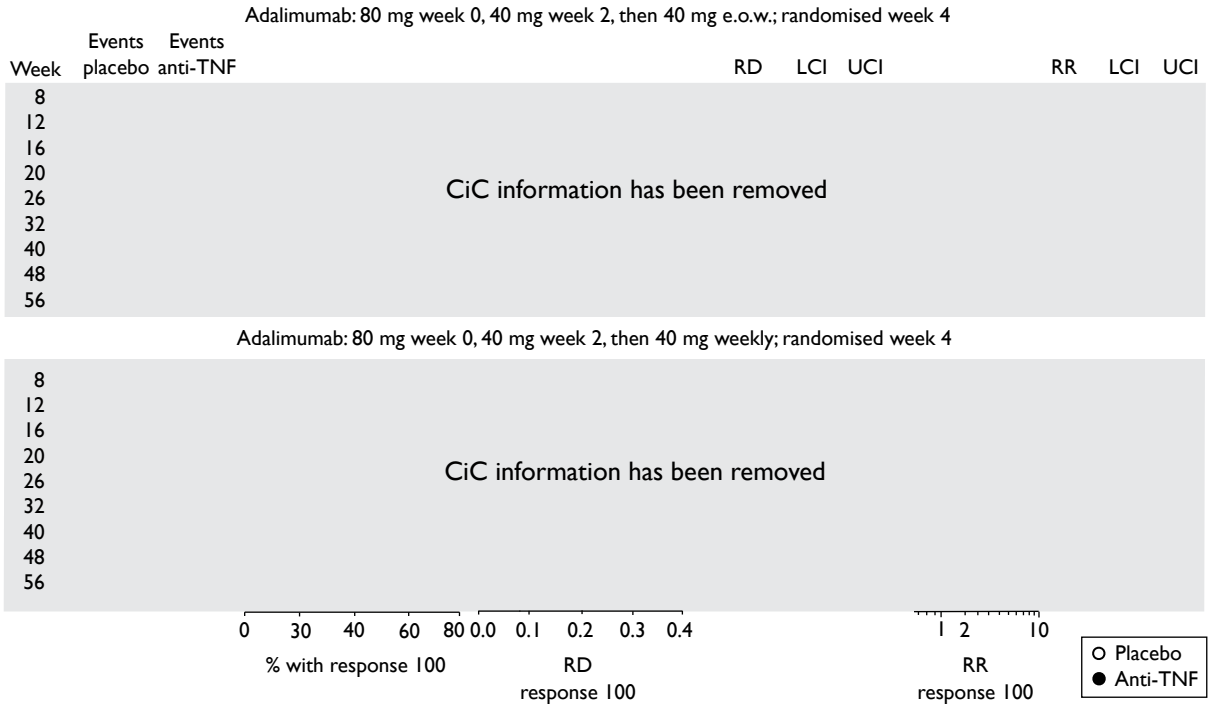

FIGURE 21 Rates of response 100 among responders in CHARM.[67] LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

TABLE 28 Remission at weeks 26 and 56 in CHARM[67]

	Number in remission (%; 95% CI)		
Dose regimen (*n*)	**Week 26**	**Week 56**	***p*[a]**
Placebo (170)	29 (17%; 12 to 23)	20 (12%; 8 to 13)	NA
40-mg adalimumab e.o.w. (172)	68 (40%; 32 to 47)	62 (36%; 29 to 43)	< 0.001
40-mg adalimumab weekly (157)	73 (47%; 39 to 54)	65 (41%; 34 to 49)	< 0.001

NA, not applicable.
a Adalimumab vs placebo; Cochran–Mantel–Haenszel chi-squared test adjusting for previous anti-TNF use.

Patient level maintenance of remission was published for weeks 26–56. In the adalimumab arms, 81% of patients in remission at week 26 sustained remission to week 56; this represented 114 patients and 27% of all those randomised to adalimumab. For patients randomised to placebo, 48% of those in remission at week 26 sustained remission to week 56. This represented 14 patients and 5% of all those randomised to placebo. The median time in clinical remission that started at any time was 127 days for the placebo group, 378 days for the adalimumab e.o.w. group and > 392 days for the adalimumab weekly group ($p = 0.002$ and $p < 0.001$ vs placebo respectively). Over 56 weeks it was possible for a patient to enter a remission state on several occasions. The publication did not make clear which occasion(s) were used in the analysis or how and if double counting was avoided.

D, other outcomes

Published mean CDAI and IBDQ scores are summarised in *Table 29*. No variance information was provided. After week 12, CDAI and IBDQ scores for patients who crossed over to increased adalimumab doses were included in the calculation of group mean scores although this was not

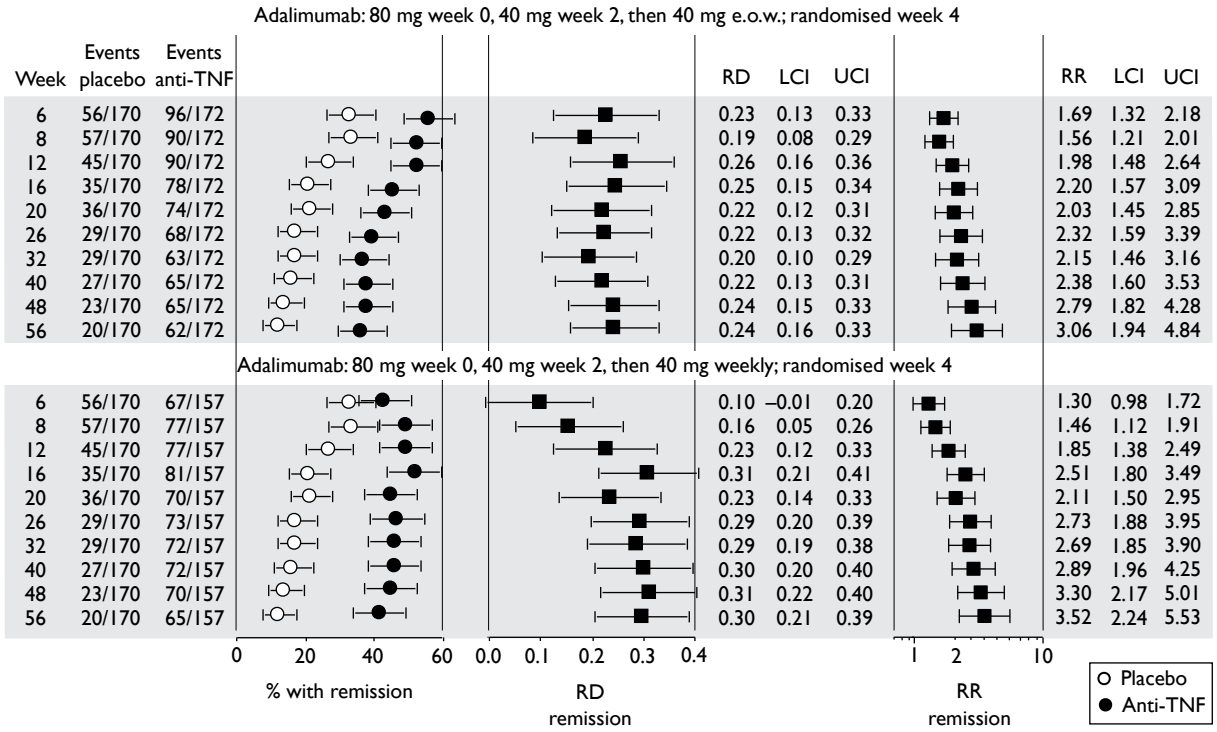

FIGURE 22 Remission rates reported during follow-up in CHARM.[67] At week 56 risk difference and risk ratio for both regimens of adalimumab versus placebo, $p < 0.0001$. LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

made explicit. Mean CDAI scores decreased and mean IBDQ scores increased, to a greater degree respectively in the adalimumab groups than the placebo group. Given that a true placebo group did not exist after week 14, the results thereafter are difficult to interpret. The last observation was carried forward; the proportion of patients evaluated at week 56 (CiC information has been removed).

From week 8 the responder patients who were receiving steroids at baseline could begin reducing steroid use (presumably at the physician's discretion). This involved 66 placebo patients, 58 and 74 patients respectively in the adalimumab e.o.w. and adalimumab weekly groups. The percentage of these patients who were in remission at week 26 and who had discontinued steroids was 3% (2/66) in the placebo group, and 34% (20/58) and 30% (22/74) in the adalimumab e.o.w. and weekly groups respectively. Corresponding percentages at week 56 were 6%, 29% and 23% respectively. The percentage who were in remission at week 26 and who were steroid free for at least 90 days was 3% in the placebo group and 19% and 15% in the adalimumab e.o.w. and weekly groups respectively. Corresponding percentages at week 56 were 5%, 29% and 20% respectively.

Hospitalisation rates Details on hospitalisation rates from the CHARM trial[67] were reported in the industry submission, referenced to published abstracts by Wu *et al.*[71] and by Feagan *et al.*[72] The latter abstract reports the hospitalisation rates in the placebo arm and the combined adalimumab arms, which were 22.4% and 14.0% respectively. The 56-week actuarial CD-related hospital admission rates for the placebo and for the combined adalimumab arms were 13.9% and 5.9% respectively. A difference in relative risk was apparent at 2 weeks after randomisation, and placebo patients had 4.5 times the risk of hospitalisation at month 3 as adalimumab patients. Wu *et al.*[71] used a Cox proportional hazard regression model and found that lower CDAI scores were associated with a decreased risk of hospitalisation and CD-related hospitalisation. Simulated

TABLE 29 Group mean CDAI and IBDQ scores reported for responders in CHARM[67]

	CDAI:mean[a]				IBDQ median[a]			
Week	Placebo ($n=170$)	40-mg adalimumab e.o.w. ($n=172$)	40-mg adalimumab weekly ($n=157$)	p	Placebo ($n=170$)	40-mg adalimumab e.o.w. ($n=172$)	40-mg adalimumab weekly ($n=157$)	p
0	318	317	310	NR	125	128	123	NR
2	215	200	203	NR	NR	NR	NR	NR
4	170	153	162	NR	166.6	174	165	NR
6	178	150	162	NR	NR	NR	NR	NR
8	183	147	155	NR	NR	NR	NR	NR
12	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR
16	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR
20	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR
26	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR
32	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR
40	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR
48	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR
56	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	NR

NR, not reported.

a Data read from graph in Colombel *et al.*[67]. Values after week 12 were calculated including values for patients who crossed over to increased adalimumab.

1-year rates indicated that a 70-point reduction on the CDAI throughout the follow-up period reduced all-cause hospitalisation risk by 28.3% and CD-related hospitalisation by 36.5% at year end. Further simulations indicated that remission was associated with a 43.7% decrease in the 1-year risk of all-cause hospitalisation and a 60.3% decrease in CD-related hospitalisation.

E, other considerations – subgroup analyses and crossover issues

Outcomes for patients with draining fistulas are included in the next section.

The manufacturer's submission to NICE provided weeks 26 and 56 results for placebo and e.o.w. adalimumab group patients who had severe disease at baseline (CDAI > 300). Results for all severe patients and for severe week 4 responders were provided allowing calculation of results for non-responders with severe CD (*Table 30*). There were 96 severe CD patients in both placebo and e.o.w. adalimumab groups. Rates of remission, response 70 and response 100 are summarised in *Figure 23*. Remission rates at week 56 in adalimumab and placebo arms were 35% and 10%

TABLE 30 Response rates for severe CD patients in CHARM[67]

		All week 4 responders		Severe CD responders		All severe CD patients		Severe CD non-responders
Outcome	Week	Placebo (n=170)	e.o.w. anti-TNF (n=157)	Placebo (n=96)	e.o.w. anti-TNF (n=96)	Placebo (n=149)	e.o.w. anti-TNF (n=135)	e.o.w. anti-TNF (n=39)
Remission	26	17%	40%	14%	36%	11%	30%	15%
	56	11.8%	36%	9%	33%	8%	27%	8%
Response 100	26	26.5%	52%	28%	56%	21%	47%	26%
	56	16.5%	44%	17%	44%	13%	36%	18%
Response 70	26	28%	54%	29%	58%	23%	47%	28%
	56	17.6%	43%	18%	45%	13%	36%	18%

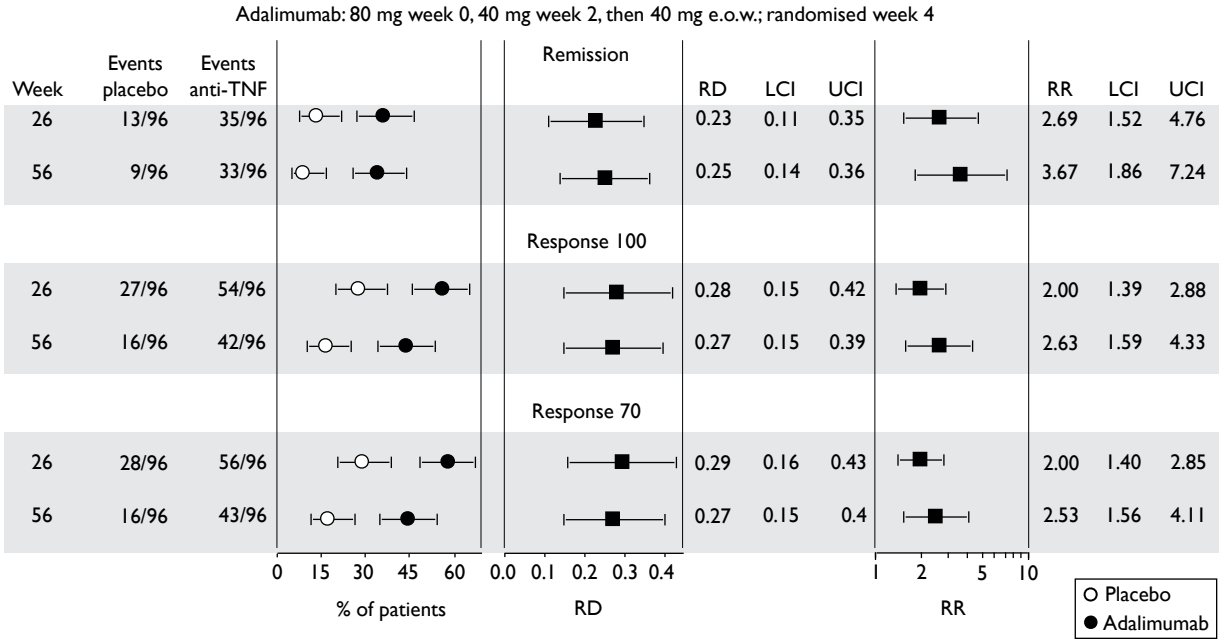

FIGURE 23 Response and remission rates for severe disease responders in CHARM.[67] LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

respectively; higher rates were recorded for the less stringent response 70 and 100 outcomes. These rates were similar to those reported for all week 4 responders (within 5%; listed in *Table 30*). The rates in the e.o.w. arm for week 4 non-responders with severe CD were about half those for week 4 responders with severe CD.

Other post hoc subgroup analyses

Several post hoc analyses explored the effectiveness of adalimumab among subgroups of patients defined according to various criteria including: baseline CRP level > or < 1 mg/ml; concomitant treatment with or without immunosuppressant medication; and previous experience of anti-TNF therapy or no previous experience. No statistically significant subgroup differences in adalimumab effectiveness were observed.

Premature withdrawal from treatment and crossover due to worsening disease

The published information about withdrawal from treatment and crossover to open-label therapy was difficult to disentangle. The Industry Trial Report provided fuller detail. Of 499 responders 29% (144) withdrew prematurely: (CiC information has been removed)% of the placebo group [(CiC information has been removed)], (CiC information has been removed)% of the e.o.w. adalimumab group [(CiC information has been removed)] and (CiC information has been removed)% of the weekly adalimumab group [(CiC information has been removed)]. The Industry Trial Report stated the overall premature discontinuation rate among all patients was (CiC information has been removed)% [(CiC information has been removed)], with 79 of these occurring before randomisation. Among all 788 randomised patients, withdrawals during the randomised phase were (CiC information has been removed) [(CiC information has been removed)%] in placebo group, (CiC information has been removed) [(CiC information has been removed)%] in the adalimumab e.o.w. group and (CiC information has been removed) ((CiC information has been removed)%) in the adalimumab weekly group, giving an overall rate of (CiC information has been removed)% [(CiC information has been removed)/(CiC information has been removed)] slightly (CiC information has been removed) than for responders only. Of patients randomised to adalimumab maintenance therapy, the rate of premature withdrawal was the (CiC information has been removed).

Crossover to open-label treatment after week 12 involved (CiC information has been removed) [(CiC information has been removed)%] of patients randomised to placebo, (CiC information has been removed) [(CiC information has been removed)%] of those randomised to adalimumab e.o.w. and (CiC information has been removed)/(CiC information has been removed) [(CiC information has been removed)] of those randomised to adalimumab weekly. These numbers represented patients experiencing worsening disease by flare or discontinued response. Transfer to open-label for patients in the weekly adalimumab group involved continuation of the same dose regimen (as crossover was described as '…switched to open-label treatment with 40-mg adalimumab eow… escalated to 40-mg weekly for those with continued non-response or recurrent flare'. After crossover '…continued non-response with open-label 40-mg weekly dosage resulted in withdrawal';[67] however, there was no published information about how long the state of flare or non-response was allowed to continue before withdrawal was implemented. The number of responder patients who crossed over to open-label was not published. The Industry Trial Report allowed calculation of crossovers and withdrawals among all randomised patients; this information is summarised in *Figure 24*.

Quality assessment (based on published report)

Randomisation, allocation concealment and blinding were adequate. Baseline characteristics were reported only for all patients, for all responders and for all non-responders, not for each of the trial arms. It was therefore not possible to judge if baseline characteristics were evenly balanced between the three arms of responders (placebo and e.o.w. or weekly adalimumab groups) that were analysed for effectiveness outcomes. The frequency of placebo injections was not documented. Information about patients who withdrew was reported. After week 12, patients with disease flare or non-response were allowed to cross over to the open-label treatment. It was difficult to determine how many responders and how many randomised patients in each group crossed over to open-label treatment. There was no statement defining how long after crossover flare or non-response was allowed to continue before withdrawal was implemented. Where necessary, the nearest or last observation was carried forward for continuous outcomes, but this was not stated explicitly and the number of missing data was not reported. A power calculation

FIGURE 24 Withdrawals from treatment and crossovers for flare or non-response in CHARM.[67] *There was a discrepancy concerning one patient in the values for the adalimumab weekly group. (CiC information has been removed.)

was conducted and based on the primary analysis of 4-week responders achieving remission at weeks 26 and 56.

The published text stated '…secondary efficacy analyses were conducted for all treated patients, including both randomised responder and randomised non-responder groups (all randomised patients who failed to achieve a clinical response at week 4)'.[67] Although this might be technically correct, in the sense that analyses were conducted, it is misleading because the results of these analyses were not reported, with the single exception of data on healing of fistulas for a subgroup of patients with fistulas at baseline and screening.

CHARM.[67] Summary of effectiveness evidence

Seven hundred and seventy-eight patients given induction injections of 80 mg and 40 mg of adalimumab separated by 2 weeks were randomised at week 4 to maintenance therapy with placebo or 40-mg adalimumab e.o.w. or weekly. Only results for responders were published. Responders were defined as patients who at week 4 had a CDAI score reduced by ≥ 70 points from baseline. At weeks 26 and 56 there were significantly more responder patients in remission in the e.o.w. and weekly adalimumab groups than the placebo group, 40% and 47% respectively versus 17% at week 26, and 36% and 41% respectively versus 12% at week 56 ($p < 0.001$ for adalimumab vs placebo). The risk difference (adalimumab–placebo) for remission reached statistical significance in favour of adalimumab from week 8 onwards and remained stable from about week 12 or 16 to the end of follow-up (week 56), indicating that most of the benefit from active intervention was delivered during the first quarter to third of the trial.

The proportion of responders (response 70) had diminished to < 50% in all groups by week 56. Response 70 rates diminished (CiC information has been removed) delivered during the first part of the trial. Premature withdrawal from randomised treatments (adalimumab and placebo) was (CiC information has been removed)%; withdrawal rate from active intervention (adalimumab) was (CiC information has been removed) responders (CiC information has been removed)% (CiC information has been removed) non-responders [(CiC information has been removed)%]. Amongst the whole trial population randomised to adalimumab maintenance therapy, (CiC information has been removed)% crossed over to open-label treatment due to flare or non-response. The distribution of crossovers between responders and non-responders was unclear.

Pooling and indirect comparisons

The two adalimumab trials, CLASSIC II[66] and CHARM,[67] differed fundamentally with respect to populations analysed for outcome results. CLASSIC II[66] reported results for responders who had achieved remission, whereas the responders in CHARM[67] had achieved only the less stringent response of a 70-point reduction in CDAI score. It would be inappropriate to combine the results from these two trials. It is relevant that the manufacturer's submission for adalimumab did not adopt a pooling approach. In a 2008 Cochrane review[73] the authors stated 'the two studies evaluating adalimumab were evaluated separately due to heterogeneity among the two trials (i.e. CLASSIC II and CHARM)'. Surprisingly, the results section of the review provided pooled results for remission (random effects model), and a further different pooled result (which may have been fixed effects) was presented in the discussion. On contacting the authors regarding these inconsistencies, we were informed that the review would be amended and the modified version, with no pooled results, is now available in the Cochrane Library.

The two infliximab trials, Rutgeerts *et al.*[58] (extension from Targan *et al.*[57]) and ACCENT I,[2,3] both employed a 10 mg/kg infliximab maintenance therapy arm and both reported results for responders based on a CDAI score reduced from baseline by ≥ 70 points. Therefore there is

potential for pooling results. However, the pre-maintenance 'induction' phases of the two trials were very different, so the populations analysed for maintenance outcomes were likely to be quite different at the start of maintenance. Responders in ACCENT I[2,3] were selected 2 weeks after a single exposure to a 5 mg/kg dose of infliximab. In contrast, responders in Rutgeerts *et al.*[58] were selected between 8 and 12 weeks after their first exposure to infliximab and were required to have a response 70 lasting 4 weeks. A further considerable difference between the responders in the two trials was the degree of exposure to infliximab prior to their selection as responders; in ACCENT I[2,3] responders were defined after a single 5 mg/kg exposure, whereas Rutgeerts *et al.*'s[58] responders could have been exposed to any of the following: one 5 mg/kg, one 10 mg/kg, one 20 mg/kg, one 5 mg/kg and one 10 mg/kg, two 10 mg/kg, one 20 mg/kg and one 10 mg/kg, or no infliximab. The cumulative effect of these differences in the responder population (up to sixfold difference in exposure, different requirement in duration of response 70, and between four- and sixfold difference in duration of induction phase) is that the populations were unlikely to be sufficiently similar for the pooling of results to be informative.

Indirect comparison between the placebo-controlled maintenance trials, so as to gain an estimate of relative effectiveness of the two anti-TNF agents, was not undertaken for this non-fistulising adult population. Indirect comparison requires that trials for different interventions of interest share a common comparator arm ('exchangeability', see Glenny *et al.*[74]). For the maintenance trials, the differences between 'placebo' groups were numerous and not easily quantifiable; different induction drugs were administered on differing numbers of occasions for different periods of time, followed by selection of responders by differing criteria representing different proportions of the randomised populations. The basis of indirect comparison depends on strict comparability of the trial arms common to the compared trials (in this case the placebo arms). In these circumstances indirect comparison would be misleading and unjustified. It is noteworthy that neither of the manufacturers' submissions performed formal indirect comparison based on these trials.

Trials recruiting patients with fistulas

Two trials, Present *et al.*[62] – an induction trial – and ACCENT II[65] – a maintenance trial – compared infliximab with placebo for adults with fistulising CD. There were no trials of adalimumab that enrolled only from this patient group. In these two trials all patients had one or more fistulas at the time of randomisation, and the main outcome measures focused on the status of fistulas during follow-up. The outcomes measured are listed in *Table 31* and the main trial characteristics summarised in *Table 32*. For reference purposes this section also includes fistula status results for the small subgroups of adult patients who had fistulas in other trials.

Present *et al.*, 1999[62] (infliximab)

Present *et al.*[62] was a small study that randomised 31 patients to placebo, 31 and 32 patients respectively to 5 mg/kg or 10 mg/kg infliximab infused at weeks 0, 2 and 6. Follow-up extended to at least week 18 with assessment visits every 4 weeks from week 2 onwards.

Primary outcome

The primary outcome was a > 50% reduction in the number of draining fistulas relative to baseline evaluated by physical evaluation and observed over at least two consecutive study visits at any time during the trial. Secondary outcomes included: complete absence of draining fistula observed over at least 4 weeks (i.e. across at least two consecutive study visits) at any time during the study, time to beginning of response and duration of response. Changes in CDAI and PDAI scores were reported for some patients.

TABLE 31 Outcomes measured in trials of fistulising CD

	% achieving 70-point response on CDAI	CDAI score (mean or median)	IBDQ score (mean or median)	PDAI score (mean or median)	Response: reduction of 50% or more of draining fistula	Complete response: absence of draining fistula	Additional outcomes
Infliximab							
Present *et al.*, 1999[62]	×	✓	×	✓	✓ (at two or more consecutive visits)	✓ (at two or more consecutive visits)	Time to beginning of response; duration of response
ACCENT II[65]	✓ (subgroup only)	✓	✓	×	✓ time until loss of response (at consecutive visits > 4 weeks apart)	✓	Subsequent response among previous non-responders, response rate in patients who lost response and crossed over

TABLE 32 Main study and population characteristics for trials in fistulising adult populations

Study[a] Drug	Study weeks (*n*)	Population: severity of CD (baseline PDAI, CDAI and IBDQ if stated)	Intestinal areas affected; fistula: *n* and location	Main concomitant medication[b]	Previous/ concomitant treatment with anti-TNF inhibitors	Intervention and comparator (dosing regimen)
Present *et al.*, 1999[62] Infliximab	18 94	≥1 draining abdominal or perianal fistula of ≥3 months' duration Mean baseline PDAI (IQR): 9 (7–10.5) placebo; 8 (7–10), 10 (8–12) infliximab groups Mean baseline CDAI (SD): 193 (92) placebo; 184 (98), 185 (97) infliximab groups (IBDQ not stated)	Mainly ileum and colon, also ileum only and colon only Fistula: 1, 45%; >1, 55%; mainly perianal fistula, a few abdominal	Aminosalicylates (mainly), also mercaptopurine or azathioprine, corticosteroids and antibiotics	Exclusion criterion: Infliximab within 3 months of study; no further details	Intravenous infusions of placebo, 5 mg/kg infliximab or 10 mg/kg infliximab at weeks 0, 2 and 6 Study visits at least every 21 days; total follow-up not stated
Sands *et al.*, 2004[65] – ACCENT II Infliximab	54 282	≥1 draining abdominal or perianal fistula of ≥3 months' duration PDAI scores not stated CDAI at baseline: 60% ≥ 150, 33% ≥ 220 Median baseline IBDQ (IQR) (responders): 168 (145–193) placebo; 155 (135–187) infliximab; 161 [136–176 (non-responders)	Mainly ileum and colon, also ileum only and colon only Fistula: 1, 44%; >1, 56%; mainly perianal fistula, some abdominal or recto-vaginal	Aminosalicylates (mainly), also mercaptopurine or azathioprine, corticosteroids and antibiotics, few methotrexate Previous medication: mercaptopurine/ azathioprine (mainly) and antibiotics, some ciclosporin, tacrolimus or methotrexate	Exclusion criterion: previously treated with infliximab	Intravenous infusions of 5 mg/kg infliximab at weeks 0, 2 and 6 for all patients; at week 14 responders and non-responders randomised to placebo or 5 mg/kg infliximab at weeks 14, 22, 30, 38 and 46

a Both studies were industry-sponsored multicentre trials conducted in the USA, Canada and Europe.
b % not on any medication not stated.

TABLE 33 Time to onset of primary outcome

Length of time to the beginning of a response[a] (days: median, IQR)				
	Placebo ($n=8$)	5 mg/kg ($n=21$)	10 mg/kg ($n=18$)	5 or 10 mg/kg ($n=39$)
Median (days)	42	14	14	14
IQR	15–72	14–42	14–42	14–42
p vs placebo	NA	NR	NR	NR

NA, not applicable; NR, not reported.
a Only patients with primary response included.

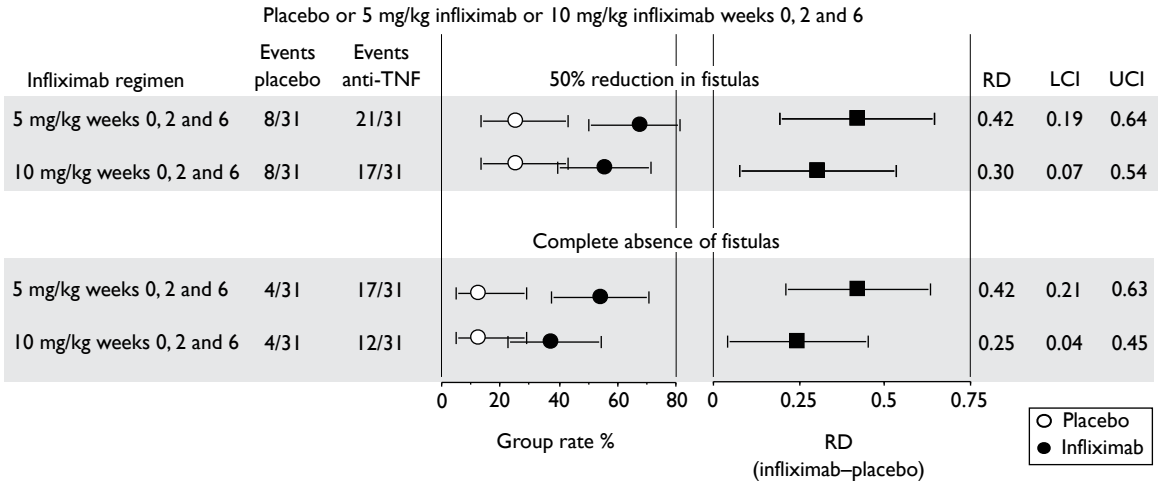

FIGURE 25 Rates and risk differences for a 50% reduction and absence of draining fistulas. LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

The results for the primary outcome (for 50% reduction in draining fistula occurring at any time over at least two consecutive clinic visits and for complete absence of draining fistula over two consecutive clinic visits) are summarised in *Figure 25*. For both these outcomes, infliximab at both dose regimens was more effective than placebo ($p=0.002$ and $p=0.02$ for 5- and 10 mg/kg regimens respectively). The point estimates for response rates were associated with substantial uncertainty because of the small group size; for the combined infliximab groups the response rate was 62% (95% CI 50% to 73%) compared with 26% (95% CI 14% to 43%) for the placebo group ($p<0.001$). For those with a response, the median time to response was 6 weeks in the placebo group and 2 weeks in the infliximab groups (*Table 33*).

Response and complete response

The median duration of response (defined as the maximum period during which the patient experienced a 50% reduction in draining fistulas) was approximately 3 months. For infliximab patients, 29/63 (46%; 95% CI 34% to 58%) experienced complete absence of draining fistulas for at least two consecutive clinic visits compared with 4/31 (13%; 95% CI 5% to 29%) of patients in the placebo group ($p<0.001$).

The median CDAI and PDAI scores reported for baseline and weeks 2 and 18 of follow-up are summarised in *Table 34*. By week 2, statistically significantly better (i.e. lower) scores were found for the infliximab groups than for the placebo group. The statistical significance of the difference between groups had weakened or disappeared by week 18. Not all patients contributed data for the analyses (i.e. this was not an ITT analysis).

TABLE 34 CDAI and PDAI scores reported in the Present *et al*. trial[62]

	Placebo ($n=25$)			Infliximab 5 mg/kg Weeks 0, 2 and 6; ($n=27$)			Infliximab 5 mg/kg Weeks 0, 2 and 6; ($n=27$)		
Outcome	Week	Median	IQR	Median	IQR	p[a]	Median	IQR	p[a]
CDAI score[b]	0	162	126–265	163	99–284	0.71	203	112–254	0.66
	2	171	114–252	108	83–203	0.04	111	89–164	0.06
	18	160	72–206	104	47–177	0.23	123	58–175	0.32
PDAI score[b]	0	9	7–10.5	8	7–10	0.69	10.0	8.0–12.0	0.31
	2	8	6–10	6	3–7	0.02	6.0	4.0–8.0	0.04
	18	7	4–9	4	1–7	0.05	5.0	3.0–8.0	0.14

a Anti-TNF vs placebo using analysis of variance procedure.
b Last observation carried forward for missing values.

Quality assessment based on published report[62]

Randomisation and blinding were adequate and allocation concealment was likely to have been adequate. Baseline characteristics were generally well balanced although there was a greater proportion of patients in the infliximab groups that had undergone previous segmental resections than in the placebo group. Draining fistulas of < 3 months' duration were excluded from the primary analysis. However, the number or frequency of these fistulas was not reported, and it was unclear if these were also excluded from the secondary outcome of a complete absence of a draining fistula. Total follow-up time for the primary outcome was unclear. No power calculation was performed. Last observation was carried forward for CDAI and PDAI analyses, but the number of missing data was unclear. There were only six premature withdrawals from treatment, four from the placebo group and one patient from each of the infliximab groups.

Present *et al.*, 1999.[62] Summary of effectiveness evidence

Patients with one or more draining fistula of more than 3 months' duration, and an unreported number of fistulas of < 3 months' duration, were randomised to placebo or 5 mg/kg infliximab or 10 mg/kg infliximab, by i.v. infusion at weeks 0, 2 and 6. More patients in the infliximab groups than in the placebo group achieved the primary outcome defined as: a reduction in the number of 3-month duration draining fistulas present at baseline by at least 50% lasting for at least two consecutive clinic visits. The percentage of patients responding to infliximab was 62% (95% CI 50% to 73%) compared with 26% (95% CI 14% to 43%) for the placebo group ($p < 0.002$). The median time to response was 2 weeks for infliximab groups and 6 weeks for placebo group. The duration of response was the same for both groups (median about 12 weeks).

More patients in the infliximab groups than in the placebo group achieved the secondary outcome of absence of draining fistula lasting for at least two consecutive clinic visits. The percentage of patients responding to infliximab for this outcome was 46% (95% CI 34% to 58%) compared with 13% (95% CI 5% to 29%) for the placebo group ($p < 0.001$).

ACCENT II[65] (infliximab)

This was a maintenance trial that recruited 306 patients who had one or more fistulas of at least 3 months' standing.[65] Of the 306 enrolled patients, 282 were assessed for 'response' at week 14 after administration of infusions at weeks 0, 2 and 6 of 5 mg/kg infliximab. 'Responders' were defined as those patients with at least 50% reduction in draining fistulas relative to baseline, observed at both weeks 10 and 14. Sixty-nine per cent (195) of patients were classified as

responders. Both responders and non-responders were randomised to placebo (96 responders, 43 non-responders) or to 5 mg/kg infliximab (99 responders, 44 non-responders), which were administered at weeks 14, 22, 30, 38 and 46. Assessment visits were scheduled at weeks 0, 2, 6, 10, 14, 22, 30, 38, 46 and 54. After week 22, patients losing response could cross over to 5 mg/kg infliximab from placebo and from 5 mg/kg infliximab to 10 mg/kg infliximab. The fistula status outcome measures were:

- loss of response – defined as a recrudescence of draining fistula, a change in therapy, a need for surgery, dropout due to lack of efficacy, or a worsening of luminal disease activity
- response – defined as 50% reduction from baseline in draining fistula observed at consecutive visits 4 or more weeks apart
- complete absence of draining fistula.

Primary outcome

The primary outcome was designated as time to loss of response in responders. The results are summarised in *Figure 26*.

The median time to loss of response after randomisation was 14 weeks in the placebo group and >40 weeks in the infliximab group ($p < 0.001$ by log rank test). In the infliximab group, 42% of responders lost response, and in the placebo group, 62% lost response. The main reasons for loss of response in the primary outcome were: change in treatment (38% of placebo, 25% of infliximab) or recrudescence of fistula (22% placebo, 16% infliximab).

Response and complete response

At 30 weeks, 33% and 64% of the placebo and infliximab groups respectively had a response (50% reduction in draining fistula from baseline for at least two consecutive visits), and at week 54 the corresponding percentages had diminished to 23% and 46% respectively ($p = 0.001$). The manufacturer's submission to NICE contained CiC information for additional weeks of follow-up. These are summarised in *Figure 27*. Prior to randomisation, except at week 2, the rates were about equal as would be expected, given that all responder patients received identical induction therapy up to week 14 and baseline characteristics were well balanced. At week 2, a surprising difference between groups was observed with higher rates for the patients subsequently randomised to infliximab. At week 14, the placebo group did not receive infliximab. After randomisation at week 14, response rates diminished in both groups. From week 22 the risk difference (infliximab–placebo) reached statistical significance in favour of infliximab, after week 30 risk differences diminished indicating that most benefit for maintenance of response from

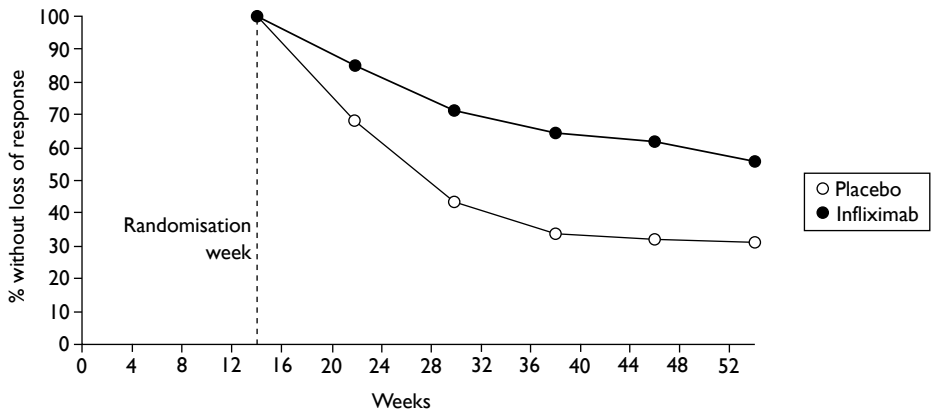

FIGURE 26 Time to loss of response by responders in ACCENT II.[65] Data taken from published graph and redrawn.

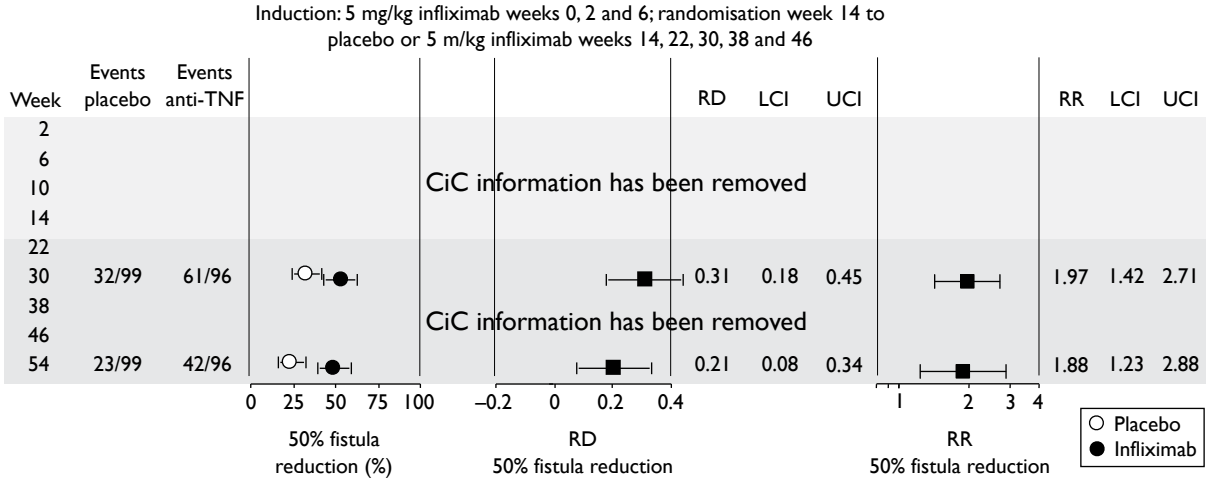

FIGURE 27 Rates and risk differences for ≥50% reduction of draining fistulas in ACCENT II[65] responders. LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

active intervention was delivered between weeks 14 and 30. By week 30 the intervention group had received two more infusions of infliximab than placebo patients.

Responders with loss of response during the post-randomisation phase were allowed to cross over after week 22 to an increased dose of infliximab. The renewed response rate in these crossover patients was reported as 25/41 (61%) in the placebo group (crossed over to 5 mg/kg dose) and 12/21 (57%) in the intervention group (crossed over to 10 mg/kg dose). However, Figure 1 of the ACCENT II[65] published report shows 50 crossovers from placebo and 28 from 5 mg/kg infliximab.

The published report provided information about the rates of 'complete response' among responders.[65] A complete response was defined as a complete absence of draining fistulas. The definition for a response required ≥50% reduction in fistulas for at least 4 weeks, a 'complete response' differed in that no minimum duration was specified. It was unclear, but likely, that this definition applied only to draining fistulas of at least 3 months' standing at baseline. The frequency of draining fistulas at baseline that were of less than 3 months' standing was not reported. The results for a complete response are summarised in *Figure 28*.

At week 2, after only a single dose of infliximab, 66% (128/195) of patients already had a 'complete response'. Unexpectedly, more patients who were subsequently randomised to infliximab had a complete response than those subsequently randomised to placebo ($p = 0.014$). By 14 weeks, 66% and 69% of responder patients who were randomised to placebo and infliximab respectively had a complete response. The rate of complete response in responders diminished in both groups after week 14. From week 22 the risk difference (infliximab–placebo) reached statistical significance in favour of infliximab and from week 30 remained stable, indicating that most benefit in maintenance of response from active intervention was delivered between weeks 14 and 30.

The rate for a complete response among all enrolled patients at week 14 was reported to be 48% (147/306); this generated a 75% [147/(99 + 96)] complete response for responders at week 14 which according to Figure 2B in the ACCENT II[65] published report corresponded to week 10 rather than to week 14.

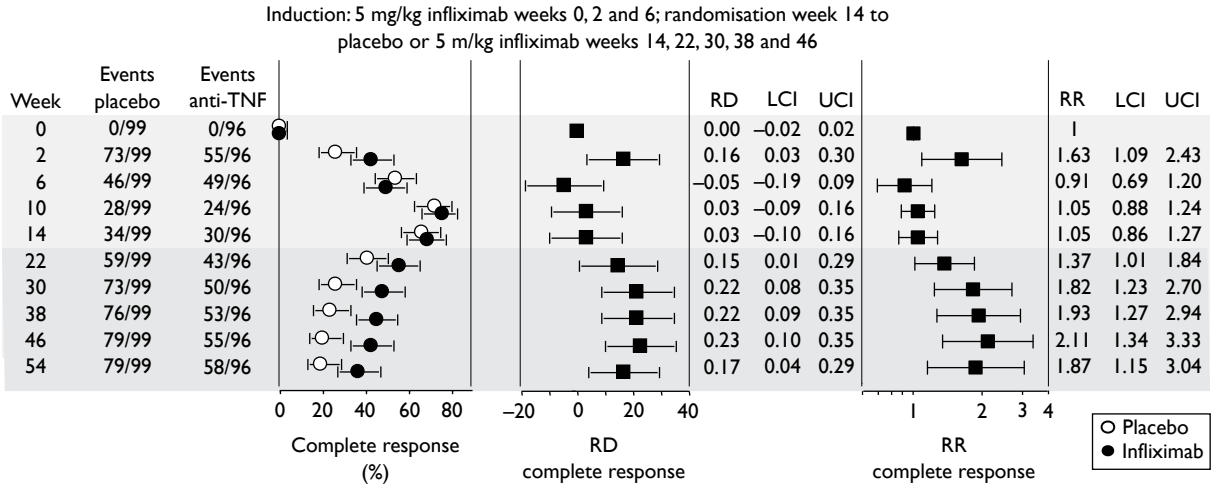

FIGURE 28 Rates, risk difference and risk ratio for complete response among responders in ACCENT II.[65] LCI, lower confidence interval; RD, risk difference; RR, risk ratio; UCI, upper confidence interval.

Hospitalisations and major surgery

The manufacturer's submission to NICE presented results for major surgery and for hospitalisation for all patients in ACCENT II[65] whether or not they crossed over. For this purpose the placebo arm was termed 'episodic treatment' and the infliximab arm 'scheduled treatment'. A 2.4-fold lower rate was reported for the scheduled treatment group. There were two important differences between these treatments. Firstly, patients in the 'episodic' arm experienced a 4-month mandatory withdrawal of active intervention (from weeks 6 to 22) not experienced by patients in scheduled treatment. Secondly, after week 22 the 'episodic' group patients were restricted to 5 mg/kg infliximab at episodes of worsening disease, whereas the 'scheduled treatment' group were able to receive 10 mg/kg. Restricted access to treatment (weeks 6–22) and restricted dosage represent biases likely to favour the 'scheduled treatment' group for any comparisons after week 6. Furthermore the 'episodic treatment' procedure was unlikely to reflect how an episodic strategy might be implemented in real world clinical practice, both with respect to the 4-month gap in active intervention and with regard to restriction of dose. Because of bias in the comparisons made and the probable dissimilarity between the trial episodic treatment and likely clinical practice, it was considered here that the hospitalisation rate for the 'episodic' treatment and the comparison with the scheduled treatment were very approximate guides.

The considerations described above also apply to the values reported for the percentages of patients requiring major surgery (13% and 2% in 'episodic' and scheduled treatment arms respectively).

Other outcomes reported for ACCENT II

The ACCENT II[65] published report presented the median decrease from baseline in CDAI score at weeks 30 and 54 for all patients. Improvements in median CDAI were statistically significantly greater for the infliximab group ($p = 0.004$). Median increases from baseline in IBDQ scores at weeks 30 and 54 were also significantly greater for the infliximab group than for the placebo group. Baseline scores for all patients by group were not provided and baseline balance was therefore uncertain. In the case of missing values, the last observations were carried forward for the CDAI and IBDQ outcomes. The results are summarised in *Table 35*.

Further results for the ACCENT II[65] trial were presented in two separate papers.[75,76] One reported a post hoc analysis of the subgroup of responder patients with rectovaginal fistulas (11 received

TABLE 35 Median CDAI and IBDQ changes ACCENT II[65]

Week	Infliximab ($n=139$)	Placebo ($n=143$)	p infliximab vs placebo
Median decrease in CDAI score from baseline			
30	42	16	0.004
54	40	15	0.004
Median increase in IBDQ score from baseline			
30	14	4	0.002
54	10	5	0.03

Baseline scores were reported for responders by group and for all non-responders, but not for all patients by group.

placebo and 14 received the 5 mg/kg dose regimen of infliximab);[75] the other paper performed a post hoc analysis on incidence of abscess development in patients responding to infliximab with closure of fistulas.[76] The first of these papers was too underpowered for firm conclusions to be drawn. In ACCENT II,[65] crossover to an increased dose of infliximab was allowed for all randomised groups (including placebo) from week 22 onwards; this resulted in the mean dose of infliximab in the placebo group (quoted as 20 mg/kg) being approximately half that of the intervention groups (quoted as 40 mg/kg). The post hoc analysis for abscess development compared these two groups and reported no statistically significant difference in rates (15% vs 19%; $p=0.526$).

Quality assessment (based on published report)

Randomisation and blinding were adequate and allocation concealment likely to be so. Baseline characteristics for responders were well balanced between placebo and infliximab arms; however, for the all-patient comparisons between infliximab and placebo arms (e.g. of change in IBDQ and CDAI scores relative to baseline) it was not possible to ascertain if groups were balanced at baseline. There was a lack of clarity in the methods section so that it was difficult to determine if the sentence '…data for patients who crossed over from placebo to infliximab were censored before crossover occurred…' referred to the survival analysis of loss of response. If it did, the reason for different handling of crossovers in the compared groups is difficult to interpret. The number of patients who withdrew prematurely was unclear except for discontinuation for AEs. No power calculation was undertaken. The last observation was carried forward as necessary for continuous outcomes, but the number of missing data was not reported.

ACCENT II.[65] Summary of effectiveness evidence

After induction infusions of 5 mg/kg infliximab at weeks 0, 2 and 6, 64% of enrolled patients were classified as responders. Responders were defined as patients experiencing at both weeks 10 and 14 a ≥50% reduction in the number of draining fistulas that were present at baseline of at least 3 months' standing.

After week 14, the median time to loss of response by responder patients was greater for patients randomised to continued infliximab treatment of 5 mg/kg at 8-week intervals than for those randomised to placebo ($p<0.001$). More responder patients randomised to infliximab at week 14 experienced a response (closure of ≥50% of draining fistula for at least 4 weeks) than did responder patients randomised to placebo, and from week 22 the risk difference (infliximab–placebo) reached statistical significance in favour of infliximab. After week 14, response rates diminished in both groups. From week 30, risk differences diminished indicating that most benefit from infliximab was delivered between weeks 14 and 30.

Other trials reporting on subgroups of adults with fistulas

Two other trials reported on effectiveness of anti-TNF therapy for closure of fistulas – the GAIN induction trial of adalimumab[64] and the CHARM maintenance trial of adalimumab.[67] In the GAIN trial,[64] at the end of follow-up (week 4) similar rates of fistula improvement were recorded for adalimumab and placebo groups (3/20 and 5/25 respectively). The CHARM trial[67] reported a measure termed 'fistula remission' for the subgroup of trial patients who had fistula at screening and baseline. Fistula remission was defined as the percentage of patients with closure of all fistulas that were draining at screening and at baseline (separated by 2 weeks). Fistula remission was observed for 30% (21/70) and 13% (6/47) of combined adalimumab groups and placebo group respectively at week 26 and for 33% (23/70) and 13% (6/47) respectively at week 56.

Paediatric Crohn's disease trials

Patients in these trials were ≤ 18 years of age. Two trials, Baldassano *et al.*[46] and REACH [A randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNFα chimeric monoclonal antibody (infliximab, Remicade®) in pediatric subjects with moderate-to-severe Crohn's disease] (Hyams *et al.*[45]), looked at the effectiveness of different doses of infliximab in paediatric CD patients. There was no placebo arm in either trial. There were no trials of adalimumab in children. The outcomes measured are shown in *Table 36* and the study characteristics are summarised in *Table 37*.

Baldassano et al.*, 2003[46] (infliximab)*

The small trial of Baldassano *et al.*[46] examined whether a single dose of infliximab induced a response in paediatric patients. Patients were randomised to a 1 mg/kg ($n = 6$), 5 mg/kg ($n = 7$) or 10 mg/kg ($n = 8$) infusion. Patients were followed up to week 12. The primary outcomes were improvements from baseline in PCDAI and modified CDAI score. Other outcomes were the percentage of patients responding and the percentage in remission.

Table 38 shows the median percentage improvement in PCDAI score at various follow-up times relative to baseline. No clear pattern relating to follow-up time or dose regimen was apparent. To what extent improvement in scores resulted from infliximab treatment is impossible to determine because of lack of an appropriate placebo control group.

Response and remission results are summarised in *Figure 29*. All estimates were associated with great uncertainty due to the small number of participants. The proportion of patients in response approached 100% after 1 week in all groups and then tended to decline during follow-up. There

TABLE 36 Outcomes measured in trials of paediatric CD

	% of patients in remission (PCDAI score < 10)	% achieving response	PCDAI score (mean or median)	Additional outcomes
Infliximab				
Baldassano *et al.* 2003[46]	✓	✓ Decrease in CDAI of ≥ 70 points OR ≥ 10 points on PCDAI	✓	Endoscopic lesion severity score (in consenting patients)
REACH[45]	✓ (or CDAI < 150)	✓ Decrease in PCDAI of ≥ 15 points and total PCDAI score < 30	✓	IMPACT III score; % discontinuing corticosteroids; change in height status (subgroup); clinical response following crossover

PCDAI, Paediatric Crohn's Disease Activity Index.
IMPACT is a measure of HRQoL in paediatric IBD.

TABLE 37 Main study and population characteristics: paediatric trials

Study Sponsor	Country	Study length/ size	Population: severity of CD (baseline CDAI and IBDQ if stated)	Intestinal areas affected	Main concomitant medication, % not on any medication	Previous/ concomitant treatment with anti-TNF inhibitors	Intervention and comparator (dosing regimen)
Baldassano *et al.*, 2003[46] Supported by Centocor	Multicentre (USA, Europe)	12 weeks $n = 21$	Moderate-to-severe active disease despite previous treatment, PCDAI ≥ 30 or modified CDAI ≥ 200 Median PCDAI 56, 45 and 41 infliximab groups (no placebo group), median modified CDAI score 455, 317 and 312 (IBDQ not stated)	Mainly ileum and colon, also colon only and gastroduodenal	Mainly aminosalicylates and corticosteroids, also mercaptopurine or azathioprine, antibiotics, few methotrexate % not on medication (if any) not stated	No details	Single intravenous infusion of 1 mg/kg infliximab, 5 mg/kg infliximab or 10 mg/kg infliximab over at least 2 hours at week 0 (No placebo group)
Hyams *et al.*, 2007 – REACH[45] Supported by Centocor	Multicentre (USA, Canada, Europe)	54 weeks $n = 103$	Moderate-to-severe CD PCDAI > 30 at baseline Mean baseline PCDAI (SD) 42.1 (9.2) and 40.1 (6.8) (infliximab groups, no placebo group) (no other baseline measures)	Mainly colon and/or ileum, also upper tract	Mainly mercaptopurine or azathioprine, also aminosalicylates and corticosteroids, few methotrexate % not on medication (if any) not stated	Exclusion criteria: previously treated with infliximab or other anti-TNF agent	Three i.v. infusions as induction therapy with infliximab 5 mg/kg (weeks 0, 2 and 6) followed by: five infusions of maintenance therapy with infliximab 5 mg/kg administered at weeks 14, 22, 30, 38 and 46 or three infusions with infliximab 5 mg/kg at weeks 18, 30 and 42

was little difference between the groups. How much of the response was intervention dependent cannot be determined because of the lack of an appropriate placebo control group that did not receive infliximab. For remission, no clear pattern relating to dose or length of follow-up was apparent. Again, because of the lack of an inactive control it is impossible to determine the contribution of infliximab to the observed results.

Quality assessment (based on published report) Randomisation and blinding were adequate and allocation concealment likely to be so. With such small numbers in each group it is not surprising that some baseline characteristics were imbalanced; notably, the 10 mg/kg group consisted almost

TABLE 38 Improvement in PCDAI score in Baldassano *et al*.[46]

	Median % improvement from baseline in PCDAI score		
	Infliximab dose		
Week	1 mg/kg	5 mg/kg	10 mg/kg
1	47	37	35
2	40	65	53
4	27	57	28
8	32	28	64
12	27	13	40

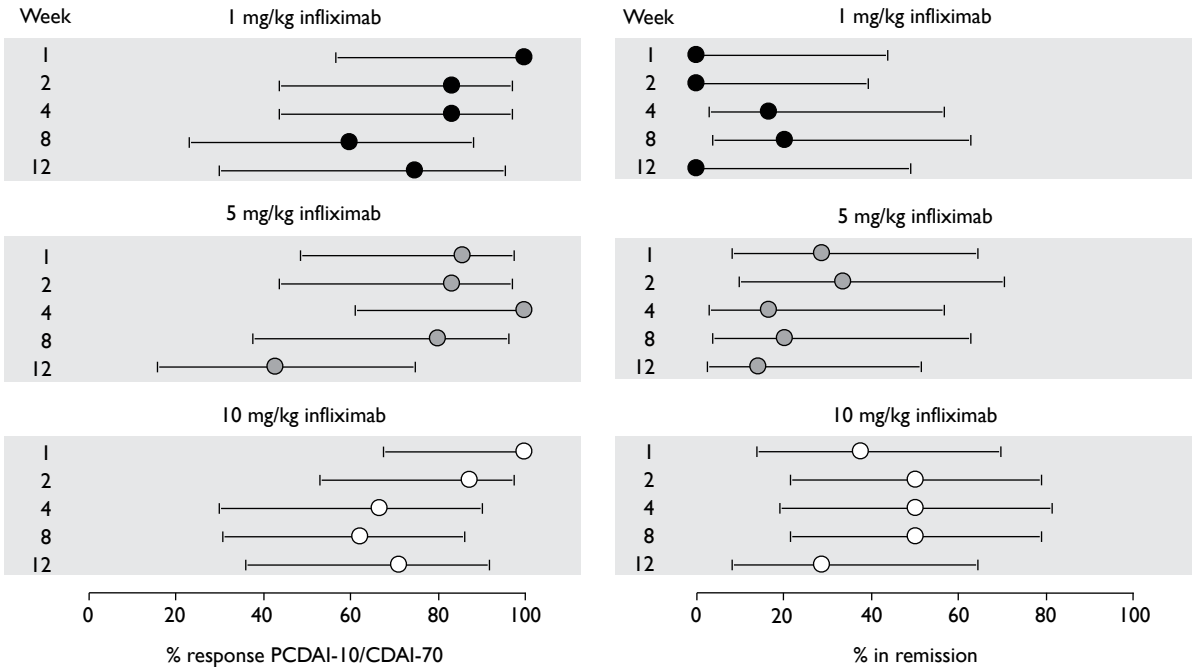

FIGURE 29 Response and remission rates reported in Baldassano *et al*.[46] (results as reported, not ITT). Response was defined as at least a 10-point reduction in PCDAI or at least a 70-point reduction in modified CDAI score; remission was defined as a PCDAI score < 10 or a modified CDAI of < 150.

exclusively of boys and the baseline CDAI score was substantially higher for the 1 mg/kg group than for the 5 mg/kg and 10 mg/kg groups. The number of patients completing the trial was reported to be 90%. No power calculation was done and analyses did not appear to be ITT.

Baldassano *et al*., 2003.[46] Summary of effectiveness evidence

An induction infusion of 1, 5 or 10 mg/kg infliximab improved PDAI scores relative to baseline. Induction increased the proportion of patients in response (40%–100% depending on dose and follow-up time) and in remission (0%–50% depending on dose and follow-up time). The study was underpowered, so these effectiveness estimates were associated with great uncertainty; no clear pattern was evident relating outcomes to dose regimen. The lack of a placebo control group renders interpretation of results problematic.

REACH[45] (infliximab)

The REACH trial[45] was called an 'induction and maintenance' study. Patients received induction doses of 5 mg/kg infliximab at weeks 0, 2 and 6. Responders were defined as those who reduced baseline PCDAI by at least 15 points and had a score of ≤ 30 at week 10. Responders (only) at week 10 were randomised to either five further doses of 5 mg/kg every 8 weeks delivered at weeks 14, 22, 30, 38 and 46 or three further doses delivered every 12 weeks at weeks 18, 30 and 42. Of 112 patients entering the induction phase, 103 were classified as responders and 99 were analysed. The lack of a placebo control group not receiving infliximab means that it is difficult to determine to what extent maintenance of response after induction was attributable to infliximab intervention. No primary outcome was identified. Response and remission results were reported for weeks 30 and 54 and weeks 10, 30 and 54 respectively. These are summarised in *Figure 30*. The differences between the two dose regimens for both response and remission at weeks 30 and 54 reached statistical significance ($p < 0.05$) in favour of the more frequent dose regimen.

The REACH publication[45] also reported changes from baseline (mean and SD) in PCDAI score, IMPACT III score (a QoL measure; scores range from 35 to 175 with higher scores representing better QoL) and daily corticosteroid use. Last observation was carried forward where values were missing. Information was provided for all 'responders' (i.e. the two trial arms combined) or separately for the two different treatment groups, at weeks 10, 30 and 54. The results are summarised in *Table 39*. The 'all responders results' do not represent a randomised comparison but rather a 'before versus after treatment' comparison for a subgroup of patients (responders) who were selected because they exhibited a favourable response. Given that a 'no-treatment control group' was not included in this trial, the analyses do not provide robust quantitative information about the effectiveness of infliximab for paediatric patients, and the favourable changes reported are difficult to interpret as an indeterminate proportion of the effects observed may have been infliximab independent.

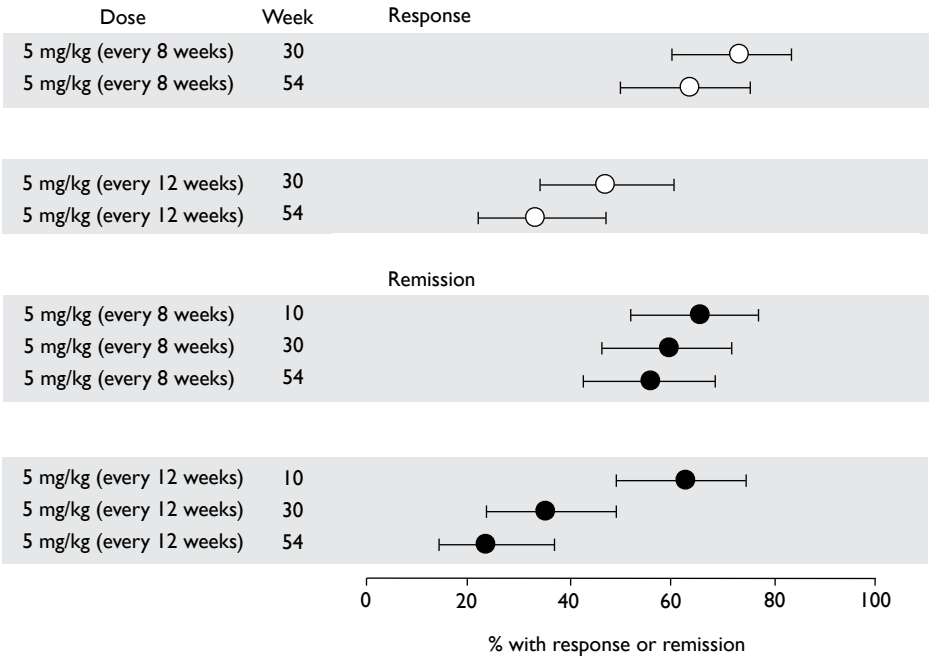

FIGURE 30 Post-induction response and remission rates for responders in the REACH trial.[45] Response defined as decrease in PCDAI of ≥ 15 points from baseline and total ≯ 30. Remission defined as a PCDAI ≤ 10 points.

TABLE 39 Changes from baseline in outcome measures reported for the REACH trial[45]

Group	Week 10	Week 30	Week 54	*n*
PCDAI: mean (SD) decrease from baseline [improvement][a]				
Doses every 8 weeks	–33.2	NR	NR	52
Doses every 12 weeks	–29.4	NR	NR	51
Groups combined	–31 (10)	–25.5 (16)	–27 (16)	103
IMPACT III: mean (SD) increase from baseline [improvement][a]				
Doses every 8 weeks	NR	24.7	26.5	NR
Doses every 12 weeks	NR	18.3	22.5	NR
Groups combined	23.9 (16)	21 (18)	24 (17)	76
Corticosteroid dose (mg/kg): mean (SD) decrease from baseline [improvement][a]				
Doses every 8 weeks	NR	NR	NR	52
Doses every 12 weeks	NR	NR	NR	51
Groups combined	0.3 (0.4)	0.39 (0.4)	0.3 (0.59)	103
Patients' corticosteroid use: n discontinued of N users (%)				
Doses every 8 weeks	12 of 24 at baseline (50%)	NR	10 of 12 at week 10 (83%)	NA
Doses every 12 weeks	3 of 12 at baseline (25%)	NR	5 of 9 at week 10 (56%)	NA
Groups combined	15 of 36 at baseline (42%)	NR	15 of 21 at week 10 (71%)	NA

NA, not applicable; NR, not reported.
a $p < 0.001$ vs baseline.
Randomisation was at week 10.

After week 10 responder patients were allowed to cross over to increased infliximab for worsening disease state. The increases in infliximab allowed included transfer from infusions every 12 weeks to every 8 weeks and increase in infusion dose from 5 mg/kg to 10 mg/kg. The proportion of patients who crossed over was 40%. The number of responder patients who withdrew prematurely was reported as 22 (21%), but it was unclear if this included withdrawals of patients who had crossed over to increased infliximab.

Quality assessment (based on published report) Randomisation was adequate and allocation concealment likely to be so. This was an open-label study with no blinding.[45] Baseline characteristics were well balanced except for steroid use. The number of patients withdrawing was reported, but it was not clear if this also included crossover patients who later withdrew. A power calculation was done and analyses were ITT.

REACH.[45] Summary of effectiveness evidence

A 10-week induction phase with infusions of 5 mg/kg infliximab at weeks 0, 2 and 6 was followed by randomisation of responders at week 10 to further 5 mg/kg infusions every 8 or 12 weeks. At week 10, 88% of enrolled patients were classified as responders. Response rates for responders diminished to less than 50% by week 54. The difference between dose regimens reached statistical significance in favour of the 8-weekly infliximab dose regimen. About 40% of patients crossed over to increased infliximab because of worsening disease status. About 20% of patients withdrew from treatment prematurely.

Results in non-responders

Published results for maintenance trials focused on early responders (determined at week 2, or week 4 in the two large trials, ACCENT I[2,3] and CHARM[67]). It is important to attempt to determine if such a subgroup analysis can be justified.

The question of whether results were published for non-responders is summarised in *Table 40*. Out of all of the maintenance trials, only two trials (ACCENT I[2,3] and II[65]) published results including initial non-responders. Additional information was obtained from the industry submission for results in responders and non-responders from the CHARM[67] trial (see *Appendix 11*). *Table 40* also details whether non-responders were randomised.

ACCENT I[2,3] (infliximab)

Results for responders and non-responders were not published separately nor presented in the manufacturer's submission. However, by subtracting CiC information for responders from published information for all patients, it is possible in theory to calculate the response and

TABLE 40 Results reported for non-responders (maintenance trials)

Study	Were non-responders randomised to maintenance treatment?	Were results reported for both responders and non-responders separately (RCT only)?
CLASSIC II[66]	No	No
(adalimumab)	Only those patients (from CLASSIC I[63]) in remission at week 0 and 4 eligible for randomisation; those not in remission at week 0 or no longer in remission at week 4 entered an open-label cohort	Results reported for patients not eligible for randomisation who entered open-label cohort
ACCENT I[2,3]	Yes	No
(infliximab)	Responders and non-responders randomised	Results for ALL patients (responders + non-responders) reported in Rutgeerts *et al.*;[2] results for responders only reported in Hanauer *et al.*[3]
		Industry submission: subgroup analysis of mucosal healing and CDEIS scores in responders and non-responders together; hospitalisation and surgery reported for responders and non-responders together
Rutgeerts *et al.*, 1999[58]	No	No
	Responders from Targan *et al.*[57] RCT eligible	No non-responders included in RCT
(infliximab)	Initial non-responders in Targan *et al.*[57] given an additional 8 weeks of open-label treatment during which they could respond and still be eligible for maintenance treatment	Proportion of non-responders at week 4 (Targan *et al.*[57] RCT) subsequently responding during open-label treatment unclear
	Unclear if any responders drawn from placebo group of RCT	
ACCENT II[65]	Yes	Yes
(infliximab, fistulising)	Non-responders randomised for secondary analysis	Results reported for response
REACH[45]	No	No
(infliximab, paediatric)	Only responders randomised (no placebo control)	No non-responders included in RCT (no placebo control)
CHARM[67]	Yes	No
(adalimumab)	Non-responders randomised for secondary analysis (randomisation stratified by responder status)	Stated that secondary efficacy analyses were conducted for total population, but results presented only for fistula closure, which relates to a subgroup of patients (15% of patients have fistula)
		Industry submission: present results (remission, CDAI decrease > 70, CDAI decrease > 100, IBDQ score) for responders and for patients with CDAI > 300
		The trial report submitted to NICE contained information on non-responders

remission rates for non-responders. Results for responders and for all patients were available in publications or CiC information in the industry submission for the following outcomes in the ACCENT I[2,3] trial:

(a) Median CDAI scores at numerous follow-up times. These were published in separate papers for responders only and for all patients.[3] No indication of variance was given, so robust analysis was not possible.
(b) IBDQ scores. These were recorded but reported differently in the two publications[2,3] (median scores for responders and a dichotomised outcome for 'all' patients); this information cannot be used for estimation of non-responder results.[3]
(c) Remission and response 70 for responder patients at multiple follow-up times. The manufacturer's submission on infliximab provided CiC results for remission and response 70 for responder patients at multiple follow-up times for ACCENT I.[2,3] Results for these outcomes for all patients were available in the public domain. It was possible to calculate the outcome for non-responder patients randomised to placebo or infliximab (5 mg/kg) by appropriate subtraction of responder rates from all-patient rates. Unfortunately, in practice this was meaningful for only the first 14 weeks of the trial because after week 14, patients who crossed over to increased infliximab dosage regimen on exacerbation of their disease contributed to the numbers achieving outcomes in the all-patient results but were discounted in the analyses for responders only.

The combined lack of complete long-term results, and the introduction of crossover to different treatments at week 14 of the trial, made it difficult to determine the rates of response of 'non-responders' in the ACCENT I[2,3] trial, and renders problematic the interpretation of these rates when the limited available data allows their calculation. *Appendix 11* provides the results calculated for non-responders in ACCENT I.[2,3]

ACCENT II[65] (infliximab)

Limited results for responders and non-responders were reported separately for this trial[65] that investigated patients with fistulas. The response rate among initial non-responders was 7/44 (16%) in the placebo group and 9/43 (21%) in the infliximab group ($p = 0.6$). A response was defined as a reduction of at least 50% from baseline in the number of draining fistulas at consecutive visits 4 or more weeks apart. The time point for this result was not stated and it is unclear whether these were patients who ever had a response during the 54-week trial. There are no details on whether these response rates were maintained. It is difficult to compare these results with those of the initial responders as the trial looked at the maintenance of response in initial responders rather than induction of response.

Adverse events

This section includes in-licence and non-licence trial results so as to include all relevant evidence. All studies reported AEs. There were six malignancies among 573 patients followed for 54 weeks in ACCENT I.[2] The most serious AEs, and/or those thought potentially to be associated with anti-TNF therapy have been tabulated. In *Table 41* trials are combined and the number of patients with selected AEs listed for treatment and placebo groups. Where there were several treatment groups, these have been combined. AEs occurring during induction or open-label periods of maintenance trials are listed separately according to availability of information (CHARM[67] and CLASSIC II[66]). There were differences in how trialists reported or grouped together AEs (see notes to *Table 42*). Where an event was not reported it is possible this was because the event did not occur. Excluding trials from the total count where the event did not occur may lead to an overestimation of the frequency of an AE. Where patients experienced more than one type of AE within a category (e.g. infusion reactions), they will have been counted more than once.

TABLE 41 Percentage of patients with selected AEs (trials combined)

Event (drug)	Treatment RCT data only	Placebo RCT data only	Induction or open-label phase only (CHARM,[67] CLASSIC II[66])
Deaths (both)	0.18% (3/1673)	0.11% (1/918)	NA
Deaths (adalimumab)	0% (0/938)	0% (0/519)	0.09% (1/1075)
Deaths (infliximab)	0.41% (3/735)	0.25% (1/399)	NA
AEs leading to withdrawal or discontinuation of treatment (both)	2.45% (43/1756)	6.36% (60/943)	NA
AEs leading to withdrawal or discontinuation of adalimumab treatment	3.84% (36/938)	8.29% (43/519)	8.65% (93/1075)
AEs leading to withdrawal or discontinuation of infliximab treatment	0.86% (7/818)	4.01% (17/424)	NA
Serious infections (both)	2.73% (47/1719)	3.42 (31/907)	NA
Serious infections (adalimumab)	1.71% (16/938)	2.50% (13/519)	1.77% (19/1075)
Serious infections (infliximab)	3.97% (31/781)	4.64% (18/388)	NA
TB (both)	0.23% (3/1323)	0% (0/707)	NA
TB (adalimumab)	0.21% (2/938)	0% (0/519)	0% (0/1075)
TB (infliximab)	0.26% (1/385)	0% (0/188)	NA
Cancer (both)	0.25% (4/1610)	0.56% (5/887)	NA
Cancer (adalimumab)	0% (0/938)	0.39% (2/519)	0% (0/1075)
Cancer (infliximab)	0.60% (4/672)	0.82% (3/368)	NA
Lupus (-like syndrome) (both)	0.29% (3/1018)	0% (0/513)	NA
Lupus (-like syndrome) (adalimumab)	0% (0/421)	0% (0/258)	0% (0/221)
Lupus (-like syndrome) (infliximab)	0.50% (3/597)	0% (0/255)	NA
Demyelinating disorders (both)	0% (0/666)	0% (0/279)	NA
Demyelinating disorders (adalimumab)	0% (0/554)	0% (0/279)	0.09% (1/1075)
Demyelinating disorders (infliximab)	0% (0/112)	NR	NA
All infusion reactions (both)	16.43% (292/1777)	8.59% (81/943)	NA
All infusion reactions (adalimumab)	17.48% (164/938)	7.71% (40/519)	12.74% (137/1075)
All infusion reactions (infliximab)	15.26% (128/839)	9.67% (41/424)	NA
Anaphylactic reaction (both)	1.79% (2/112) (possible reactions)	NR	NA
Anaphylactic reaction (adalimumab)	NR	NR	NR
Anaphylactic reaction (infliximab)	1.79% (2/112) (possible reactions)	NR	NA

NA, not applicable; NR, not reported; TB, tuberculosis.

Adverse events leading to withdrawal included worsening of CD, infection or obstruction. Serious infections included sepsis, colitis, abscess and pneumonia. Injection site reactions included burning, rash, pain, bruising or irritation, while i.v. infusion reactions included pruritus, chest pain, flushing, dizziness, dyspnoea, injection site irritation and nausea. Very few deaths were reported.

Little difference was found between treatment and placebo groups for the selected AEs. The only cases of tuberculosis and lupus-like syndrome occurred in the treatment groups. AEs leading to withdrawal were slightly higher in the placebo groups and infusion reactions slightly higher in the treatment groups.

Table 42 lists AEs according to trial. It appears that for reporting of AEs, the placebo groups of the maintenance trials also included patients who crossed over to a treatment group. For ACCENT I,[2,3] ACCENT II,[65] CHARM[67] and CLASSIC II,[66] crossover was specified as an option

TABLE 42 Number of patients with selected AEs

	Infliximab							Adalimumab					
Study	Baldassano *et al.*, 2003[46]	Hyams *et al.*, 2007[45] REACH	Present *et al.*, 1999[62]	Sands *et al.*, 2004[65] ACCENT II	Targan *et al.*, 1997[57]	Hanauer *et al.*, 2002[3] ACCENT I	Rutgeerts *et al.*, 1999[58]	Hanauer *et al.*, 2006[63] CLASSIC I	Sandborn *et al.*, 2007[64] GAIN	Colombel *et al.*, 2007[67] CHARM	Colombel *et al.*, 2007[67] CHARM	Sandborn *et al.*, 2007[66] CLASSIC II	Sandborn *et al.*, 2007[66] CLASSIC II
Study duration (weeks)	**12 weeks (I, P)**	**54 weeks (M, P)**	**18 weeks (I, F)**	**54 weeks (M, F)**	**4–16 weeks (I)[a]**	**54 weeks (M)**	**48 weeks (M)**	**4 weeks (I)**	**4 weeks (I)**	**4-week induction period (*N*=854)**	**56 weeks (M) (*N*=778)**	**56 weeks (M)**	**Open-label cohort**
Deaths – Rx	NR	0/112	0/63	0/138	NR	3/385	0/37	0/225	0/159	1/854	0/517	0/37	0/221
Deaths – placebo	NA	NA	0/31	0/144	NR	0/188	1/36	0/74	0/166	NA	0/261	0/18	NA
AEs leading to withdrawal or discontinuation of treatment – Rx	NR	12/112	1/63	5/138	2/83 Unclear	45/385	6/37	2/225	2/159	54/854	30/517	2/37	39/221
AEs leading to withdrawal or discontinuation of treatment – placebo	NA	NA	0/31	12/144	0/25 Unclear	5/188	0/36	2/74	4/166	NA	35/261	2/18	NA
Serious infections – Rx	NR	9/112	3/63	4/138	1/83	14/385	NR	2/225	0/159	10/854	14/517	0/37	9/221
Serious infections – placebo	NA	NA	0/31	9/144	1/25	8/188	NR	0/74	4/166	NA	9/261	0/18	NA
TB – Rx	NR	NR	NR	NR	NR	1/385	NR	0/225	0/159	0/854	2/517	0/37	0/221
TB – placebo	NA	NA	NR	NR	NR	0/188	NR	0/74	0/166	NA	0/261	0/18	NA
Cancer – Rx	NR	0/112	NR	0/138	NR	4/385	0/37	0/225 Lymphoma	0/159	0/854	0/517	0/37 Lymphoma	0/221 Lymphoma
Cancer – placebo	NA	NA	NR	0/144	NR	2/188	1/36	0/74 Lymphoma	0/166	NA	1/261	1/18 Lymphoma	NA
Lupus (-like syndrome) – Rx	NR	0/112	0/63	NR	NR	2/385	1/37	0/225	0/159	NR	NR	0/37	0/221
Lupus (-like syndrome) – placebo	NA	NA	0/31	NR	NR	0/188	0/36	0/74	0/166	NA	NR	0/18	NA

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	Infliximab							Adalimumab					
Study	Baldassano *et al.*, 2003[46]	Hyams *et al.*, 2007[45] REACH	Present *et al.*, 1999[62]	Sands *et al.*, 2004[65] ACCENT II	Targan *et al.*, 1997[57]	Hanauer *et al.*, 2002[3] ACCENT I	Rutgeerts *et al.*, 1999[58]	Hanauer *et al.*, 2006[63] CLASSIC I	Sandborn *et al.*, 2007[64] GAIN	Colombel *et al.*, 2007[67] CHARM	Colombel *et al.*, 2007[67] CHARM	Sandborn *et al.*, 2007[66] CLASSIC II	Sandborn *et al.*, 2007[66] CLASSIC II
Study duration (weeks)	**12 weeks (I, P)**	**54 weeks (M, P)**	**18 weeks (I, F)**	**54 weeks (M, F)**	**4–16 weeks (I)[a]**	**54 weeks (M)**	**48 weeks (M)**	**4 weeks (I)**	**4 weeks (I)**	**4-week induction period (*N*=854)**	**56 weeks (M) (*N*=778)**	**56 weeks (M)**	**Open-label cohort**
Demyelinating disorders – Rx	NR	0/112	NR	NR	NR	NR	NR	NR	NR	1/854	0/517	0/37	0/221
Demyelinating disorders – placebo	NA	NA	NR	NR	NR	NR	NR	NR	NR	NA	0/261	0/18	NA
All infusion reactions – Rx	0/21	19/112	4/63	22/138	2/83	80/385	1/37	66/225	17/159	111/ 854 Injection-site reaction	80/517 Injection-site reaction	1/37	26/221
All infusion reactions – placebo	NA	NA	0/31	24/144	0/25	17/188	0/36	12/74	17/166	NA	9/261 Injection-site reaction	2/18	NA
Anaphylactic reaction – Rx	NR	2/112 Possible reaction	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Anaphylactic reaction – placebo	NA	NA	NR	NR	NR	NR	NR	NR	NR	NA	NR	NR	NA

F, fistulising; I, induction; M, maintenance; NA, not applicable as no placebo arm; NR, no details reported (i.e. not stated in paper that this event did or did not occur); p, paediatric; Rx, active treatment (anti-TNF) group; TB, tuberculosis.

a Additional follow-up for open-label patients.

Baldassano *et al.*:[46] did not use category of serious infection (one pancreatitis, one sinusitis/appendicitis, two upper respiratory tract infections).

Present *et al.*:[62] did not use category of serious infection, but listed infections under serious AE (pneumonia and abscesses).

ACCENT II:[65] during long-term follow-up: two deaths, two cases of cancer and one of multiple sclerosis (all patients had received infliximab at some point).

Targan *et al.*:[57] two infusion reactions required discontinuation of infusions (unclear if led to discontinuation of study/treatment altogether); did not have category of serious infection but two infections required hospitalisation.

Rutgeerts *et al.*:[58] placebo patient who died was same one who had lymphoma (had induction treatment with infliximab); one patient withdrawn because of infusion reaction, unclear if further infusion reactions.

CHARM:[67] two cases of TB occurred during post-randomisation open-label therapy.

for those patients who had a non-response or experienced a disease flare. There were no details regarding potential crossovers from placebo to treatment in Rutgeerts *et al.*[58] ($n = 73$). See section on quality for details on number of crossovers from placebo groups (see *Quality assessment* sections and *Appendix 12*).

Crossover to treatment may have had an effect on the types and numbers of AEs reported in the placebo groups; for example an increase of those types of AEs associated with the treatment (e.g. infection) and/or an underestimate of AEs associated with no treatment (e.g. worsening of CD). It should be noted that in the maintenance trials, all patients (including those subsequently randomised to placebo) initially received the study drug during the induction phase; the effects of this may have carried over into the placebo phase of the RCT.

None of the maintenance trials reported AEs for patients according to whether they had ever or never received the treatment during the RCT phase of the study. As some of the AEs reported are very rare, it is possible that any differences between treatment and placebo groups are due to chance.

Development of antibodies

This section describes all included studies. *Table 43* lists numbers of patients developing antibodies to anti-TNF agents, nuclear antibodies and antibodies to double-stranded deoxyribonucleic acid (DNA). Most (10/11) studies reported the development of antibodies to the respective anti-TNF agent;[2,3,45,46,57,58,62–66] four studies[2,3,45,65,66] reported anti-nuclear antibodies and eight studies[2,3,45,46,57,58,62,65,66] reported anti-double-stranded DNA antibodies.

Five induction trials reported the proportion of patients with antibodies to an anti-TNF agent;[46,57,62–64] these ranged from 0% to 6% (adalimumab: 0%, 1.3%; infliximab: 0%, 3.3%, 6%). All reported antibody development either for the intervention group only, or split by placebo and intervention group, except Present *et al.*,[62] which reported antibodies for placebo and intervention group together. Targan *et al.*[57] included patients from the post-RCT open-label extension. This was also the longest follow-up study among induction trials (16 weeks) and had the highest level of antibodies (6%).

Five maintenance trials reported antibodies to an anti-TNF agent;[2,3,45,58,65,66] these ranged from 2.6% to 17% (infliximab: 2.9% to 17%; adalimumab: 2.6%). All patients were exposed to anti-TNF during induction. A patient's subsequent exposure was variable according to randomisation group and crossover to active intervention or escalated dosage regimen. Three studies reported antibodies for the intervention and placebo groups together (ACCENT II,[65] Rutgeerts *et al.*[58] and CLASSIC II[66]). The majority of patients in CLASSIC II[66] came from the open-label cohort component of the study. The lowest antibody levels occurred in CLASSIC II[66] (adalimumab); the other large adalimumab maintenance trial (CHARM[67]) did not measure antibodies.

Seven studies listed the proportion of inconclusive samples,[2,3,45,57,58,62,64,65] which were generally high and ranged from 14% to 'most' patients. These samples had detectable concentrations of anti-TNF agent, which could compete for the detection of antibodies to the anti-TNF agent in the immunoassay used, and would therefore not give a valid result. It is unclear whether the overall percentages of antibodies to the anti-TNF agent would have been different if they could have been measured in all patients.

As with the AEs described above, it should be noted that patients in the placebo groups of the maintenance trials would have all received the treatment as part of induction and may also have crossed over to a treatment group during later stages of the trials.

TABLE 43 Antibodies to anti-TNF agent and DNA

	% evaluated Abs	Patients with Abs to anti-TNF agent	Patients with anti-nuclear Abs	Patients with Abs to double-stranded DNA
Adalimumab				
Hanauer *et al.*, 2006 CLASSIC I[63] INDUCTION	NR	PLAC: 1/74 (1.4%) +ve (assumed *n*) ADA: 1/225 (0.4%) +ve (assumed *n*)	NR	NR
Sandborn *et al.*, 2007 GAIN[64] INDUCTION	Appears to be measured in all	PLAC: 0/166 (0%) +ve ADA: 0/159 (0%) +ve Presence of measurable ADA precluded determination of Abs in *most* patients treated with ADA	NR	NR
Sandborn *et al.*, 2007 CLASSIC II[66] MAINTENANCE	269/276 (97.5%; includes 221 from open-label cohort) for anti-ADA Abs 185/276 (67.0%; includes 221 from open-label cohort) for anti-nuclear and anti-DNA Abs	7/269 (2.6%) +ve All groups including open-label cohort	36/185 (19.5%) +ve At baseline and/or at final visit	33/185 (17.8%) +ve At baseline and/or at final visit
Colombel *et al.*, 2007 CHARM[67] MAINTENANCE	Not measured	Not measured	Not measured	Not measured
Infliximab				
Baldassano *et al.*, 2003[46] INDUCTION CHILDREN	21/21 (100%) NB no PLAC group	0/21 (0%) +ve	NR	0/21 (0%) +ve
Hyams *et al.*, 2007 REACH[45] MAINTENANCE CHILDREN	105/112 (93.8%) for Abs to INF 91/112 (81.3%) for anti-nuclear Abs 99/112 (88.4%) for anti-DNA Abs Note that no PLAC group; includes patients who were not randomised to maintenance therapy	3/105 (2.9%) +ve 21/105 (20.0%) –ve 81/105 (77.1%) inconclusive sample (detectable INF concentration)	23/91 (25.3%) +ve	7/99 (7.1%) +ve
Present *et al.*, 1999[62] INDUCTION FISTULISING	92/94 (97.9%) for Abs to INF Unclear for anti-DNA Abs (appears all in INF groups only)	3/92 (3.3%) +ve 13/92 (14.1%) inconclusive sample INF and PLAC groups	NR	8/63 (12.7%) +ve INF groups only
Sands *et al.*, 2004 ACCENT II[65] MAINTENANCE FISTULISING	258/282 (91.5%) for Abs to INF 254/282 (90.1%) for anti-nuclear Abs 243/282 (86.2%) for anti-DNA Abs	44/258 (17.1%) +ve 80/258 (31.0%) –ve 134/258 (51.9%) inconclusive sample Not detailed by group	INF: 56/122 (45.9%) +ve PLAC: 24/132 (18.2%) +ve	INF: 27/116 (23.3%) +ve PLAC: 8/127 (6.3%) +ve
Targan *et al.*, 1997[57] INDUCTION	101/108 (93.5%) for Abs to INF 98/108 (90.1%) for anti-DNA Abs Note that samples include post-RCT open-label patients	6/101 (5.9%) +ve who received INF blinded or as open label Note that in 2/3 INF patients, INF was still detectable and may have interfered with assay	NR	3/98 (3.1%) +ve who received INF blinded or as open label

continued

TABLE 43 Antibodies to anti-TNF agent and DNA (*continued*)

	% evaluated Abs	Patients with Abs to anti-TNF agent	Patients with anti-nuclear Abs	Patients with Abs to double-stranded DNA
Hanauer *et al.*, 2002 and Rutgeerts *et al.*, 2004 ACCENT I[2,3] MAINTENANCE	442/573 (77.1%) for Abs to INF Note that number with Abs reported according to actual treatment received bearing in mind that patients crossed over	PLAC: 41/442 (9.3%) +ve INF: 23/442 (5.2%) +ve In 46% of patients INF still detectable therefore inconclusive	PLAC: 63/180 (35%) +ve INF groups: 363/648 (56%) +ve	PLAC: 19/173 (11%) +ve INF groups: 123/362 (34%) +ve
Rutgeerts *et al.*,[58] 1999 MAINTENANCE	71/73 (97%)	7/47 total (14.9%) +ve PLAC: 5/NR INF: 2/NR 24/71 (33.8%) inconclusive as measurable INF in sample	NR	2/47 total (4.3%) +ve PLAC: 0/ND INF: 2/ND

–ve, negative; +ve, positive; Abs, antibodies; ADA, adalimumab; INF, infliximab; NR, no details reported; PLAC, placebo.

The proportions of anti-nuclear antibodies were variable: 25% in REACH[45] (infliximab), 18%/46% [active treatment (anti-TNF) group (Rx)/placebo] in ACCENT II[65] (infliximab), 35%/56% (Rx/placebo) in ACCENT I[2,3] (infliximab) and 19% in CLASSIC II[66] (adalimumab).

Antibodies to double-stranded DNA were measured in three infliximab induction trials[46,57,62] (range 0%–13%) and four maintenance trials[2,3,45,58,65] (range 4%–34%); only one adalimumab trial (CLASSIC II,[66] 19%) measured this parameter.

Given the proportion of missing data (inconclusive samples), the varying numbers of patients receiving treatment in different trials (those who crossed over) and the relatively small number of trials, it is not possible to conclude that one of the interventions is more or less likely to result in the development of antibodies to the anti-TNF agent. Whether different types of assays were used for the detection of antibodies or whether there were differences in the number of frequency of assessments, which could have led to differences between studies or drugs, was not investigated.

Based on the results for all patients (responders and non-responders) from the ACCENT I trial,[2] it appeared that scheduled treatment led to the formation of fewer antibodies to infliximab than 'episodic' treatment (28% in placebo/episodic treatment arm, 9% in 5 mg/kg scheduled arm and 6% in 10 mg/kg scheduled arm). It should be noted that the comparison between 'episodic' and scheduled treatment is not a randomised one (see *Quality assessment* of ACCENT 1). Given that the 'episodic' group included patients who crossed over from the scheduled treatment groups and the fact that 46% of total samples were inconclusive, it is unclear how robust these results are.

Safety issues; rare serious adverse events

Information extracted from the RCTs included for review of clinical effectiveness provides little long-term evidence about safety. Anti-TNF therapies have now been licensed for multiple indications and data about rare serious AEs have gradually accumulated. In this section the relevant safety issues following from these data are briefly reviewed.

Bongartz *et al.*[77] meta-analysed rates of malignancy and of serious infection reported in placebo controlled RCTs of infliximab and adalimumab in rheumatoid arthritis. Information in published papers and from the US FDA website was used for the analysis. Odds ratios (anti-TNF versus placebo) for malignancy and infection were 3.3 (95% CI 1.2 to 9.1) and 2 (95% CI 1.2 to 3.1)

respectively, and the numbers needed to harm were 154 and 59 respectively over a treatment period of 3–12 months. Higher drug doses were associated with greater risk. Similar results were reported in a meta-analysis conducted by Shoor.[78]

Tumour necrosis factor-α has an important role in the host immune response to *Mycobacterium tuberculosis* and in the immunopathology of tuberculosis.[79] Patients to be treated with anti-TNF agents should be screened for tuberculosis before starting anti-TNF therapy, they should be monitored for tuberculosis during therapy and those with latent tuberculosis should be appropriately treated prior to initiation of anti-TNF therapy. A 2007 publication (Raval *et al.*[79]) detailed 130 infliximab-associated cases of tuberculosis spontaneously reported to the US FDA between 1 November 2001 and 30 May 2006. In 45% of cases there was extrapulmonary disease. In a subset of 67 cases notified after the addition of a tuberculosis warning to the boxed medication it was noted that in six instances no test had been performed and that of 47 tuberculin skin tests performed, 34 gave a negative result. The false-negative rate was unknown. These results emphasise the requirement for vigilance by physicians caring for patients treated or about to be treated with anti-TNF therapies.

Ramos-Casals *et al.*[80] identified 233 cases of autoimmune disease apparently associated with anti-TNF therapies. Of these, 17 occurred in CD patients. Anti-TNF agents infliximab, adalimumab and etanercept were associated with various autoimmune manifestations including lupus, vasculitis and interstitial lung diseases. Overall incidence rates or rates for individual anti-TNF agents are unknown.

Elevated TNF-α is associated with heart failure and its level is correlated with severity of heart failure. Case reports ($n = 47$) reviewed by Kwon *et al.*[81] indicate that anti-TNF therapy might trigger new onset heart failure in a subset of patients and might exacerbate the condition of some patients. The SPCs carry warning of this potential risk.

Treatment with monoclonal antibodies has been associated with potentially fatal induction of progressive multifocal leuco-encephalopathy. A 2008 systematic review of primary data by Socal *et al.*[82] identified 29 cases most of which ($n = 23$) were associated with rituximab therapy which depletes the B-cell population. The single instance associated with anti-TNF treatment was reported for a 74-year-old woman given etanercept for rheumatoid arthritis.[83]

Discussion of results and assessment of effectiveness

Patient heterogeneity

Patient heterogeneity may affect results across different trials. The inclusion criteria of the trials specified a CDAI score between 220 and 400 or 450. The inclusion of patients already at a CDAI level close to remission could have improved the remission rates found. However, if patients already had a low CDAI count, achieving a reduction of 70 or 100 points would have been harder to achieve. The opposite would be more likely to be true for patients with very high initial CDAI scores. Therefore, it is unlikely that the initial wide spread of CDAI scores would have much impact on the results unless there were more patients at one end of the spread than the other. Mean CDAI scores at entry did not vary greatly between trials, so it appears unlikely that patient populations taken as a whole differed substantially between trials with respect to this parameter. Nevertheless populations probably did differ between trials as the placebo rates were heterogeneous. The corollary is that CDAI is not necessarily a reliable indicator of the seriousness of disease or of its likely progression. The CDAI score is a summary score and patients can achieve the same score yet have problems with very different aspects of their disease. Similarly, if a patient had a reduction of 70 points, that could be achieved in a variety of different ways. It is also uncertain whether a reduction of 70 or 100 points means the same in terms of reduction of disease severity for patients starting at different ends of the severity spectrum.

Cohort studies (e.g. Munkholm *et al.*[25]) demonstrate that most CD patients, at some time in their disease history, experience 'highly active disease' and that they cycle between highly active and quiescent periods of varying durations. Whether CD is severely debilitating for an individual depends to some extent on the frequency with which the episodes of highly active disease are repeated. Cohort studies show that this varies between patients. For these reasons a patient's CDAI score at a particular time, such as at recruitment into a trial, is not a good indicator for the likely duration of that level of disease activity or of the likely subsequent recurrence of highly active disease.

The licence indications for infliximab and adalimumab specify 'severe' CD but do not define how severe disease may be determined. It has been assumed that this is a CDAI score of $\geq$300. Trials have recruited patients having 'moderate-to-severe CD' defined according to CDAI scores of between 220 and 450, or 220 and 400; it is therefore unclear to what extent these populations fully reflect the intended licensed population.

Induction trials – placebo rates

CD is a chronic relapsing and remitting disease. Induction trials selected patients in relapse. On average, irrespective of treatment, relapsed patients will tend to improve, i.e. remit with time (their CDAI scores will reduce as they regress to the mean). This tendency would be reflected in relatively high rates of improvement in placebo groups in placebo-controlled trials and also in variation in these rates dependent on the relapse–remission cycling characteristics of each of the patients enrolled in the different trials.

The rates of response (reduction in CDAI of 70 or 100 points) and of remission in the placebo arms of the included induction trials varied from trial to trial and in some trials reached high levels (see *Appendix 13* for details). Except in the Targan *et al.*[57] trial of infliximab, by week 4 one-third or more of placebo patients had already achieved the least stringent measure of improvement (response 70). Similarly, at least 20%–25% achieved response 100 by week 4. Varied and high rates of placebo response have previously been documented for many CD intervention trials (Su *et al.*[84]). For dichotomous outcomes, variable placebo rates can profoundly influence effect size values such as risk difference and risk ratio. Thus placebo and intervention rates in two trials of 10% and 20% respectively in one and 30% and 40% respectively in the other generate identical outcome measures for risk difference (0.1 or 10%) but considerably different measures for risk ratio (2.0 and 1.3 respectively). For this reason, both placebo and intervention rates and both risk difference and risk ratio effect sizes have been presented in this report for most outcomes in the results section. The CIs quoted were not adjusted for repeated measures.

These high and varied placebo rates probably result from three influences: the tendency for CDAI scores to regress to the mean; a placebo effect; and possibly the effect of concomitant treatments allowed in the trials. The variation in placebo rates makes comparisons between trials problematic and indicates that CDAI scores alone are unlikely to be good prognostic indicators. Although recruited populations in the trials conformed to similar ranges, means or medians of CDAI score, they are likely to be clinically dissimilar.

Induction trials – effect sizes

By week 4 all induction trials, except for CLASSIC I[63] at the lower dose level for adalimumab (80/40 mg/kg weeks 0 and 2), exhibited statistically significant effect sizes for anti-TNF relative to placebo for remission and response, irrespective of whether these were measured in terms of risk difference or risk ratio. The trial of infliximab by Targan *et al.*[57] was remarkable in that the effect sizes observed were much greater than those seen in the other trials; placebo rates were notably lower in Targan *et al.*[57] than in any other trials. Targan *et al.*[57] was the earliest anti-TNF induction RCT and was a relatively small trial, so the point estimates of effectiveness were associated with

more uncertainty than was the case for the larger induction trial of adalimumab (GAIN[64]). Since the publication of Targan *et al.*,[57] no infliximab induction trial has been reported that can provide confirmatory evidence for the large effect size point estimates from the Targan *et al.*[57] trial. The response 70 rate at 4 weeks in the intervention arm of Targan *et al.*[57] was 81%. In the induction phase of the ACCENT I[2,3] maintenance trial of infliximab, the response 70 rate at week 4 was considerably less at 59%. ACCENT I[2,3] patients were administered the same dose at week 0 and patient baseline characteristics were similar to Targan *et al.*,[57] e.g. very similar CDAI and IBDQ scores. The contribution of infliximab to the initial 59% response 70 rate in ACCENT I[2,3] cannot be gauged because of lack of an appropriate control group.

The follow-up in the published adalimumab trial reports was to 4 weeks only, and there is no reliable evidence on the effectiveness of induction with adalimumab beyond this time period. Targan *et al.*[57] provided data on infliximab for some patients up to 16 weeks (4 weeks' induction + 12 weeks' open label).

Maintenance trials – general comments on trial design

The maintenance trials conformed to what have been called 'adaptive' trial designs. The main features of such designs have been reviewed by Chang and Chow.[85] ACCENT I,[2,3] CHARM[67] and CLASSIC II[66] trials had adaptive trial design of the type described as 'drop-the-loser' with in some cases 'adaptive treatment switching'.[85] An inherent problem of 'drop-the-loser' design is that groups that are dropped may contain valuable information regarding the response to treatment under study. A further problem concerns how such studies should be powered; whether for the interim analysis at the point when 'losers' are dropped, or for the final analysis involving winners only. With treatment switching come problems of identifying the target population for the therapy of interest and a precise definition of the therapy provided. Treatment switching can lead to a change to a different hypothesis being tested. Chang and Chow state 'From a statistical point of view adaptations to trial and or statistical procedures could (i) introduce bias/variation to data collection, (ii) result in a shift in location and scale of the target population, (iii) lead to inconsistency between the hypothesis being tested and the corresponding statistical tests'.[85] In summary, these trials are susceptible to difficulties of analysis and interpretation.

Maintenance trials in adult populations wholly or predominantly of non-fistulising patients

For each drug, one large maintenance trial has been published that employed within-licence treatment regimens: the CHARM[67] trial (adalimumab) and the ACCENT I[2,3] trial (infliximab). The interpretation of results from the maintenance trials was hampered by the nature of the trial designs, most of which allowed for scheduled crossovers into other treatment arms (or to 'open-label treatment'). This led to a proportion of patients in the placebo arms of the trials receiving variable amounts of drug. In order to comply with an ITT analysis, these patients (and those who withdrew) were mainly counted as treatment failures for binary outcomes such as remission or response. Not all trials clearly defined the handling of missing data or data for patients who crossed over. Where there were missing continuous data, the last observation carried forward was used in ACCENT I[2,3] but not in CHARM,[67] the effect of which on results is unclear.

There were particular concerns over the ACCENT I trial (Rutgeerts *et al.*[2] publication), as its stated aim of comparing episodic with scheduled treatment is misleading as no patients were randomised to an episodic treatment arm. Proper comparison of two strategies has been implemented by Breban *et al.*[86] who randomised patients with ankylosing spondylitis to induction with infliximab followed by continuous treatment or followed by treatment adapted to symptom recurrence. Similarly, Menter *et al.*[70] conducted an unbiased comparison of continuous and intermittent infliximab strategies for psoriasis by re-randomising at the start of the compared strategies (week 14) patients who had initially been randomised (week 0) to different infliximab

induction regimens. There were also uncertainties regarding the impact of methods for handling of missing data in the analysis including both responders and non-responders.

Responder/non-responder subgroups

The interpretation of the maintenance trials was further complicated by the fact that a subgroup of patients (responders) were selected for analysis or randomisation at varying time points after an induction period during which all patients received the study drug. For both of the large maintenance trials of within-licence treatment regimens (CHARM[67] – adalimumab; ACCENT I[2,3] – infliximab) the published effectiveness results all focused on the 'responders' subgroup. Separate results for non-responders were not reported (see *Table 40*), although both CHARM[67] and ACCENT I[2,3] randomised both responder and non-responder patients. The definition of responders differed somewhat between the two trials. Furthermore, the induction phases used in both trials differed with respect to duration and number of induction doses administered. The consequence of these considerations is that attempting any comparisons of effectiveness between the trials is very problematic. The proportion of patients categorised as responders in each of these trials was 64% for CHARM[67] and 58% for ACCENT I.[2,3]

It is known from trials where results were also reported for (randomised) non-responders that initial non-responders can still respond later, so it is unclear which patients this subgroup of responders actually represents in clinical practice. It is possible that a subgroup of responders chosen at a different time point would have led to different results. There is no published evidence or information in the manufacturers' submissions to show that compared with non-responders, responders benefit more from the treatment (compared with placebo). The selection of responders at different time points in different trials also hampers any comparisons between the trials.

Reporting effectiveness results for a subgroup but not for all randomised patients (or not for all patients who commenced treatment) appears at odds with usual practice. For example, in placebo-controlled randomised trials of anti-TNF agents (infliximab, adalimumab and etanercept) for the treatment of rheumatoid arthritis, results for all patients have been analysed and presented.[87] Dichotomising patients into responders and non-responders makes clinical sense only if a 'response' at the time of the dichotomisation is a good prognostic tool for identifying those patients most likely to benefit from maintenance of treatment. In order to find this out, the comparison of results for responders and non-responders is required, which, unfortunately, is the precise analysis that was not undertaken in these trials. Thus there is no evidence available to indicate that subgrouping patients in the ways described is a useful practice. The usefulness of the results reported for responders only is therefore questionable.

The ACCENT I[2,3] trial dichotomised patients according to their response at 2 weeks after the induction infusion of infliximab. The decision to do this may have been derived from previous research. The 1997 induction study of Targan *et al.*[57] provided data up to 4 weeks after a single infusion of infliximab at 5 mg/kg. This study reported that the mean CDAI score in the placebo group remained constant from weeks 2 to 4, while the risk differences (infliximab vs placebo) for remission (score < 150 points) and for a 70-point reduction in CDAI score increased from 0.37 to 0.44 and from 0.62 to 0.65 respectively. Placebo rates for these outcomes remained constant from weeks 2 to 4. Although the study was small and the point estimates were associated with considerable uncertainty, these results imply that some patients not responding at 2 weeks do in fact go on to respond at a later time. In ACCENT I[2,3] (CiC information has been removed).

In the absence of appropriate analyses it appears that dichotomising patients as early as 2 weeks after a single infliximab infusion is probably premature and does not appear to be a clinically meaningful procedure.

In the CHARM trial[67] the time chosen for categorisation into responders and non-responders (at week 4) was not based on efficacy data but was 'based on pharmacokinetic model estimates for when maximal drug concentrations should be present'. CiC results were available for non-responder patients at weeks 12, 26 and 56, so that it was possible to calculate the response rates among all randomised patients. The risk difference and risk ratio results for remission, response 100 and response 70 are summarised in *Figures 31* and *32* respectively. (CiC information has been removed.)

FIGURE 31 (CiC information has been removed.)

FIGURE 32 (CiC information has been removed.)

The two large maintenance trials (CHARM[67] and ACCENT I[2,3]) provided evidence that for the subgroups of patients defined as 'responders', anti-TNF therapy was more beneficial than placebo with respect to the proportions of patients exhibiting remission or response (70 or 100). Rates at multiple follow-up times extending to week 56 for CHARM[67] (remission rates) were reported in the published paper. For the ACCENT I[2,3] trial, results for weeks 30 and 54 (response 70 and remission) only were published, but CiC information for multiple time points was provided. The higher rates of response for intervention versus placebo might lead to the conclusion that extended therapy over the prolonged follow-up is beneficial and/or necessary for maintenance of response. However, examination of all the available information indicates that nearly all benefit observed for intervention over placebo was generated early on and that risk differences thereafter remained relatively stable or decreased. These results imply that prolonged treatment after the initial benefit has been attained is uneconomical and, as anti-TNF agents are associated with significant health risks, may be clinically ill-advised. The dose regimens required to attain this early benefit are likely to be different for adalimumab and infliximab.

The published results for the CHARM[67] trial graph '% patients maintaining remission' (Figure 2B in CHARM[67] publication) versus follow-up time depicted increased rates of remission following after decreased remission rates, demonstrating that patients who achieved remission at late follow-up times are counted as 'maintaining remission' and that in fact, the point prevalence of remission is represented in the graph rather than maintenance of individual patients in remission. If this is the case, a late time point (e.g. 30 or 54 weeks) value reported does not necessarily inform about maintenance of response during follow-up as it is possible that those registered as 'in response' may only have achieved this status just prior to the time point reported. It was unclear, but appeared possible, that point prevalence of response was the statistic reported in the ACCENT I[2,3] published reports; however, (CiC information has been removed).

The most appropriate way to determine the ability of anti-TNF agents to maintain response in patients who were defined as responders is time-to-event analysis with statistical comparison using a log rank test. For ACCENT I,[2,3] median time to treatment failure was 19 weeks and 38 weeks for placebo and 5 mg/kg infliximab groups respectively ($p = 0.002$); however, the definition of treatment failure used in this analysis was complex, did not correspond to a loss of response 70 status, and its clinical impact was difficult to gauge. The CHARM[67] trial (adalimumab) reported median duration of remission for those responders who achieved remission starting at any time during follow-up. The median times were 127 days for the placebo group, 378 days for the 40 mg/kg adalimumab e.o.w. group and > 392 days for the 40 mg/kg weekly dosage regimen group.

Trials recruiting patients with draining fistula

One induction trial provided evidence that infliximab promotes fistula closure to a greater extent than placebo. The ACCENT II[65] trial of infliximab maintenance treatment (IMT) focused on responders (69% of patients receiving induction doses). IMT promoted closure of fistulas to a statistically significantly greater extent than did placebo. There was evidence that a reduction of dose frequency from every 4 weeks to every 8 weeks was associated with poorer maintenance of fistula closure. Limited evidence from the CHARM[67] trial suggested that adalimumab may also promote fistula closure.

It is possible that fistula closure may not necessarily be a desirable outcome as it may result in increased development of abscesses. A post hoc analysis of patients participating in the ACCENT II[65] trial found no significant difference in abscess incidence between two groups receiving different mean dosages of infliximab. Interpretation of these results is problematic because results for the most appropriate comparison (placebo vs infliximab) were not available.

Trials recruiting paediatric patients

Two trials of infliximab, one induction and the other maintenance, reported on the treatment of paediatric patients. Unfortunately, in these trials all patients received infliximab, and no reliable inferences regarding the effectiveness of the intervention were possible because the spontaneous response rates in the population were unknown. The more frequent of the two dosage regimens used in the REACH[45] trial (5 mg/kg every 8 or 12 weeks) resulted in statistically significant greater rates of response and remission, a dose response relationship that likely implies beneficial effect of infliximab relative to placebo or standard treatment, but a placebo-controlled trial would have provided far stronger evidence of effectiveness.

Differences in effectiveness of anti-TNF agents; indirect comparisons

No head-to-head trials were found that compared the effectiveness of adalimumab and infliximab. However, the existence of placebo-controlled induction and maintenance trials for both drugs means that adjusted indirect comparisons of effectiveness were theoretically feasible using methods described by Glenny *et al.*[74]

The indirect comparison of trials was hampered in this case by a number of factors. One of these was differing placebo rates found for induction trials and unknown or uncertain placebo rates in maintenance trials (because all patients receive active intervention early in the trial). Patients with CD can experience spontaneous clinical improvement without treatment. Su *et al.*[84] conducted a meta-analysis of CD trials looking at placebo rates for remission and response (based on the CDAI). The authors found substantial heterogeneity between placebo rates and found that these were in the main attributable to follow-up duration, number of follow-up visits and CDAI score at entry to the trial (see *Appendix 13*). Because of the variation in placebo rates in the induction trials, indirect comparison was not made.

Indirect comparison of effectiveness using maintenance trials was judged unlikely to deliver valid results. For responders, the placebo arms of compared trials were not truly comparable because the groups had received different anti-TNF induction drugs on differing numbers of occasions and for different periods of time; furthermore, the 'responder' groups consisted of different proportions of the randomised populations according to differing criteria. For all patients' results again placebo groups were not truly similar between trials and, additionally, availability of results for all patients in the adalimumab trials was limited (see *Appendix 11*); furthermore, the permitted crossover of variable proportions of placebo group patients to active intervention at weeks 12 and 14 of the CHARM[67] and ACCENT I[2,3] trials would render analyses unreliable.

Adverse events

The large number of crossovers in the trials made the comparison of AE rates between treatment and placebo arms difficult, as many patients in the placebo arms will have received some study drug. In addition, the maintenance trials either gave an induction bolus of the drug at the start of the trial then randomised to treatment or placebo, or enrolled patients from a previous induction trial. Similarly, it is difficult to tell what the true rates for the development of antibodies are for each of the drugs, again due to crossovers and induction doses. It was not within the remit of this project to examine the test accuracy of antibody determination used in the trials. Increased risk of malignancies and of infection is evidenced from published information about anti-TNF agents used in all their indications. Vigilance with respect to tuberculosis and patients with potential or suspected heart failure should be mandatory.

Summary of effectiveness results

There were no included RCTs with severe CD patients only. They all included moderate-to-severe CD.

1. The general pattern of results is similar for the two drugs.
2. There is a good initial, clinically significant, improvement for the majority of patients when given induction treatment with infliximab or adalimumab. The short duration induction trials demonstrated that the majority of CD patients with moderate-to-severe disease gained clinical benefit from a single i.v. infusion of infliximab (5 or 10 mg/kg) or two subcutaneous injections of adalimumab (80 mg and 40 mg or 160 mg and 80 mg) separated by 2 weeks. Published estimates for the proportion benefiting depended on the measure of clinical response employed and were associated with considerable uncertainty (e.g. 95% lower CI to upper CI ranged from 13% to 66% and 16% to 47% for remission at week 4 from infliximab and adalimumab respectively depending on dose and trial). Obtaining a valid estimate of effectiveness for the two drugs and for their relative efficacy was plagued with difficulties contingent on the small number of trials, their small size, differences between the populations examined, and uncertainties concerning the most appropriate induction regimen to be used and the imprecision of trial results.
3. Although there exists a core of responders of indeterminate size who maintain an anti-TNF dependent response, in general the initial good response is not well maintained with extended treatment. This is evidenced in three ways:
    i. The percentage of patients in response (or with remission) fades away after the first weeks or so of maintenance therapy.
    ii. Large numbers of patients drop out of treatment. In ACCENT I,[2,3] 34% of patients dropped out, some before dose escalation, some after; in the active treatment arms, 25% withdrew in ACCENT I[2,3] and (CiC information has been removed)% in CHARM.[67] Among responders in CHARM,[67] about (CiC information has been removed)% withdrew from active treatment.
    iii. Large numbers of patients required dose escalation and/or transfer to open label (CHARM[67]) because of worsening disease. In ACCENT I,[2,3] 68% in the 5 mg/kg arm required dose escalation, as did 49% of those in the higher dose arm. In CHARM[67] about 30% in the adalimumab arms crossed over to escalated dose or open-label therapy.

These results indicate that during extended treatment an appreciable proportion of patients decide there is an unsatisfactory balance between the actual benefit of anti-TNF and its perceived benefits. The withdrawal rates in these trials are not similar to other monoclonal antibody interventions and contrast with the > 90% compliance over 52 weeks observed for i.v. weekly infused eculizumab.[88] The high requirement for dose escalation reflects efforts to resuscitate a fading response; the continuing dropout rate after escalation shows that these efforts meet with limited success.

Conclusions

Evidence from at least one induction and one maintenance trial for each drug administered within the licensed dose regimen demonstrates that for selected patients, relative to SC, these anti-TNF agents (infliximab and adalimumab) deliver statistically significant benefits of disease remission and improvement based on CDAI binary measures. Remission, response 70 and response 100 rates measured in maintenance trials indicate that for 'responders' nearly all benefit is achieved in about the first 12 weeks of treatment. Thereafter risk differences (anti-TNF minus placebo) remain relatively stable. These results imply that a short burst of treatment is likely to be more clinically effective and cost-effective than prolonged treatment and that after about 12 weeks the likelihood the intervention will be clinically effective and cost-effective will steadily diminish as treatment is extended unless other favourable outcomes additional to those based on CDAI measures are delivered later than 10–12 weeks.

The recruitment of patients who may not have failed alternative treatments together with the selective reporting of outcomes for early responders in the maintenance trials means it is difficult to gauge the effectiveness of these drugs in maintaining favourable outcome among the whole patient population with moderate-to-severe CD who are resistant to other treatments. Because of inappropriate study designs, heterogeneity of patients, incomplete and/or selective reporting of outcomes and lack of head-to-head trials, no convincing objective evidence was available to indicate whether one drug was superior to another either in respect to effectiveness or to safety.

Chapter 4

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

Introduction

This chapter explores the published cost-effectiveness literature on the costs and benefits of TNF-α inhibitors. Within the UK, the licensed anti-TNF treatments are adalimumab and infliximab. The following section goes on to describe the results of a systematic literature review of these treatments for CD.

When assessing the economic impact of CD, costs can be divided into direct costs and indirect costs. Direct costs refer to the costs of an intervention itself and include the value of all resources consumed in the provision of an intervention, including all side effects occurring as a result of treatment, and all future health-care expenditures contingent on either the intervention or side effects. Direct costs include all goods, services and other resources used, both within and outside of the health-care sector. Health-care costs include all medication, diagnostic tests, supplies, staff and medical facility costs. Costs outside health care can include the costs to the patients and to other public agencies. Indirect costs include those resources consumed that are not directly paid for by any party. As the ability of patients to work is related to general health and the time spent in treatment, indirect costs include productivity gains and losses. Indirect costs also include the productivity costs of unpaid carers including family members.

In CD, the perspective taken may have a significant impact on the costs associated with the disease and the overall conclusions drawn from the evidence. Several perspectives can be adopted and the NICE reference case recommends concentrating only on the direct health-care and public social service (PSS) costs. A researcher may also wish to consider a societal perspective that includes direct and indirect costs to all parties as a sensitivity analysis in an economic evaluation.

Methods for reviewing cost-effectiveness

Search strategy

A comprehensive literature search on the cost and cost-effectiveness of adalimumab, infliximab, certolizumab pegol and natalizumab for the treatment of CD from a UK perspective was conducted. Natalizumab and certolizumab pegol were originally part of this technology appraisal so were included in the searches; they were subsequently dropped from the appraisal after completion of searches.

Studies on costs, QoL, cost-effectiveness and modelling were identified from the following sources:

- bibliographic databases: MEDLINE (Ovid) 2000 to May/June 2007, EMBASE (Ovid) 2000 to May/June 2007, Cochrane Library [NHS Economic Evaluation Database and DARE (Database of Abstracts of Reviews of Effects)] 2007 Issue 2, and HEED (Health Economic Evaluations Database) (June 2007)
- industry submissions
- internet sites of national economic units.

Searches were not limited by language. Full search strategies can be found in *Appendix 14*.

In addition, searches for cohort studies of infliximab for CD and also clinical guidelines for CD were undertaken for background information for the decision analytic model. Full details can be found in *Appendix 14*.

Inclusion and exclusion criteria

Only studies meeting the following criteria were included:

- *Study design:* fully published economic evaluations only (abstracts without full publication were excluded).
- *Population:* patients with CD (adults or children).
- *Intervention:* adalimumab or infliximab (any dosage/treatment regimen).
- *Comparator:* conventional treatment without TNF-α inhibitors including no treatment, placebo, dietary intervention, drug treatment with aminosalicylates, methotrexate, corticosteroids (prednisolone, budesonide and hydrocortisone), azathioprine, metronidazole or surgical intervention.
- *Outcomes:* cost–utility, cost-effectiveness.

Inclusion, quality assessment and data extraction strategies

Two reviewers independently reviewed studies for inclusion using title and abstract. Disagreements were resolved by discussion. After this initial sift, full papers were obtained and assessed for inclusion. All studies were quality assessed using a standard checklist (Drummond and Jefferson[89]) by two independent reviewers. If a substantial part of the economic evaluation was missing because of the material being commercially in confidence, formal quality assessment methods were not used. Data extraction of included studies was performed by one reviewer, extracted data was then checked by a second reviewer.

Results of systematic review of existing cost-effectiveness studies

Inclusion and exclusion of studies

Using the search strategy and previous knowledge of the literature, an initial 814 papers were identified. Initial sifting identified 64 articles for further investigation. These articles identified seven further papers that could have provided relevant information for economic modelling but were not included in the systematic review as they were not cost-effectiveness studies.

Quantity and quality of included studies

Only four full papers met the review criteria and were subsequently reviewed. These were Arseneau *et al.*[90] from the USA, Jaisson-Hot *et al.*[7] from France, Marshall *et al.*[6] from Canada and Clarke *et al.*[5] from the UK. A further two papers were available in abstract form only. Given the difficulty of extracting reliable information from this format, these were not formally reviewed. Several excluded papers provided either the costs or benefits of treatment but not both.

None of the four papers declared any conflicts of interest. Two of the four papers were peer-reviewed published works by independent researchers,[7,90] one was commissioned by the Canadian Collaborating Centre for Health Technology Assessment (CCHTA),[6] and one was a Health Technology Assessment (HTA) report from the UK[5] commissioned by NICE. Given the restrictions on CiC information in HTA reports, the UK HTA was not quality assessed using the checklist.

Of the three quality-assessed studies, the CCHTA report[6] scored highly in comparison to the remaining two papers, and was both clearly written and transparent. These remaining two

papers[7,90] omitted several key features (including an incremental analysis of all comparators), and resource usage was outlined in cost terms only.

Characteristics of economic studies

All four studies conducted cost–utility analyses of infliximab and were reported in a total of five papers.[5–7,90,91] The HTA study[5] considered non-fistulising and fistulising disease, Marshall *et al.*[6] and Jaisson-Hot *et al.*[7] considered non-fistulising disease only, and Arseneau *et al.*[90] considered fistulising disease only. No published economic studies were found for adalimumab in CD.

Within economic analyses of infliximab in CD, a lack of relevant observational data has led to the widespread use of information from a relevant study conducted in Olmstead County, and in particular the model constructed in Silverstein *et al.*[26] Using 24 years of data, Silverstein *et al.*[26] constructed a Markov model of the course of CD to calculate the excess lifetime costs of the disease. The model considered seven states (remission, mild disease, drug-responsive severe disease, drug-dependent severe disease, drug-refractory severe disease, surgery and postsurgical remission) plus death. This model was not an economic evaluation, but has been highly influential in the modelling carried out in non-fistulising CD.

Gregor *et al.*[92] elicited HRQoL values from 180 consecutive Canadian CD patients. This evaluation provided both standard gamble and time trade-off data for hypothetical chronically active CD, acute disease and remitted states, and also by the patient's own health and CDAI status. This information was also used in a number of the economic models reviewed here.

Non-fistulising disease

Within the published models, the comparator treatment strategies comprised surgery and medical treatment,[7] placebo[5] or usual care[6] in populations that were resistant/non-responsive to standard therapy. Only one model was UK-based,[5] with the others based in France[7] and Canada.[6] The French model[7] was lifetime-based, with the Canadian model[6] taking a 1-year time frame. The time frame in the UK model[5] was unclear, with the treatment considered up to three retreatments within a single year, but stated that the time frame of treatment was '1 or more years'.

The French,[7] Canadian[6] and UK[5] models used the Olmstead County data when estimating transition probabilities. The French[7] and Canadian[6] models used this data to model states where infliximab was not used (in the French case, following surgery, and in the Canadian model, from baseline). In the modified industry model in the UK HTA report,[5] these Olmstead data were used to define post-remission health states for the infliximab arm. Clark *et al.*[5] noted that the use of this information was likely to lead to bias if used to populate a Markov model that moved CD patients responding to treatment into a remitted state. They noted that the prognosis of those in a remitted state following disease flare and infliximab treatment was likely to differ from those who had not experienced a disease flare in the observational cohort.

Both the French[7] and Canadian[6] models used a third-party payer perspective and, while not described, the UK HTA report[5] likely used an NHS/PSS perspective in line with the NICE reference case.[93]

Fistulising disease

In fistulising disease, the comparator treatment strategies comprised placebo (Clark *et al.*[5]) or the combination of 6-mercaptopurine/metronidazole (6MP/met) and/or infliximab in different regimens (Arseneau *et al.*[90]). Both studies (one UK, Clark *et al.*;[5] one US, Arseneau *et al.*[90]) used a 1-year time frame. The US model used a third-party payer perspective but the UK model was unclear on this point but again probably took an NHS/PSS perspective. A lack of existing clinical data beyond 18 weeks required Arseneau *et al.*[90] to make strong assumptions about both the

effectiveness of infliximab as second-line and reinfusion therapies, and the longer term chances of fistula recurrence.

The four models considered the cost-effectiveness of infliximab treatment for 70-kg adult CD patients (Clark *et al.*[5] fistulising and non-fistulising, Arseneau *et al.*[90] and Marshall *et al.*[6]). In the remaining study the assumed weight of the Markov cohort was unclear.[7]

Calculation of cost data

With the exception of Marshall *et al.*[6] (non-fistulising Canadian model) and Arseneau *et al.*[90] (fistulising US model), the assessed models reported costs and resource usage poorly. None of the remaining models reported resource use separately from costs, and in many cases the costs of individual items was not given. In the UK HTA model,[5] the source of the cost data was not given. Expert opinion was used to estimate resource use items in two models (Jaisson-Hot *et al.*[7] and Marshall *et al.*[6]).

As the models were typically of 1 year's duration, there was no discounting. In the single French analysis[7] of a longer duration (lifetime), a discount rate of 5% was used. (While the US analysis[90] is only 1-year in duration, it claimed to use a discount rate of 3%. It was not clear how this discounting was calculated.)

Health outcomes and data sources

Effectiveness in non-fistulising disease

In the UK model,[5] many of the clinical data were removed for confidentiality reasons. Effectiveness in the model was based on two scenarios where the effectiveness of infliximab was either aggregated across doses (Scenario 1) or based on the 5 mg/kg dose (Scenario 2). Scenario 1 gave lower effectiveness estimates and was used in the company submission. Values for both scenarios were given in summary tables. The French model[7] calculated effectiveness data from published evidence (Targan *et al.*[57]) and expert opinion, but details were unclear. The Canadian model[6] used effectiveness data from the Targan *et al.*[57] and Rutgeerts *et al.*[58] trials.

Effectiveness in fistulising disease

The US model by Arseneau *et al.*[90] converted pooled data from 12 studies to calculate transition probabilities. The model assessed benefits through fistula improvement rather than closure, so that the improved state included both complete closure and symptomatic improvement. While acknowledging that clinically relevant end points were a subject of debate, the authors acknowledge that this choice of definition was likely to increase the effectiveness of treatment and may have biased estimates.

The UK HTA model[5] used data from the Present *et al.*[62] study for fistulising disease, but no details of precise estimates were given.

Utility estimates

Utility estimates were based on the study by Gregor *et al.*[92] in the three non-fistulising models. As the Gregor *et al.* estimates did not include fistulising states, separate estimates were used in the models for fistulising disease. The US fistulising model by Arseneau *et al.*[90] used standard gamble utilities from 32 CD patients and 20 healthy volunteers, while Clark's (UK) modified industry model[5] used an unpublished algorithm based on CDAI and PDAI scores from the Gregor *et al.*[92] data.

Cost-effectiveness results

The comparison of cost-effectiveness results across studies is always problematical. For comparison purposes, the methods used were to transform cost estimates based on purchasing

power parities[94] (as appropriate) and reflate according to all-item UK retail price index figures[95] to provide estimates in 2006 pound sterling where possible. Where the base year for costs was not given, figures could not be reflated and the original stated values are used here.

Differences in comparators, methods, data and the non-disclosure or removal of pertinent information prevent reliable interpretation of the results of such comparisons. In these results, caution should be taken in the interpretation, as ICERs relate to the cost of increasingly more effective treatments while cost-effectiveness ratios may be compared with a common comparator. The former is preferred as it allows assessment of the marginal costs and effectiveness of treatment.

In only two[6,90] of the models were total costs and effectiveness data given for all the compared strategies. In only one[6] of the models was it possible to calculate ICERs. Back-calculation of figures was avoided as this may have introduced errors, while transforming provided figures is hazardous given that they are not displayed to sufficient precision.

In non-fistulising disease, the UK model[5] compared single and 'episodic' treatment with placebo. Against placebo, episodic treatment (defined as a single 5 mg/kg dose plus up to three 5 mg/kg retreatments within a single year) was estimated to have an ICER of £62,016 per quality-adjusted life-year (QALY) when using effectiveness data from the 5 mg/kg dose group (base year not given). Treatment with a single dose of infliximab (no episodic reinfusions) was found to be less cost-effective.

The French model[7] estimated the cost-effectiveness against usual care only. As neither total nor incremental QALY figures were given (and back-calculating is not reliable), incremental figures could not be calculated. Against usual care, 'episodic' treatment and maintenance treatments of infliximab were estimated to have cost-effectiveness ratios of €63,700 and €784,057 per QALY (base year not given) respectively.

The converted results from the Canadian model[6] suggested an ICER of £105,900 per QALY for single dose versus usual care, £280,600 per QALY for 'episodic' versus single-dose infliximab, and £407,000 per QALY for maintenance versus 'episodic' treatment with infliximab.

In fistulising disease, the UK model[5] suggested a cost-effectiveness ratio of £102,000 (base year unclear) for initial infliximab treatment versus placebo. In the US model[90] (converted to 2005 pounds sterling), only cost-effectiveness ratios could be calculated as the outcomes figures were not given with sufficient precision. Against the comparator treatment of 6MP/met, the interventions had cost-effectiveness ratios of £274,100 per QALY (infliximab, with 6MP/met as second-line treatment), £278,000 per QALY (infliximab, with infliximab reinfusions as second-line treatment) and £290,770 per QALY (6MP/met + episodic infliximab reinfusion).

Sensitivity analysis

The reporting of sensitivity analyses was variable, with probabilistic sensitivity analysis conducted in only the Canadian model.[6] This analysis suggested that usual care was favoured up to a threshold of approximately £105,000 per QALY, with a single dose of infliximab favoured between this figure and approximately £251,000 per QALY in non-fistulising disease (converted figures). While this study suggested that the rate of surgical admissions for drug-refractory treatment had little effect on cost-effectiveness, it was sensitive to the variations in the cost of infliximab. With a sufficiently large price reduction it suggested that infliximab treatment may have become cost-effective.

In the UK study[5] for non-fistulising disease, the one-way sensitivity analyses conducted on utility, duration of response and the rate of averted surgeries did not result in any ICER below £40,000 per QALY (base year not given).

In fistulising disease, the UK model[5] varied the rate of success in retreatment and reclosure of fistulas alongside the level of cost offset owing to averted surgeries. In no case did this produce a ratio below £80,000 per QALY. In the other fistulising model (USA),[90] all ICERs remained above £79,000 per QALY (converted figures) regardless of the changes made in one-way sensitivity analyses other than in the price of infliximab. Only where the price of infliximab was reduced to £160 per dose (a reduction of 90% from the modelled price) did the ICER for 'episodic' reinfusion fall marginally below £30,000 per QALY (converted figures).

Author conclusions

All of the studies considered were conducted by non-industry authors, with the Canadian[6] and UK[5] studies commissioned by national HTA bodies. The remaining studies[7,90] did not disclose any industry affiliation.

The results of all non-fistulising studies suggested that infliximab was not necessarily cost-effective over the usual range for thresholds. The study by Jaisson-Hot *et al.*[7] (France) suggested that 'episodic' infliximab treatment could possibly have been cost-effective, but that maintenance treatment may not have justified the increased costs required. The study by Clark *et al.*[5] (UK) suggested that the cost-effectiveness was relatively insensitive to changes in the key assumptions in their model but that the key criterion for the cost-effectiveness of 'episodic' treatment would have been the duration of benefit.

The study by Marshall *et al.*[6] (Canada) was limited by the use of non-Canadian data, the need to convert utility data to populate estimated states, the use of expert opinion to inform resource usage and the lack of longer term clinical data. They noted that while CD may severely impact morbidity and affect productivity, there was no detailed information available on productivity losses to make allowances for this. They justified the relatively short time frame in his model with the lack of clinical data to populate a longer term model.

In fistulising disease, Clark *et al.*[5](UK) stated that the cost-effectiveness ratios were high under even the most favourable assumptions for retreatment and closure in the industry model. The study by Arseneau *et al.*[90] (USA) suggested that the high cost-effectiveness ratio for infliximab was due to both the high incremental cost of infliximab and a similar effectiveness to 6MP/met treatment. They acknowledged the difficulties with the 'fistula improvement' state and noted that infliximab may have been more effective if it had promoted closure rather than merely symptomatic improvement. The availability of only 18-week data was also acknowledged as a difficulty.

Conclusions

There have been no published studies on the cost-effectiveness of adalimumab alone or in comparison to infliximab. Given the lack of comparison between both alternative treatments considered here, it was not possible to infer the relative cost-effectiveness of treatments from existing evidence. Also, while the indirect productivity costs of non-treatment may be appreciable in CD, these costs were not included in the cost-effectiveness studies owing to a lack of evidence as to their magnitude.

All four studies[5–7,90] reviewed were conducted by non-industry authors, with the Canadian[6] and UK[5] studies commissioned by national HTA bodies. The remaining studies[7,90] did not disclose any industry affiliation. Taken together, the papers suggested that single use or 'episodic'

treatment with infliximab has a relatively high cost-effectiveness ratio for both non-fistulising and fistulising disease. Maintenance therapy was considered only for non-fistulising disease and this is partly due to its potentially prophylactic role in this disease group. Both models considering maintenance infliximab therapy suggested that it would have a particularly high cost-effectiveness ratio relative to both SC and 'episodic' infliximab treatment.

Full details for included studies of study characteristics, models used, costs and resources, efficacy data, total costs and outcomes, sensitivity analyses and author conclusions can be found in *Appendix 15*.

Critique of the submission on infliximab by Schering-Plough

Model structure and inputs

The economic component of the Schering-Plough submission[96] took the form of three cost–utility analyses from the perspective of the health service provider. The model structures were informed by the structure of ACCENT I[2,3] and included the 'episodic' treatment over which concern has been previously expressed (see *Glossary*). The term 'infliximab clinical discretion' (ICD) has been used in place of 'infliximab episodic treatment' here.

The three models in the Schering-Plough submission were: a version considering cost-effectiveness of IMT compared with ICD and SC without infliximab among patients with severe active CD (CDAI scores 220–400) in England and Wales (MODEL A); a second version comparing IMT against SC in fistulising CD (MODEL B); and a third model considering paediatric CD patients (MODEL C).

Infliximab maintenance treatment consisted of 5 mg/kg infliximab at week 0, 5 mg/kg infliximab at weeks 2 and 6 and every 8 weeks thereafter. Those receiving ICD received an induction dose of 5 mg/kg infliximab at week 0 and thereafter 5 mg/kg infliximab *according to clinical discretion*. Those receiving SC received a placebo infusion at weeks 2 and 6 and every 8 weeks thereafter.

MODELS A–C were primarily based on data from two recent trials, ACCENT I[2,3] and ACCENT II.[65] Further trial data came from Targan *et al.*,[57] Present *et al.*[62] and REACH.[45] ACCENT I[2,3] was designed to compare a single 5 mg/kg infusion of infliximab followed by maintenance or a placebo for patients with CD. Participants were recruited from across North America, Europe and Israel. Participants must have had CD for > 3 months and a CDAI score of between 220 and 400. All participants were given 5 mg/kg infliximab at week 0. At week 2, whether participants were responders or not, they were randomly assigned to one of the following three groups:

- Group I: placebo infusion at weeks 2 and 6, and every 8 weeks thereafter to week 46 ($n = 188$).
- Group II: 5 mg/kg infliximab at weeks 2 and 6, and every 8 weeks thereafter to week 46 ($n = 192$).
- Group III: 5 mg/kg infliximab at weeks 2 and 6, followed by 10 mg/kg every 8 weeks thereafter to week 46 ($n = 193$).

Response was defined as a decrease in CDAI score of ≥ 70 points and a minimum 25% reduction in total CDAI score. After week 14, patients who initially responded but experienced exacerbation of symptoms could cross over to 5, 10 or 15 mg of infliximab on an 'as needed' or 'episodic' basis.

The ACCENT II[65] trial compared long-term treatment regimens for patients with fistulising CD. Participants all had CD with single or multiple draining fistulas and were recruited from across

North America, Europe and Israel. All participants were given 5-mg infliximab at weeks 0, 2 and 6. At week 14, all patients, regardless of whether they were responders, were randomly assigned to one of the following two groups:

- placebo infusion at weeks 14, 22, 30, 38 and 46, and follow-up at week 54 ($n = 99$)
- 5 mg infliximab at weeks 14, 22, 30, 38 and 46, and follow-up at week 54 ($n = 96$).

In this trial, response was defined as a reduction of at least 50% from baseline in the number of draining fistulas at consecutive visits 4 weeks apart. After week 22, patients in the placebo group who experienced a loss of response could crossover to IMT of 5 mg/kg infliximab.

MODEL A used a Markov model to simulate the progression of patients and to calculate the cost per QALY of the infliximab treatment over a 5-year period. For severe active CD, the model states were active, remission, death, non-responding active (patients who failed to respond either initially by week 2 or discontinued treatment in the second week due to loss of response), surgery, post-surgery remission and post-surgery complications. MODEL B (fistulising) replicated this but expanded the active state to: active + fistula closure, active + fistula, remission + fistula closure and remission + fistula. In the severe active model, patients stayed in the active state (on treatment) for the first 2 weeks before movement to other states. In contrast, patients stayed in the active state for the first 14 weeks within the fistulising model, as assessment of these patients in ACCENT II[65] occurred at this point. Transition probabilities for the active state were based on ACCENT II[65] and Present *et al.*[62] trial results. The transition probabilities for the 'on treatment' health states were estimated from the Targan *et al.*[57] and ACCENT I[2,3] studies; while the transition probabilities for the 'off treatment' health states were estimated from the literature. MODEL C (paediatric) mirrored those of the severe active model with transition probabilities based on data from the Targan *et al.*,[57] ACCENT I[2,3] and REACH[45] studies.

The probability of surgery and post-surgery states were obtained from a variety of sources (Marshall *et al.*,[6] Wolters *et al.*[97] and Jess *et al.*[98]). The authors assumed an equivalent surgery rate (64%) in all three models (severe active, fistulising and paediatric). Post-surgery complications were estimated from Marshall *et al.*,[6] which showed no significant differences between groups with and without infliximab prior to surgery, so a weighted average was used. Recurrence rates were based on those from Wolters *et al.*;[97] while the study contained data from nine European countries this did not include the UK, so expert opinion was sought to confirm the similarity of the estimates with the UK.

The methods for the estimation of quantities and unit costs were, in the main, comprehensively described. The cost of hospitalisation and assessments used data taken from Jewell[8] (a UK study). This retrospective observational study ($n = 205$) compared resource use 6 months pre- and 6 months post infliximab. The pre-infliximab figures were used for SC. Data on post-surgery health states (post-surgery remission and post-surgery complications) were not available so resource use was estimated by an expert panel (consisting of UK gastroenterologists) and the average estimates taken. The cost of immunomodulators was excluded from the analysis on the basis that the efficacy of the treatment would not have been affected (the authors did a post hoc analysis of ACCENT I[2,3] and II[65] trials that indicated that there was no significant difference in infliximab treatment effect with or without immunomodulators). AEs were assumed to be included in the infusion and hospitalisation costs. The cost of infliximab infusions was estimated using an average adult body weight of 60 kg, which the authors stated was based on previous guidance from NICE. A cost of administering infliximab of £96 was suggested by the authors but was incompletely referenced. The closest match found[99] suggests a cost of £257.50 per infusion, which was considerably higher than suggested by the manufacturer.

Health-state utilities were based on a number of different data sources. For severe active CD, health-state preferences for pre surgery were taken from a Spanish study [$n = 201$ CD patient responses to EuroQoL-5 Dimensions (EQ-5D) and converted into utilities using UK tariffs].[100,101] Surgery and post-surgery preferences were based on data from a secondary care database of patients in Cardiff and The Vale of Glamorgan, Wales.[34] No information was available for complications post surgery, and a utility value of 0.4 was assigned. The authors justified the value given in terms of complications that would lead to significant hospitalisation.

The transitional probabilities were subject to sensitivity analyses with the exception of post-surgery health states because no treatment effect was assumed beyond surgery. One-way sensitivity analyses was conducted on patient weight, time horizon, discount rate, baseline age and infliximab administration cost, and the resultant cost per QALY was reported.

Model results

The results of the analysis are shown in *Table 44*.

The results in MODEL A were analysed using both a probabilistic sensitivity analysis (which contained flaws) and a univariate sensitivity analysis [patient weight 70 kg (vial sharing) or 80 kg; time horizon at 2 years or at lifetime; discount rate changes; baseline ages of 30 and 60 years vs 45 years; increased administration costs]. In MODEL A the dominance of ICD over SC remained in all univariate analyses except patient weight 80 kg where it remained highly cost-effective. While the industry submission concluded that maintenance was cost-effective against SC, the relevant comparison where ICD is feasible is between maintenance and ICD. Here, the ICER for maintenance treatment over ICD remains above £400,000 in all analyses.

Critique of the industry submissions for infliximab

The design of the cost–utility analysis is in line with what would be expected for this type of submission but the results are limited by a number of factors. While the comparators appear to be justified, the analysis comparing both SC and infliximab maintenance to ICD care is hampered by the definition of 'episodic care' used for the ICD comparison. Although episodic care was described as treatment 'as required', no further details were given.

TABLE 44 Cost-effectiveness of infliximab (Schering-Plough submission)

Time	Treatment	Mean costs (£)	Difference (£)	Mean QALYs	Difference	ICERs (£ per QALY)
Severe active CD						
5 years	IMT	31,040	4831	2.145	0.186	25,903
	SC	26,209		1.959		
5 years	ICD	25,501	–708	2.133	0.174	ICD dominates
	SC	26,209		1.959		
5 years	IMT	31,040	5539	2.145	0.011	457,386
	ICD	25,501		2.133		
Fistulising						
5 years	IMT	36,626	6049	2.449	0.202	30,005
	SC	30,577		2.247		
Paediatric						
5 years	IMT	33,504	5833	2.566	0.420	13,891
	SC	27,672		2.146		

The analysis relied heavily, but not exclusively, on the ACCENT I[2,3] and II[65] trials. The information used in the economic analysis did not compare treatments consistently across those who were potential responders and non-responders to anti-TNF treatment. This is likely to overestimate the effectiveness of IMT in the industry submission. In addition, the costs of those who did *not* respond do not appear to have been included, giving lower estimated costs. Both scenarios produce a lower cost per QALY.

In line with the other industry submissions, the primary comparison is with SC. The rationale for this comparator is that the majority of patients eligible for biological treatments in England and Wales still receive SC. While the authors cite market research as evidence of this, unfortunately the information cited is not in the public domain. Also, the ACCENT I[2,3] and II[65] trials were conducted outside the UK, so it is not possible to determine how 'standard care' in the trials compares to that in the UK.

Throughout the submission, a CDAI score of 220–400 was used to indicate severe active CD. While there is no formal quantification of the level at which moderate CD becomes severe active, 220 is lower than has been used in a number of other studies, which makes comparison difficult.

Evaluating MODEL A: active CD (220 < CDAI < 400)

Clinical effectiveness of the comparators in the economic model

The economic model compared maintenance (IMT), ICD and SC. As the details of ICD treatment are unclear, it is not possible to satisfactorily verify or interpret the model. In particular, the description of ICD treatment neither guarantees episodic care nor precludes the use of maintenance treatment. Thus, it both is extremely broad in definition and does not guarantee that clinically identical individuals would receive the same treatment. ICD is limited in the degree to which it represents an identifiable treatment strategy.

Much of the model was based on the ACCENT I[2,3] trial. This trial distinguished between those who did and did not respond by week 2 on both the placebo maintenance and infliximab maintenance arms (of which the economic analysis considers only the 5 mg/kg dosage). The placebo arm in the ACCENT I[2,3] trial included treatment with (1a) placebo maintenance treatment and (1b) ICD at 5 mg/kg for those not responding to 1a. The infliximab arm in the ACCENT I[2,3] trial included treatment with (2a) maintenance at 5 mg/kg and (2b) ICD at 10 mg/kg treatment for those not responding to (2a).

Hanauer *et al.*[3] compared the outcomes for week 2 responders (1a) with treatment (2a), with those crossing to (1b) and (2b) considered to be treatment failures. Rutgeerts *et al.*[2] attempted to compare outcomes for both week 2 responders and non-responders in their initial and crossover treatment, attempting to compare (1a) plus (1b) with (2a) plus (2b). The economic model attempted to compare (1a) plus (1b) (as ICD) against only (2a) (as infliximab maintenance).

Confidential clinical information in the industry submission suggested that, however constituted, ICD provides very similar clinical outcomes to maintenance therapy. The clinical study report included data on how many patients retained a response to treatment at week 30. Among week 2 responders, 51% of those receiving IMT retained a response, as against (CiC information has been removed) of those receiving SC (placebo) at week 30 (week 54 clinical study report). The ICD arm is based on those failing on placebo treatment receiving infliximab at 5 mg/kg. All those receiving infliximab on ICD would have been considered failures and on this basis, it would have been expected that ICD would have the same effectiveness in retaining a response as placebo treatment.

A clearer comparison is available using the week 30 clinical study report that includes data for week 2 responders and non-responders, those who crossed over, and those who received protocol-prohibited medication changes or surgery. At 30 weeks, (CiC information has been removed) of patients receiving ICD maintained a clinical response to treatment. As it would be expected that non-responders would have poorer outcomes than responders, these results may have underestimated the effectiveness of ICD for week 2 responders. Given this, it would not be surprising for ICD to match maintenance therapy in health outcomes achieved, and any advantage for maintenance over ICD is likely to be very minor. As maintenance therapy patients received infliximab regularly, whereas ICD patients received infliximab according to clinician discretion (at the same dosage), ICD would be less expensive than maintenance. It appears that IMT is very unlikely to be cost-effective against ICD.

Use of trial data in MODEL A

Although the treatment scenarios were well presented, there were some limitations which were primarily associated with the sample characteristics of the studies used. The active CD treatment strategies estimated were based on ACCENT I[2,3] data together with data from another smaller study – Targan *et al.*.[57] The Targan *et al.*[57] study was used for transitions between week 0 and week 2, with transitions following week 2 estimated using ACCENT I.[2,3] The use of Targan *et al.*[57] data is questionable as they come from a smaller trial preferred in place of a larger trial which provided less positive results (ACCENT I[2,3]).

The economic model also appeared to use two different populations in active CD, with both the SC (placebo) and ICD arms using week 2 responders and non-responders and the maintenance arm using week 2 responders only. If week 2 responders do indeed have a better response than week 2 non-responders, then this is likely to bias the comparisons in the economic model. Given the data above, this bias may account for any positive effect found for infliximab maintenance against ICD.

Assessment group revisions to MODEL A

The cost of drug infusions was estimated using an average adult body weight of 60 kg, which the authors state was based on previous guidance from NICE.[1] This is likely to have underestimated the cost per QALY. The Targan *et al.*[57] trial recorded mean body weights of between 68 and 74 kg (for different treatment groups), while for ACCENT I[2,3] these are recorded only in the (confidential) clinical study reports (CiC information has been removed). ACCENT I aside, there were four larger trials (Targan *et al.*,[57] CLASSIC I,[63] GAIN[64] and CHARM[67]) in the clinical effectiveness section in adults (where $n > 100$) that gave mean weight of included patients – approximately 71.5 kg.

A weight of 60 kg exactly corresponds to the use of three 100-ml vials of infliximab, and the model therefore assumed no wastage. A revised model was constructed by the assessment group. In this model a weight of 70 kg was used, which remains conservative given that no wastage is incorporated into the model. The price of infliximab within the model was also increased to reflect the cost as published in the *British National Formulary* (£419.73).[102] In the revised model, administration costs were taken to be half of a day case – H26 (Day Case Rheumatology) – in line with a 2006 HTA report,[99] which was £293.67 when adjusted to 2006 prices using the Personal Social Services Research Unit (PSSRU) NHS Pay and Prices Index.[103] The cost-effectiveness of ICD, IMT and SC was calculated using a probabilistic sensitivity analysis (1000 iterations) with cost-effectiveness acceptability curves (CEACs) calculated (*Figure 33*).

The conclusions of the MODEL A as revised by the evidence review group differ from those of the industry MODEL A, a result of these input changes and correction of errors in the industry sensitivity analysis. For threshold levels between £0 and £2466 per QALY, placebo had the highest

chance of being cost-effective. For threshold levels between £2466 and approximately £481,000 per QALY, ICD treatment had the highest chance of being cost-effective. Infliximab treatment according to clinical discretion appears to be cost-effective at thresholds of £20,000–30,000 per QALY, although this is contingent on a series of caveats, including the ill-defined nature of the 'episodic' intervention itself.

Evaluating MODEL B: fistulising CD

Use of trial data in MODEL B

For fistulising CD, the industry submission stated that evidence from the ACCENT I[2,3] trial suggested that maintenance infliximab therapy may bring significant QALY gains related to improved QoL (as opposed to improved life expectancy) in adults with fistulising CD. However, it is not possible to ascertain from the submission or from published papers of the trial whether the sample included adults with fistulising CD. The submission did however report evidence presented in the ACCENT II[65] trial (fistulising CD patients) that showed a significantly longer time to loss of response for infliximab maintenance than for placebo maintenance and significantly improved CDAI scores for the infliximab group versus the placebo group.

The fistulising CD strategies were based on responders only. The ACCENT II[65] trial showed that 69% of the sample were responders after the induction period. There was, however, no placebo comparison during this period so it is not possible to determine the proportion of patients who would have gone into remission without infliximab. While the proportion of responders was higher than the ACCENT I[2,3] trial, the definition of a responder differs and the time at which they were assessed as a responder/non-responder was much later (14 weeks rather than 2 weeks). This highlights the arbitrary nature of the time point chosen to identify responders and the impact it may have had on the results.

The treatment strategy was modelled on the Present *et al.*[62] trial (0–14 weeks) and the ACCENT II[65] trial (14–54 weeks). The Present *et al.*[62] trial, like the Targan *et al.*[57] trial, had relatively small numbers in each arm (31–32). The ACCENT II[65] scheduled maintenance arm excluded those who switched to 10-mg 'episodic' treatment after week 22. Again it is not clear how SC in the UK compares with that in the Present *et al.*[62] trial (recruitment was in the USA and Europe) and the ACCENT II[65] trial.

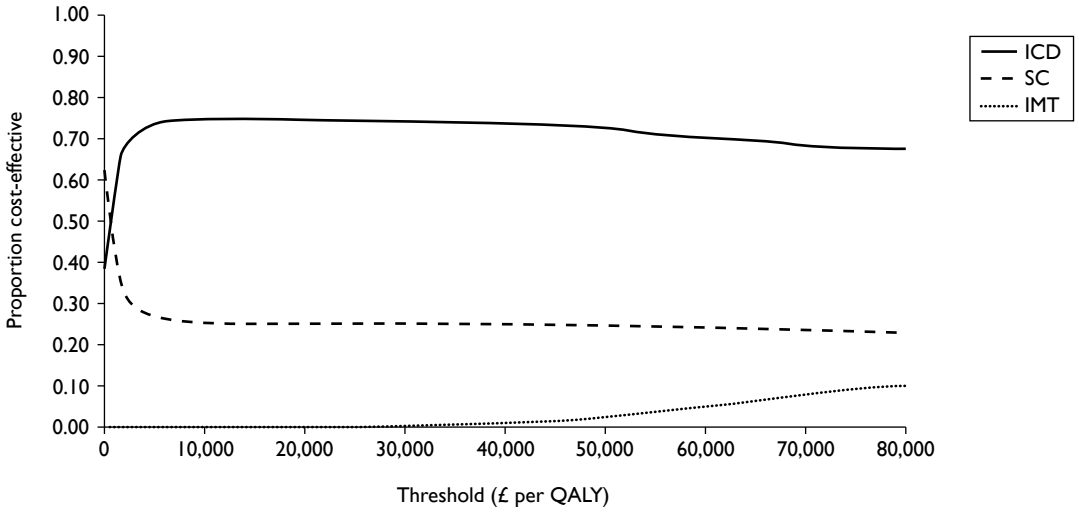

FIGURE 33 Cost-effectiveness acceptability curve for active CD.

Assessment group revisions to MODEL B

As with severe active CD, the cost of drug infusions was estimated using an average adult body weight of 60 kg which the authors state was based on previous guidance from NICE.[1] Questions remain about the suitability of this figure given that it is lower than the values found in clinical trials on which the analyses are based. As above, a figure of 70 kg was used for the average weight of patients, which changed both the cost of infliximab and administration costs to a more accurate figure.

The health-state utilities within MODEL B were based on two different sources:

- A Spanish study ($n = 201$ CD patients) measuring EQ-5D then converted into utilities using UK tariffs which assumed that the preferences measured are concordant with UK patient preferences.[100,101]
- A secondary care database of patients in Cardiff and The Vale of Glamorgan, Wales, measuring surgery and post-surgery preferences. This was based on a small sample size and looked at surgery (< 2 months after surgery, $n = 17$) and remission post surgery (i.e. > 2 months with no recurrence/complication $n = 21$).[34]

Despite specific utility estimates being available for the fistulising CD model, they were not used because they are generally higher than the utilities found in the Spanish study, which was used to provide values in the severe active CD model. The authors stated that the estimates were not in accordance with the NICE reference case[93] because they were taken from CD patients and healthy individuals ($n = 32$ and $n = 20$ respectively). The utilities allocated assumed that patients with fistula closure had identical utilities to patients without fistulas. For all other fistula states 0.15 was deducted from utility estimates, the authors gave no explanation for this figure but did include the variable in the sensitivity analysis. While the assessment group notes this as an issue, no changes were made to MODEL B on this point.

The model was rerun using the revised weight and correcting the probabilistic sensitivity analysis for calculation errors. The CEAC for maintenance versus SC suggests that maintenance care was more likely to be cost-effective against SC as the threshold value increased. At £20,000 and £30,000 per QALY, infliximab treatment was found to be cost-effective 32.5% and 48.1% of the time respectively. Following the weight adjustment and recalculation of the CEAC, the curve shifted downwards. Now, at £20,000 and £30,000 per QALY infliximab treatment was found to be cost-effective only 6.3% and 19.1% of the time respectively (*Figure 34*).

Evaluating MODEL C: paediatric Crohn's disease

The economic model provided with the industry submission contained both circular references and broken links. While broken links may be repaired with the provision of the files containing the information on which the model is based, the file was not available. Any analysis conducted on this model would necessarily be based on such computational guesswork and would not withstand scrutiny. Although they had received opportunities to do so, Schering-Plough provided a working version of its paediatric model only at a sufficiently late stage that it was not possible to verify either the model structure or its assumptions. At this stage, three variants of a model outlined were provided and a cursory examination was sufficient to discover important – and within the available time frame – unresolvable flaws. It was therefore not possible to provide a report of the models provided beyond the brief summary of the original (unverified) submission that appears below.

Use of trial data in MODEL C

For paediatric CD, the submission states that evidence from the ACCENT I[2,3] trial 'suggested that maintenance infliximab therapy may bring significant QALY gains, related to improved QoL (as

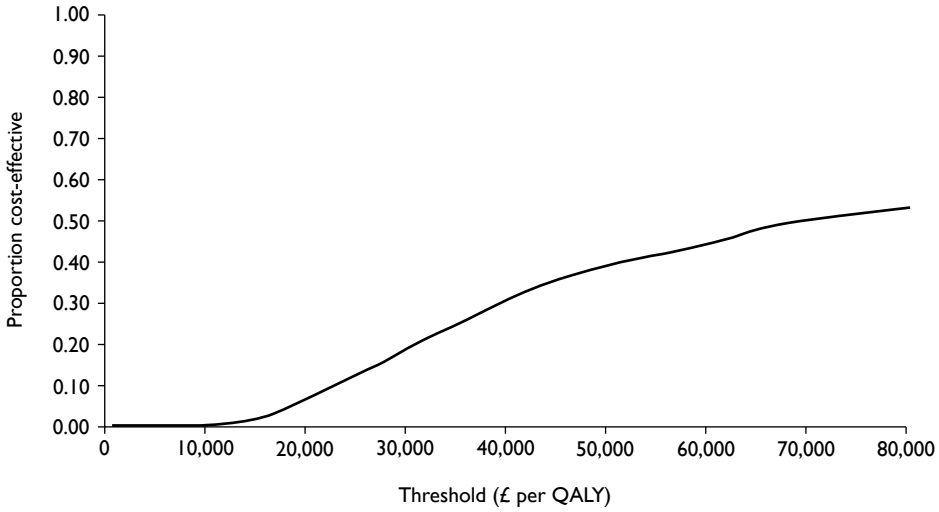

FIGURE 34 Cost-effectiveness acceptability curve for fistulising CD (IMT versus SC).

opposed to improved life expectancy) in adult and paediatric patients with CD'. While the sample characteristics provided in the trial summary do not show whether paediatric CD patients were included in ACCENT I,[2,3] a paper in *The Lancet*[3] reporting on the ACCENT I[2,3] trial gave the patient age range as 18–76 years, suggesting no paediatric patients were included. It is difficult to tell whether the authors' statement is based on data from these subgroups or previous evidence.

Paediatric CD strategies were based on data from Targan *et al.*,[57] REACH[45] and ACCENT I.[2,3] For both the scheduled maintenance and SC arms, the model was based on the Targan *et al.*[57] trial response rates at week 2. The Targan *et al.*[57] study was not a paediatric study and no age range was given (the mean ages that were given at baseline of those receiving 20 mg and 10 mg of chimeric monoclonal antibody cA2 were 36 and 39.3 years respectively). As there was a small sample in Targan *et al.*[57] it is unlikely that a subsample of paediatric patients was used. The transitions of these Targan *et al.*[57] study responders were estimated using data from the REACH[45] trial (at between 2 and 54 weeks). The REACH[45] trial was a paediatric study that compared scheduled maintenance at 8 weeks versus every 12 weeks. While the study assessed response only at week 10, the response rate was particularly high (99/112) compared with the ACCENT I[2,3] and II[65] trials. However, the REACH[45] study did not have a placebo arm so it is not possible to determine the proportion of patients who would have been classified as responders without infliximab.

The comparison of the two treatment strategies used in the model is inappropriate. The SC arm was based on ACCENT I[2,3] data from week 2 onwards. Like the Targan *et al.*[57] study, ACCENT I[2,3] is not a paediatric study; thus the paediatric SC treatment strategy is based only on adult study data; paediatric data are used only in the infliximab scheduled maintenance arm. As with the adult comparisons, the paediatric model was based on an optimistic assumption of 40-kg weight. Of the paediatric studies used in the analysis, the mean weights recorded were between 45 and 55 kg and 42 and 48 kg.

Discussion of the Schering-Plough submission

The Schering-Plough submission included three submodels considering (1) active CD for the CDAI range covered in the ACCENT I[2,3] trial including both moderate and more severe forms of CD, (2) fistulising CD and (3) paediatric CD. The industry submissions contained errors, some of which were resolved by the manufacturer following the consultation period on the draft

HTA report. Others could not be corrected, such as the selective use of responders in only the infliximab maintenance arm in the active CD model.

For active CD, the corrected models suggested that infliximab treatment (ICD) could be cost-effective, while maintenance care was unlikely to be cost-effective even at several times the normal threshold values. The lack of detail on what constitutes ICD or 'episodic' treatment is unhelpful. To the degree that they can be investigated, the models provided by Schering-Plough mostly meet the standards in the NICE reference case[93] (*Table 45*). There remain issues regarding the selection of studies, the use of data within the selected studies and some inputs used in the modelling. The utility values used in one model rely on a small sample, but are broadly in line with the reference case.[93]

Critique of the submission on adalimumab by Abbott

Introduction to the evaluation

An economic analysis was conducted for Abbott for their submission[4] to NICE by Analysis Group. The submission comprised two economic models – one comparing the cost-effectiveness of adalimumab as a maintenance therapy against SC and one comparing the cost-effectiveness of adalimumab and infliximab as maintenance therapies. This latter model will be relevant only where both adalimumab and infliximab have been first justified as maintenance therapies versus SC. Where one or both maintenance therapies are not cost-effective versus SC, this comparison provides no information to decision-makers.

TABLE 45 Compatibility of the industry model with the NICE reference case[93]

Element of health technology assessment	Principles	
Defining the decision problem	The scope developed by the Institute	Yes
Comparator	Alternative therapies routinely used in the NHS	Yes
Perspective on costs	NHS and PSS	NHS only
Perspective on outcomes	All health effects on individuals	Yes
Type of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to reflect any differences in costs or outcomes between the technologies compared	Yes
Synthesis of evidence on outcomes	Based on a systematic review	Partial; doubt remains on selection of studies
Measure of health benefits	QALYs	Yes
Description of health states for calculation of QALYs	Health states described using a standardised and validated generic instrument	Yes
Method of preference elicitation for health-state valuation	Choice-based method, for example, time trade-off, standard gamble (not rating scale)	Yes
Source of preference data	Representative sample of the public	Partial; one source of particularly small sample size
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity position	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Modelling methods	Structural assumptions and data inputs clearly documented and justified	Partial; assumptions made not justified
	Probabilistic sensitivity analysis should be conducted	Yes

This evaluation therefore begins by concentrating on the former model assessing the cost-effectiveness of adalimumab as a maintenance therapy. The model considers both fistulising and non-fistulising forms of CD together, and comprises a printed economic submission and accompanying working model in EXCEL. The economic model contained several assumptions that were not fully explained or justified at its initial submission. Abbott took the opportunity in responding to the draft assessment report to clarify some of these issues raised and their model incorporates elements of the health economic critique to their earlier version.

Model inputs and structure

The stated aim of the company's primary submission was to produce a comparison of lifetime maintenance on adalimumab versus SC. The adalimumab arm of the models was based on data up to week 56 in the CHARM[67] trial, which were then extrapolated to also produce a lifetime analysis by assuming that all those responding at week 56 would continue to respond for the remainder of their lives. A regression based on the CLASSIC I[63] trial was used to provide SC outcomes for the CHARM[67] arm. The company's comments received regarding the modified model are acknowledged below.

All patients enrolled in the CHARM[67] trial had baseline CDAI scores between 220 and 450. In this trial, all patients were given open-label 80 mg at week 0, 40 mg at week 2 and then randomised blind at week 4 to a placebo, adalimumab 40 mg e.o.w. or adalimumab 40 mg weekly. After week 12, those who did not respond to randomised treatment (defined as a drop of less than 70 points in CDAI) were switched to open-label adalimumab 40 mg e.o.w., as were those 'responders' who experienced a treatment flare after week 12. Those not responding to open-label adalimumab 40 mg e.o.w. were switched to adalimumab 40 mg weekly. Those not responding to 40 mg weekly were returned to SC.

In the CLASSIC I[63] trial, patients had a baseline CDAI between 220 and 450 and had had no previous exposure to any anti-TNF therapy. There were 299 individuals who were randomised to either placebo ($n = 74$) or adalimumab induction regimens in weeks 0 and 2 of 40 mg and 20 mg ($n = 74$), 80 mg and 40 mg ($n = 75$), or 160 mg and 80 mg ($n = 76$) respectively. All patients were followed for 4 weeks, and the primary end point was the proportion with a CDAI score < 150 in week 4.

The industry submission compared the cost–utility of the 40 mg adalimumab e.o.w. strategy versus SC. As the standard arm of the CHARM[67] trial began with adalimumab induction at 80 mg in week 0 and 40 mg in week 2, this did not provide suitable estimates for either the cost or the effectiveness of SC. As the placebo arm in the CLASSIC I[63] trial received no adalimumab, the economic submission used these data to predict health states in the SC arm.

The models in the industry submission were based on both the 56 weeks of the CHARM[67] trial and an extrapolation to give a lifetime model. The 56-week model included no discounting, the longer model used a discount rate of 3.5% for both costs and benefits. The lifetime model assumed that health remains constant across the group (in terms of the profile of health states) from week 56 to death and assumed a baseline age of 37 years (in line with the average age for CHARM[67]), with life expectancy of 66 years. There was no mortality between years 37 and 66 due to treatment, CD or other causes.

The model structure was based around four health states defined as remission (CDAI < 150), moderate (150 ≤ CDAI < 300), severe (300 ≤ CDAI < 450) and very severe (CDAI ≥ 450). Patients enrolled in the CHARM[67] trial had baseline CDAI scores between 220 and 450, and fell in only the moderate and severe categories at baseline. Utility data were based on these health states. Costs were calculated based both on trial arms (for anti-TNF medication costs) and on the time

spent in each of these disease states (for hospitalisation costs and all other costs). Overall costs and QALY benefits for the CHARM[67] trial were calculated for the baseline moderate and severe groups ($150 \leq CDAI < 450$) and the baseline severe subgroup ($300 \leq CDAI < 450$).

Univariate sensitivity analyses were conducted that modified the method of imputing states for those leaving the trial, incorporated indirect costs and made several other changes to the cost assumptions. Using details in the revised industry model for adalimumab versus SC, it was possible to replicate the multivariate sensitivity analysis provided in the revised model.

Estimates of standard care outcomes

The relationship between CDAI-based health states and prognostic factors was estimated using the CLASSIC I[63] trial using an ordered probit regression that predicted the chances of an individual falling into each of the four states (remission, moderate, severe and very severe). Variables were included for baseline CDAI, previous anti-TNF exposure, corticosteroid use, fistulising disease, and time and treatment dummy. Health states for the first 4 weeks in the SC arm were found by applying this regression to the clinical factors observed in the CHARM[67] 40-mg e.o.w. arm. It was assumed that the proportion of people in each health state would remain constant from week 4 onwards. Although patients previously receiving such treatment were excluded from the CLASSIC I[63] trial, the previous use of anti-TNF treatment appeared as a predictor in the ordered probit regression. It is unclear how this effect was estimated.

Estimates of adalimumab maintenance outcomes

The adalimumab outcomes were estimated using data derived from the CHARM[67] trial data. Within the CHARM[67] trial, 778 patients were randomised but 854 patients were enrolled at week 0 in order to achieve this sample. The 76 patients [(CiC information has been removed) with $CDAI \geq 300$] who withdrew prior to week 4 did so for a variety of reasons, including AEs (45), lack of efficacy (13) and, in one case, death. (This death was judged not to be related to the use of adalimumab by the CHARM trial investigators.[67])

The revised industry model incorporated the costs of these non-randomised individuals by including them within the adalimumab modelling arm. Given that the 260 individuals receiving adalimumab comprised approximately one-third of the randomised CHARM cohort, it was assumed that one-third of the non-randomised individuals would have been randomised to this arm. The individuals who were not expected to receive a standard adalimumab course were modelled as if they were SC patients but each incurred an additional £974 in medication costs.

Those expected to be able to receive a standard adalimumab course (i.e. those randomised at 4 weeks) were modelled as the 40-mg e.o.w. arm from the CHARM[67] trial, based on randomisation at 4 weeks. CHARM[67] randomisation was stratified by 4-week response (reduction in CDAI of 70 points from baseline). At 12 weeks, those not responding (reduction in CDAI of 70 points from baseline) could be shifted to open-label treatment and leave the randomised study. *Figure 35* shows the comparison between the randomised data at 4 weeks and the observational groups defined at 12 weeks. Of the 260 individuals, only (CiC information has been removed) received their scheduled treatment at week 56.

FIGURE 35 Clinical data: CHARM[67] evidence versus that used in the economic model. (CiC information has been removed.)

Those patients removed from the trial at 12 weeks were referred to in the industry submission as 'deleted non-responders' in the diagram shown in *Figure 36* (reproduced as non-CiC) from the

economic submission. Missing individuals were those who discontinued from the trial for other reasons, including disease flares and protocol violations.

The economic model included a mixture of those responding and not responding at 4 weeks. The results in the economic model therefore differ from the coprimary clinical end points of the trial, which concerned week 4 randomised responders only.

In the main analysis, the economic model used the last value carried forward (LVCF) to impute missing values. As a sensitivity test, the model included results where the course of the patient's disease reverted back to the state the patient was in prior to adalimumab therapy ('simulated placebo').

Health-state costs and utility estimates

Each health state was linked to an expected number of hospitalisations using a Poisson regression model based on a variety of clinical and background characteristics. This was used to construct patient-level predictions of hospitalisation events per year. The unit cost was estimated using published UK data (Bassi *et al.*[37]) and inflated using PSSRU figures to produce a cost per hospitalisation of £7441 in 2006 pound sterling. The CHARM[67] trial did not record CD-related surgeries, and so this hospitalisation factor incorporated the cost of surgery. (Note that the submission was inconsistent whether the hospitalisation figure applied per year or over the 56 weeks of CHARM.[67])

Other non-hospitalisation disease costs (excluding anti-TNF medication) were estimated using Bassi *et al.*[37] Bassi *et al.* used a seven-state classification for CD states similar to Silverstein *et al.*[26] The model assumed that 'very severe' corresponded to 'indicated for surgery' in Bassi *et al.*,[37] with 'severe', 'moderate' and 'remission' corresponding to 'severe, drug-refractory', 'mild disease' and 'remitted' states. Estimated non-hospitalisation disease costs are given in *Table 46*.

Table 46 also displays utility estimates for the four health states that were based on a reanalysis of previously published primary standard gamble data (Gregor *et al.*[92]). These estimates were based on 180 consecutive Canadian patients presenting with CD between December 1995 and December 1996.

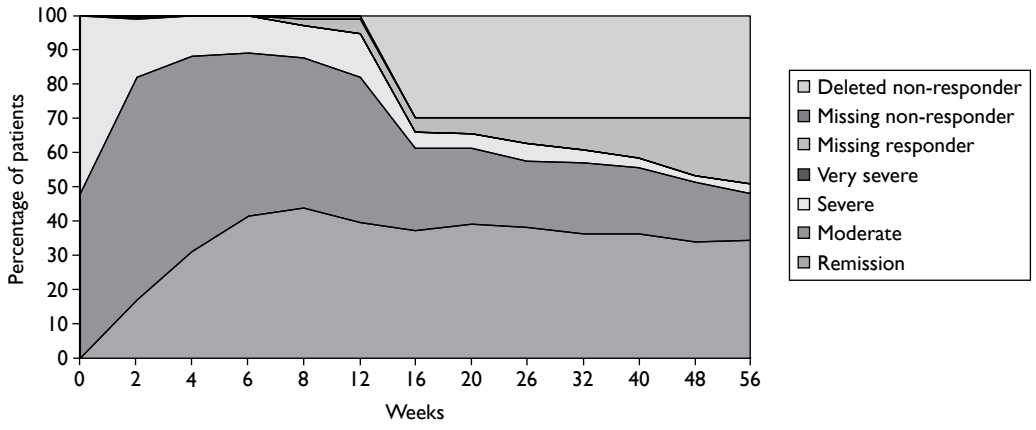

FIGURE 36 Adalimumab outcomes from the CHARM[67] trial.

Adalimumab cost estimates

The cost per 40-mg adalimumab dose was assumed to be £357.50, with one dose necessary every 2 weeks per patient after an initial three-dose induction in the first 4 weeks. No administration costs were included.

Results of the adalimumab industry submission

The results reported here refer to the adalimumab industry submission produced in response to comments in the draft assessment report. The industry submission 56-week model suggested that for baseline moderate and severe patients ($150 \leq CDAI < 450$), the incremental cost of adalimumab 40-mg e.o.w. treatment was £2496 for an incremental increase of 0.0823 QALYs (*Table 47*). The estimated ICER was £30,319. For patients with severe disease ($300 \leq CDAI < 450$), the incremental costs and benefits were estimated at £1254 and 0.1045, giving an ICER of £11,998 per QALY.

In the original submission, the univariate sensitivity analysis suggested that for patients with severe CD, adalimumab was close to or below £20,000 per QALY for a variety of different assumptions. When considering both moderate and severe CD together, the baseline assumption was close to £30,000 per QALY and typically exceeded this whenever any adverse change was made to the model assumptions. While the industry submission included an induction regimen at 160 mg and 80 mg at weeks 0 and 2, it should be noted that this was not used in the CHARM[67] trial and the results will differ if it is associated with higher AEs. This did not change significantly in the second model.

The second industry submission model assumed that parameters for hospital and health-state related costs were distributed according to gamma distributions. Utilities for the remission state were assumed to be distributed according to a beta distribution, with constant ratios between all

TABLE 46 Health-state based parameters in the industry submission

Health state	CDAI score	Non-hospitalisation disease costs[a]	Utility
Remission	< 150	8.45	0.859
Moderate	$150 \leq CDAI < 300$	23.66	0.795
Severe	$300 \leq CDAI < 450$	43.11	0.693
Very severe	≥ 450	78.55	0.433

a 2006 pound sterling prices.

TABLE 47 Results from the industry 56-week model

	Moderate and severe			Severe only		
	Adalimumab	Standard care	Difference	Adalimumab	Standard care	Difference
QALYs	0.8566	0.7743	0.0823	0.8384	0.7339	0.1045
Drug costs	£6533	£0		£7119	£0	
Health-state related costs	£1249	£2049		£1429	£2407	
Hospitalisation	£2028	£5265		£2598	£7485	
NHS costs	£9810	£7315	£2496	£11,146	£9892	£1254
ICER	**£30,319**			**£11,998**		

four utility values (*Table 48*). When estimating uncertainty in adalimumab outcomes, a Dirichlet distribution was used based on the time spent in each state by the 260 patients within CHARM.[67]

In the second industry model (based on 1000 samples), adalimumab treatment was estimated to be cost-effective below £20,000 per QALY in 62.8% of samples, and below £30,000 per QALY in 80.9% of samples. *Figure 37* is based on 5000 samples and gives similar results (61% and 79%, respectively).

Evaluating the industry submission for adalimumab maintenance versus standard care

The inputs to the industry model of adalimumab maintenance were modified to investigate the robustness of the model. The revised model used the 'simulated placebo' method of imputing missing values. Those leaving the CHARM[67] trial did so because of disease flare or other issues requiring protocol violating treatments, and so their health may have been poorer than an 'equivalent' simulated SC outcome (which represented expected health at 4 weeks). The 'simulated placebo' assumption is more neutral with respect to the prognosis of those leaving blinded CHARM[67] treatment than the LVCF used in the industry model.

Aside from a preference for 'the simulated placebo', the major differences between the second industry model and the revised industry model are the assumptions made regarding the use of adalimumab beyond the study period. In both the first and second industry models it was assumed that all those receiving adalimumab at 56 weeks would continue to do so for their entire

TABLE 48 Parameter distributions for distributions

Type	Health state	Type	A	B
Hospitalisation costs (£)		Gamma	6.25	1190.56
Health-state related costs (£)	Remission	Gamma	6.25	1.35
	Moderate	Gamma	6.25	3.79
	Severe	Gamma	6.25	6.90
	Very severe	Gamma	6.25	12.57
Utilities	Remission	Beta	3.5280	0.5791

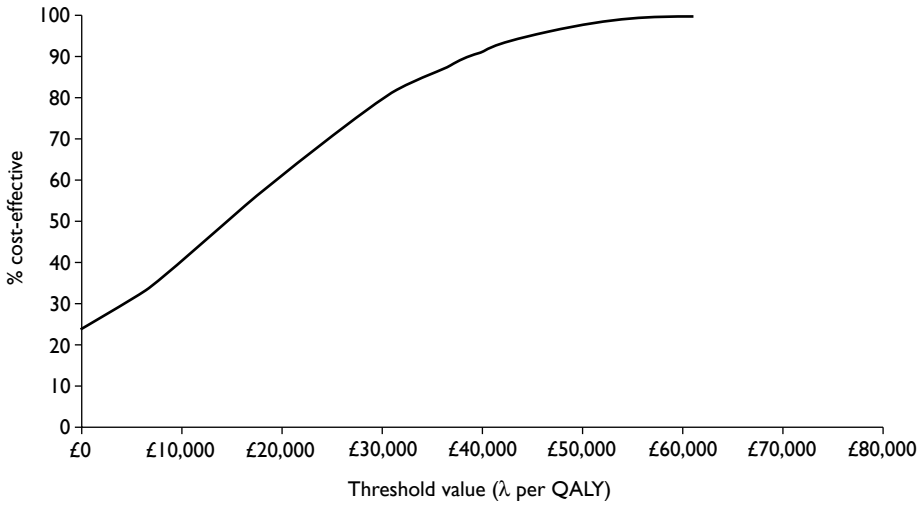

FIGURE 37 Cost-effectiveness acceptability curve for severe disease (LVCF method).

lives. In the revised model, the rate of withdrawal from adalimumab maintenance post 56 weeks was increased from zero to that of the CHARM 40-mg e.o.w. arm. Outcomes for patients with moderate CD were also inferred as a separate subgroup where this was possible. Unless otherwise indicated, the model description here is kept as in the industry submission.

The industry model's use of CHARM data

The clinical end points of the CHARM[67] trial related to week 4 responders (a reduction in CDAI of 70 points from baseline), and all published data referred to this group. This causes difficulties in interpreting the data, as terms were duplicated with few caveats. Where published data and the industry clinical submission referred to responders and non-responders, they did so based on a comparison of baseline and 4-week data (randomisation); the economic submission appeared to define this split using baseline versus week 12 data. However, the remission rates for moderate and severe patients do appear to be broadly in line with an all-comers analysis of the trial.

The CHARM[67] trial randomised patients at 4 weeks to one of three (blinded) arms: placebo care, adalimumab 40 mg e.o.w. and adalimumab 40 mg weekly. This blinded treatment stage in the trial was maintained for 12 weeks for all randomised patients. Those who did not achieve a sufficient improvement in health at 12 weeks were termed 'non-responders' in the economic model, which appeared to define this as a reduction of < 70 points in CDAI from baseline. It appears that week 12 non-responders were moved to open-label 40-mg e.o.w. treatment, as were week 12 responders who experienced disease flares after 12 weeks. Those receiving open-label e.o.w. treatment could subsequently move to weekly treatment as required, and then subsequently to SC following persistent non-response.

Outcomes beyond 56 weeks

The initial industry submission did not adequately describe the assumptions used in constructing its economic model. This was particularly problematic when considering lifetime costs and effects, as this extrapolated data at the end of CHARM trial[67] for an additional 37 years. The industry models suggested an average expected adalimumab 40-mg e.o.w. use of 13.3 vials per year after year 1, which was consistent with the numbers receiving e.o.w. treatment at 56 weeks. However, with an approximately constant number of people leaving the trial's adalimumab arm from week 7 onwards within CHARM, it could be predicted when the last individual would cease to receive adalimumab on this until-flare maintenance regimen. With the limited data made available from the economic model, it was predicted that the last dose of adalimumab corresponding to the blinded treatment on CHARM[67] would have occurred in week 189. A lifetime model was not necessary here as – under the assumptions of the placebo method of imputing lost values – the SC and adalimumab model arms would have been identical after 4 years, therefore a 4-year time frame would have sufficed.

In analysing this information, the assessment group used a 'best guess' interpretation of the industry model in which only blinded treatment was costed within the model. Subsequent communication verified that the industry model included all treatments received, including open-label 40-mg e.o.w. and weekly regimens. This highlights some unresolved issues within the data and apparent difficulties with adherence. On a period-by-period basis (e.g. weeks 12–16, weeks 16–20, etc.), those on a 40 mg weekly dosage receive only (CiC information has been removed)% of the *total* dosage received by those on a 40-mg e.o.w. dosage, which is lower than the 200% that would be expected. If all patients who received treatment had the indicated dose, then on a period-by-period basis after week 12 it appears that only (CiC information has been removed)% of patients prescribed 40 mg e.o.w. and (CiC information has been removed)% of patients prescribed 40 mg weekly went on to receive it. This suggested that many individuals appeared to miss scheduled treatment on 40 mg e.o.w., and that those shifted on to 40 mg weekly were even less likely to actually receive it. This may indicate issues in the tolerability of adalimumab and its long-term acceptability for patients.

The accurate analysis of long-term adalimumab usage relies, at the very least, on better data about both the longer term acceptability of treatment to those still 'on' treatment, and the assessment of how many patients are now formally off treatment. It is possible to infer vastly different profiles of future usage (and hence benefit) from the CHARM data. Given CiC data provided by Abbott in the consultation process, little confidence can be placed in either the original or revised model beyond the 56 weeks of CHARM. For this reason, outcomes beyond a 1-year time frame are not considered further here. A lifetime model for adalimumab usage is warranted, and as the evidence base improves it may be possible to analyse such issues in greater depth.

Separating moderate and severe subgroups

At randomisation (week 4), the CHARM[67] 40-mg e.o.w. arm included 125 patients with moderate CD (CDAI between 150 and 300) and 135 with severe CD (CDAI between 300 and 450). The industry submission provided the expected frequency of health states, adalimumab use and hospitalisations for both moderate and severe, and severe only groups. This allowed separate outcomes to be inferred for those with moderate disease within the 56 weeks of the CHARM model. These are reported below.

Results of revised adalimumab model

The industry submission predicted an ICER of £11,998 per QALY at 56 weeks for those with a baseline CDAI at or above 300. With the preferred 'placebo method' of imputing missing data, this rose to £30,964 per QALY. The industry submission did not predict an ICER for the moderate subgroup. In the estimates presented here, it was found that treatment was far less cost-effective than for the severe subgroup, and above £100,000 per QALY using the 'placebo method' of imputing missing data.

In the 56-week model it appears that treatment for severe patients is likely to approach £30,000 per QALY under more conservative assumptions, but will fall below £20,000 per QALY under optimistic assumptions. For moderate patients, even optimistic assumptions appear to give relatively large ICERs for adalimumab treatment.

The numbers in *Table 49* suggest that treatment of those with severe disease ($300 \leq CDAI < 450$) will be cost-effective under optimistic (LVCF) assumptions, and marginally over £30,000 per QALY with the preferred and more conservative assumptions. There is less ambiguity surrounding the treatment of those with moderate disease ($150 \leq CDAI < 300$). Even under optimistic assumptions, the smaller additional health benefit of 0.0589 comes at a higher incremental cost, leading to an ICER above £60,000 per QALY.

Figure 38 shows the CEAC for the treatment of severe disease where the (conservative) simulated placebo method is used. Across 5000 samples, 24.4% of ICERs fell below £20,000 per QALY and 44.1% fell below £30,000 per QALY. These figures compare to 61.2% and 79.1% respectively using LVCF.

For moderate disease, *Figure 39* shows the CEAC for the optimistic case (LVCF). Here, only 1.4% of samples fall below £20,000 per QALY and only 7.9% fall below £30,000 per QALY. Under the pessimistic assumption (simulated placebo) these figures fall to 0.04% and 2.0% respectively.

Discussion of adalimumab industry submission

Neither the analysis of the 56-week CHARM[67] trial data nor the lifetime adalimumab economic model used the modified ITT analysis on which the major clinical findings of the published CHARM[67] trial were based. In reviewing the economic evidence, there are concerns over the comparators used in the adalimumab model. Given the structure of the CHARM[67] trial, SC could have been compared with an induction only dose of adalimumab, an until-flare maintenance

TABLE 49 Cost-effectiveness of adalimumab in the second industry models: severe and moderate subgroups; and imputation method

	Severe patients only			Moderate patients only		
	Adalimumab	Standard care	Difference	Adalimumab	Standard care	Difference
Values imputed using LVCF – optimistic estimate						
QALYs	0.8384	0.7339	0.1045	0.8769	0.8180	0.0589
Drug costs	£7119	£0		£6029	£0	
Health-state related costs	£1429	£2407		£1046	£1663	
Hospitalisation	£2598	£7485		£1465	£2868	
NHS costs	£11,146	£9892	£1254	£8540	£4531	£4009
ICER	**£11,998**			**£68,065**		
Values imputed using simulated placebo – pessimistic estimate						
QALYs	0.8225	0.7339	0.0886	0.8605	0.8180	0.0425
Drug	£7119	£0		£6029	£0	
Health-state related costs	£1565	£2407		£1205	£1663	
Hospitalisation	£3952	£7485		£2099	£2868	
NHS costs	£12,636	£9892	£2744	£9333	£4531	£4802
ICER	**£30,964**			**£113,008**		

regimen (based on blinded treatment in CHARM[67]) and a lifetime regimen (based on blinded and open treatment in CHARM[67]). As the results for an induction only regime appear as the 'standard care' arm of the CHARM[67] trial, it should have been included in the economic submission.

Previous use of other anti-TNF therapy is an important predictor of response to adalimumab that is not addressed within the industry submission. In the CHARM[67] trial, patients with previous experience of anti-TNF therapy were excluded only if they had no clinical response to the therapy, or had used it in the past 12 weeks. Fifty per cent of all CHARM[67] patients had had prior exposure to anti-TNF therapy. As the clinical response was superior in those who had not previously received anti-TNF treatment, it is highly likely that cost-effectiveness would be superior in this group. Given that the 56-week revised model suggested a relatively high cost-effectiveness ratio even for the severe subgroup, this may be an important consideration.

A lack of clarity over the source and interpretation of data has hampered the analysis of the economic submission. Overall, the economic model met most of the requirements of the NICE reference case[93] (*Table 50*), but crucial elements of the model could not be verified. The analysis here has attempted to address concerns over the methodology and interpretation of the economic model. It appears that the cost-effectiveness ratio for moderate CD patients is particularly high at 56 weeks, and it is not at all clear that this figure will approach cost-effectiveness even over a longer period of time. The cost-effectiveness of adalimumab treatment is far more favourable for patients with severe CD.

Industry submission comparison of adalimumab and infliximab maintenance therapies

The Abbott submission[4] also included a cost model comparing adalimumab and infliximab maintenance regimens. The stated aim of the maintenance comparison was to compare

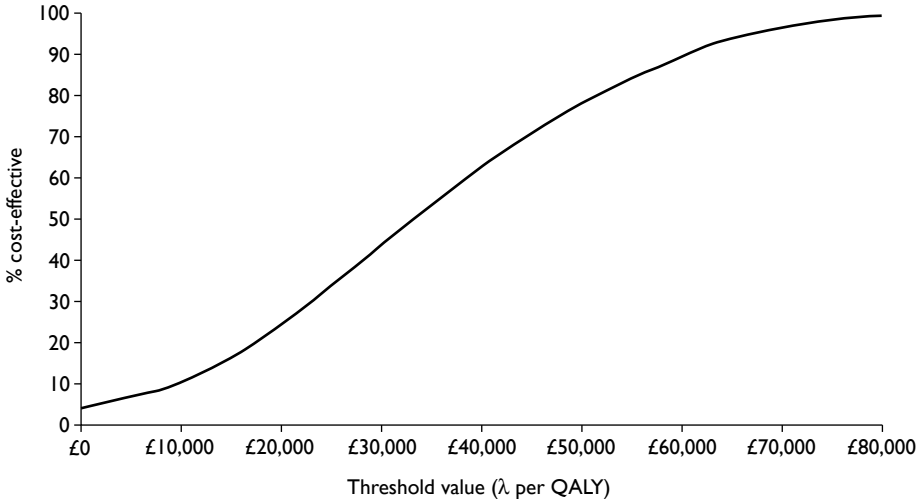

FIGURE 38 Cost-effectiveness acceptability curve for severe disease (placebo method).

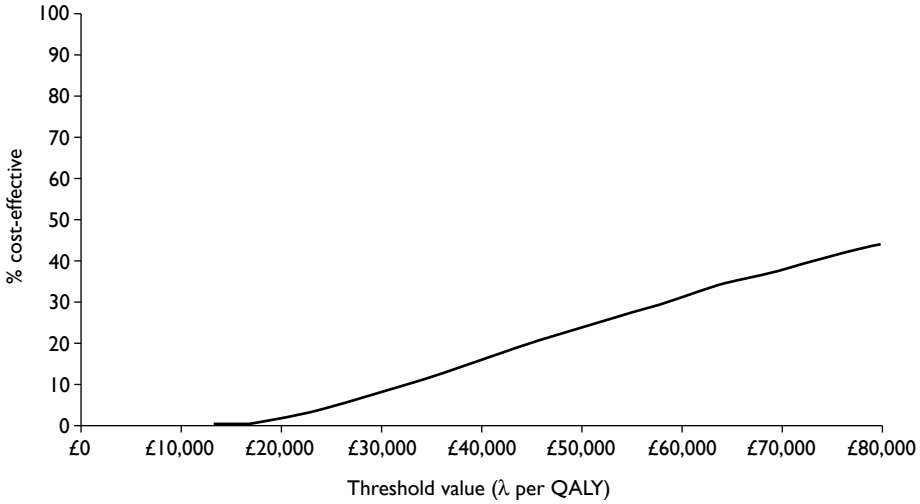

FIGURE 39 Cost-effectiveness acceptability curve for moderate disease (LVCF method).

adalimumab against infliximab on the basis that infliximab is the alternative most likely to be displaced by the prescription of adalimumab. However, neither adalimumab maintenance nor infliximab maintenance would be the most appropriate comparator in such an analysis. Owing to a lack of trial results comparing these treatments directly, the comparison is secondary in nature.

The infliximab comparator used appears to combine those who were judged to be responders and non-responders on the 5 mg/kg arm of ACCENT I[2,3] using the Rutgeerts *et al.*[2] data including both 5 mg/kg standard dosage and 10 mg/kg 'as needed' dosage. The adalimumab comparator used adalimumab maintenance at 80-mg/40-mg induction with 40-mg dosage e.o.w. The adalimumab outcomes were found using a weighted sample from the CHARM[67] trial for those with CDAI between 220 and 400 (in line with ACCENT I[2,3]) and with weights derived so that the same gender distribution, median age and CDAI quartile figures (lower quartile, median, upper quartile) held across the infliximab and modified adalimumab groups. Those with CDAI above 400 were excluded from the analysis for comparability with the ACCENT I[2,3] trial. Those who had previously used anti-TNF treatments were not excluded from the adalimumab group, although

TABLE 50 Compatibility of the model with the NICE reference case

Element of health technology assessment	Principles	Met requirements of NICE reference case
Defining the decision problem	The scope developed by NICE	Yes
Comparator	Alternative therapies routinely used in the NHS	Partial. Not all relevant comparators are used for the adalimumab
Perspective on costs	NHS and PSS	NHS only
Perspective on outcomes	All health effects on individuals	Yes
Type of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to reflect any differences in costs or outcomes between the technologies compared	Not applicable, given limits of evidence based
Synthesis of evidence on outcomes	Based on a systematic review	Partial. Details unclear and not necessarily reproducible
Measure of health benefits	QALYs	Yes
Description of health states for calculation of QALYs	Health states described using a standardised and validated generic instrument	Yes
Method of preference elicitation for health-state valuation	Choice-based method, for example, time trade-off, standard gamble (not rating scale)	Yes
Source of preference data	Representative sample of the public	No. Patient values used
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity position	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Modelling methods	Structural assumptions and data inputs clearly documented and justified	No
	Probabilistic sensitivity analysis should be conducted	Yes

this was an exclusion criterion in ACCENT I.[2,3] Missing data for both comparators were inferred using LVCF.

The adalimumab arm costs were found by assuming that all those receiving adalimumab and not responding at week 12 would have continued to receive it, which led to higher costs than in the main model. The infliximab arm drug costs were assumed to include an average wastage of 0.5 vials per infusion. Hospitalisation costs were estimated using the Poisson regression for the adalimumab group and observed hospitalisations (plus inferred data from the adalimumab group) in the infliximab group. The model used an excess hospitalisation of 0.098 per infliximab patient per 56 weeks.

As the infliximab data used remission/non-remission rather than the four health states of the main adalimumab model, the health status based costs were estimated using the frequencies reported in Bassi *et al.*[37] A cost of £38.48 per week was calculated for non-remission costs, and the cost of remitted patients per week was assumed to be £8.45. Overall, the model suggested an excess cost for infliximab patients of £4414 over 56 weeks, of which the majority was due to medication costs (£3526).

While this model also attempted to compare health outcomes, no summary quantitative figures were provided on which to base a cost–consequences analysis, cost-effectiveness or a cost–utility analysis. Using the proportion of patients in remission (partially inferred using LVCF assumptions), it was claimed that adalimumab led to a higher proportion of patients in remission from week 6 onwards. In conjunction with the cost findings, the model claimed that adalimumab maintenance dominated infliximab maintenance.

This model is reported but not analysed in depth. The model compared adalimumab maintenance against infliximab maintenance without comparing either against a standard treatment. As a comparison of non-standard treatments, it fell outside the scope of the assessment. Furthermore, given that both adalimumab and infliximab maintenance appeared to have ICERs far outside the suggested ranges, the results of this model are of little practical relevance to the decision problem faced.

It was also noted that the infliximab regimen modelled here included the 10 mg/kg dosage only. Given the uncertainty relating to which treatments were actually received by patients in ACCENT I,[2,3] on what basis these treatments were received, and to what degree the treatments received would be legitimate in a NHS context, it would be difficult to place any confidence in this model.

Independent economic assessment

Introduction

The overall decision problem for this appraisal was 'What is the cost-effectiveness of anti-TNFs in the management of moderate-to-severe CD in the UK NHS?'. In order to undertake cost-effectiveness analyses to address this decision problem it was necessary to (a) define moderate and severe CD; (b) specify the specific roles for anti-TNFs in the management of CD that were to be evaluated; and (c) specify the patient groups for whom cost-effectiveness would be assessed. The first part of this section addresses these questions. The second part describes the de novo cost-effectiveness model developed to answer the decision problem, and provides base-case results. A series of sensitivity analyses to explore the impact of uncertainty in key model parameters on the estimates of cost-effectiveness were then undertaken. The section finishes with a discussion of the implications of the results of this model.

Disease severity can be expressed in terms of current status or life course. It can be measured using a wide range of indices including frequency of symptoms, severity of symptoms, biochemical activity levels and intensity of treatment required. Available evidence does not provide a strong basis for differentiating CD severity in terms of life course. Munkholm *et al.*[25] reported that 'The clinical course of CD differs markedly over time, with ever-relapsing cases, to a quiescent course with remission for several years, interrupted by years with relapse'. No predictive factors have been found for the subsequent course with regard to age, sex, extent of disease at diagnosis and treatment in the year of diagnosis.

The current severity of CD is difficult to assess, and a global measure encompassing clinical, endoscopic, biochemical and pathological features is not available.[39] The most widely used disease activity measures include the CDAI, the HBI or Simple Index, a simplified version of the CDAI, and the PDAI. A commonly used HRQoL measure is the IBDQ. Other measures include the CDEIS.

The CDAI is the measure used most extensively in the anti-TNF clinical trials. It measures current disease severity using a recall period of the previous 7 days. Variables captured in the measure include number of liquid stools, abdominal pain, general well-being, extraintestinal complications, use of antidiarrhoeal drugs, abdominal mass, haematocrit and body weight. Scores range from 0 to 600. Values of < 150 are suggestive of quiescent disease (remission) and values > 450 are associated with very severe disease.[40] Some investigators have arbitrarily labelled CDAI scores of 150–219 as mildly active disease and scores of 220–450 as moderately active disease.[39]

Given that the anti-TNF trials use CDAI to measure disease severity and to determine response, the cost-effectiveness analysis used the following definitions of disease severity:

- severe disease: CDAI > 300
- moderate disease: 220 < CDAI ≤ 300.

It should be noted that in line with the decision problem and the use of CDAI in the trials, this definition says nothing about the frequency of relapse. A patient who has been in remission for 5 years and relapses with moderate disease refractory to standard therapy is as much a target for treatment with anti-TNFs as a patient who has had two relapses in the last 12 months, with moderate disease that is refractory to standard therapy.

The scope for this appraisal identified three categories of use of anti-TNFs in the management of CD: induction, episodic and maintenance. There is some uncertainty as to the precise definition of each of these categories.

Maintenance therapy is perhaps the most straightforward to define. It can be described as the chronic use of anti-TNF therapy to maintain remission in patients who have responded (and continued to respond) to anti-TNF therapy when in relapse. In maintenance therapy, the key challenges in arriving at a working definition are:

(a) What is the criterion for defining a patient as a responder? Is it the achievement of remission (achieving a CDAI score below a defined threshold) or improvement (a defined minimum fall in their CDAI score)?
(b) In those currently receiving treatment, is non-response identified by looking at their response over a period of time, or their response after a certain number of treatments?

Defining 'episodic' treatment is less straightforward (see *Glossary*). Seven different working definitions of episodic treatment were identified in the literature and submissions to this appraisal. In the previous appraisal of anti-TNFs in the management of CD, episodic treatment was defined as giving up to three additional courses of treatment when a patient experienced a disease relapse if that patient initially responded to anti-TNF therapy. The relapse could have occurred once in several years or much more frequently. The key uncertainties in this definition are the same as with maintenance therapy above.

Induction treatment is the use of anti-TNF therapy with the aim to achieve remission. It is not straightforward to draw a distinction between repeated use of anti-TNF as induction on the one hand and episodic therapy as described above. Induction therapy may merely be the initial application of anti-TNF to a patient in relapse which establishes his or her responder status prior to the subsequent provision of 'episodic' or maintenance therapy. To consider the cost-effectiveness of induction therapy divorced from its value in informing future decisions on 'episodic' or maintenance therapy would be clinically unrealistic and would produce an inaccurate estimate of its cost-effectiveness. As with 'episodic' and maintenance treatment, the definition of response and the identification of responders are important issues.

Given the problems with assessing the cost-effectiveness of induction therapy in isolation, one-off induction therapy has not been modelled. Instead, the cost-effectiveness of 'induction' as a series of individual induction treatments received when a patient falls into relapse that is non-responsive (or given past treatment expected to be unresponsive) to standard therapy was examined. Thus a repeated reinduction treatment was considered here. Each individual induction treatment was composed of an appropriate dosage regimen based on clinical trial information.

Those who did not respond within 8 weeks of induction (i.e. after induction doses at 0, 2 and 6 weeks for infliximab and 0 and 2 weeks for adalimumab) were deemed non-responders and transferred to SC. In maintenance, treatment occurred every 8 weeks for infliximab and every 2 weeks for adalimumab. On relapse, doses increased to match the higher induction regime. For infliximab, treatment occurred at relapse, relapse + 2 weeks and relapse + 6 weeks. For adalimumab, treatment occurred at relapse (at the higher induction dose), then relapse + 2 weeks, relapse + 4 weeks and relapse + 6 weeks at the standard dose in line with maintenance treatment. Remission status following this reinduction dose was assessed at relapse + 8 weeks, and subsequent treatment was determined by whether or not remission was achieved: maintenance treatment continued where remission was achieved by 8 weeks; treatment reverted to SC where remission was not achieved at 8 weeks.

There are a number of alternatives to defining responder status. Within the trials, responders were defined in two distinct ways: (1) patients whose CDAI improved by a pre-specified amount following administration of anti-TNF; and (2) patients who achieved remission following administration of anti-TNF. For the purpose of economic evaluation the first approach to defining a responder was problematic as it said nothing about the relative improvement in health for any given reduction in CDAI score. Both the health gain associated with any given improvement in the CDAI and the value attached to the health gain would depend upon the pre-treatment CDAI. Defining responders using a pre-specified improvement in CDAI does not differentiate between patients for whom treatment controls the disease and patients for whom treatment merely reduces the severity of the symptoms. Thus it was not possible to ascribe a robust utility value for the health of responders defined in this way. By contrast, patients in remission (CDAI < 150) will typically have few CD-specific symptoms and this is a health state for which it would be possible to ascribe a robust utility value. For this reason, response was defined as achieving remission following anti-TNF therapy. This method of defining responders may bias results against treatment in patients with severe disease for whom achieving an absolute reduction in CDAI score may be more difficult. By using an absolute score for response rate it is not possible to take account of all possible health benefits that a patient may gain from a large change in relative response. Yet, as stated above, there is no possible way of determining the health gain associated with a particular relative reduction in CDAI score given the data available. So even when considering the possible bias this approach might introduce in to the model, it is still the only methodologically appropriate way of valuing health states.

The scope for this appraisal identified a number of patient groups for whom the NICE Appraisals Committee would be interested in obtaining specific estimates of the cost-effectiveness of anti-TNF therapy: adults; children; severe CD; moderate CD; fistulising; and non-fistulising.

The randomised placebo-controlled trial evidence for the anti-TNFs did not include paediatric trials, even though infliximab does have a licence for use in the paediatric population. In the absence of estimates of effectiveness that can be used to model the magnitude of effect for anti-TNFs compared with SC, robust modelling of the cost-effectiveness of anti-TNF therapy in a paediatric population was not possible. However, to assist the committee in its deliberations; a scenario analysis using the adult models was presented, where paediatric administration and drug costs were substituted for the adult costs. This was equivalent to assuming that treatment was equally effective in paediatric and adult populations and that all other costs of treatments and utilities gained remained the same.

Separate models are presented for patients with moderate and severe disease, as the value of the health gain associated with remission will be systematically different for these two patient groups, as would be the likely costs of managing relapse.

While the trials of anti-TNFs differentiated between fistulising and non-fistulising disease, it was not possible to identify a long-term usual care cohort study for fistulising patients. In the absence of this evidence, the trial-based evaluations submitted by the manufacturers provided the best available estimates of the likely cost-effectiveness of treatment in the fistulising population. However, it is important to emphasise the difference in the characteristics of the trial populations and the characteristics of the population who are the focus of the decision problem for this appraisal as defined in the NICE scope – i.e. *all* patients with moderate-to-severe disease that is refractory to standard treatment.

The trial populations were patients in relapse. However, frequency of relapse was not an inclusion criterion for treatment in the decision problem for this appraisal. Patients who relapse more frequently have more capacity to benefit from an effective treatment and therefore, assuming effectiveness is not lower in patients who relapse frequently, treatment would be more cost-effective in those patients than in the population defined for this appraisal.

In summary, de novo cost-effectiveness analyses for adults with moderate-to-severe CD were presented, where response was defined as remission within 8 weeks. The objective of the cost-effectiveness analysis was to estimate the incremental cost per QALY between (a) SC, (b) induction therapy and (c) maintenance therapy for moderate and for severe disease.

Model structure

The NICE methods guide recommends that models of chronic diseases normally adopt a lifetime horizon because exacerbations in chronic diseases usually relate to reduced life expectancy.[93] Analysing a cohort of patients followed from 1993–4 to 2003–4, Wolters *et al.*[97] reported that there was no significant CD-specific mortality, with the age at diagnosis being the only significant association with mortality. As none of the clinical trials provided evidence of an impact upon mortality, it was reasonable to assume there was no differential mortality rate and, therefore, a lifetime horizon would not add meaningfully to the precision of the cost-effectiveness estimate. The time horizon for the Markov model was 1 year (with sensitivity analyses of 5, 10 and 20 years) and the cycle duration was 4 weeks, i.e. the model had 13 cycles and did not include mortality. All models were constructed and analysed in TREEAGE PRO 2008 (TreeAge Software Inc., Williamstown, MA, USA). Both the induction and maintenance model started with a cohort of patients suffering from an SC-refractory relapse.

In the absence of time-dependent transition probabilities for the natural history of the cohort with moderate-to-severe CD at onset, a natural history cohort that reflects the average transition rate over time was used. If the appropriate data had been available, the preferred model structure would have been a time-dependent state transition model, allowing the possibility to capture more accurately the performance of the therapies in the early phase of the disease, where relapse rates are notably higher, as in the short-duration RCT data provided by the manufacturers. In the absence of such data a balance must be struck between the potential underestimate of treatment in the early stages of the disease and the overestimate of the value of maintenance therapy in longer established disease.

Conceptually, the cost-effectiveness model developed was an expanded version of a four-state Markov model. At any time and on any given treatment, a patient was in remission, in relapse, undergoing surgery or in post-surgery remission. For ease of identification, each state is identified by a prefix showing the type of treatment received be it SC, maintenance (MNT – in this chapter only when referring to the Markov model) or induction (IND – in this chapter only when referring to the Markov model). For example, those who received SC therefore occupied states SC remission, SC relapse, SC surgery or SC post-surgery remission within the Markov model. *Figure 40* shows the basic structure of the SC model.

The models for induction and maintenance treatments were conceptually similar: each involved one set of states for anti-TNF treatment and another for SC treatments (where necessary). For IND there were three treatment-related states – remission and surgery-related (IND remission, IND surgery, IND post-surgery remission). There were also two relapse states, one for each 4-week period in which response was assessed (IND relapse and IND relapse 2). Those failing to respond to treatment after 8 weeks of continued relapse (i.e. passing through both IND relapse and then IND Relapse 2) transited to the SC states (SC remission, SC relapse, SC surgery, SC post-surgery remission). In order to correctly assign anti-TNF costs, this occurred through a temporary transition state which was identical to SC relapse in its transition probabilities and utility and which only differed in its costs. Maintenance treatment used the same structure as induction.

Transition probabilities for the SC states were based on the Silverstein *et al.*[26] cohort and the derivation process is detailed in *Standard care transition probabilities*. Transition probabilities for the IND model assigned a treatment effect by using relapse to remission probabilities from RCT evidence. Transition probabilities for the MNT model assigned the treatment effect by using the this same relapse to remission data and, by inference, a lower remission to relapse rate. Details of the derivation of IND and MNT models are given in *Induction transition probabilities and Maintenance transition probabilities* below.

Standard care transition probabilities

The population of interest for this appraisal was an inclusive one, rather than the tightly defined populations often found in clinical trials. Therefore, it was important to identify evidence from a population cohort that included patients who were resistant to standard therapy. It was also important the cohort reported data from the time before the advent of biological therapy.

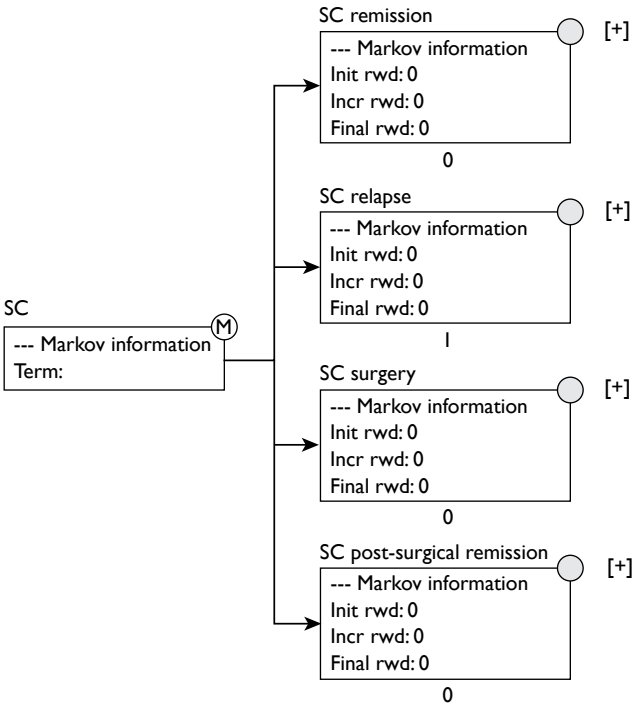

FIGURE 40 Schematic of SC arm of de novo cost-effectiveness model. Incr, incremental; Init, initial; rwd, reward.

The frequently cited study by Silverstein *et al.*,[26] as mentioned above, met these criteria. This study reported a 2-monthly transition matrix estimated from 20 years' follow-up of an inception cohort of 174 patients. Patients were characterised as being in one of eight states: remission, mild, drug-responsive, drug-dependent, drug-refractory, surgery, post-surgery remission and death. *Figure 41* shows a schematic of Silverstein *et al.*'s[26] Markov model.

As the model did not include death as a state, this had to be removed from the Silverstein *et al.*[26] matrix when estimating transition probabilities. A relationship existed between the SC remission and SC relapse states and the Silverstein *et al.*[26] states for mild disease (mild) and active disease (drug-dependent, drug-responsive, drug-refractory). Within Silverstein *et al.*,[26] patients were effectively managed with non anti-TNF treatments in both the drug-dependent and drug-responsive states; these states were therefore combined to form the SC remission state. In contrast, in the drug-refractory state, the patient was not effectively managed by treatment

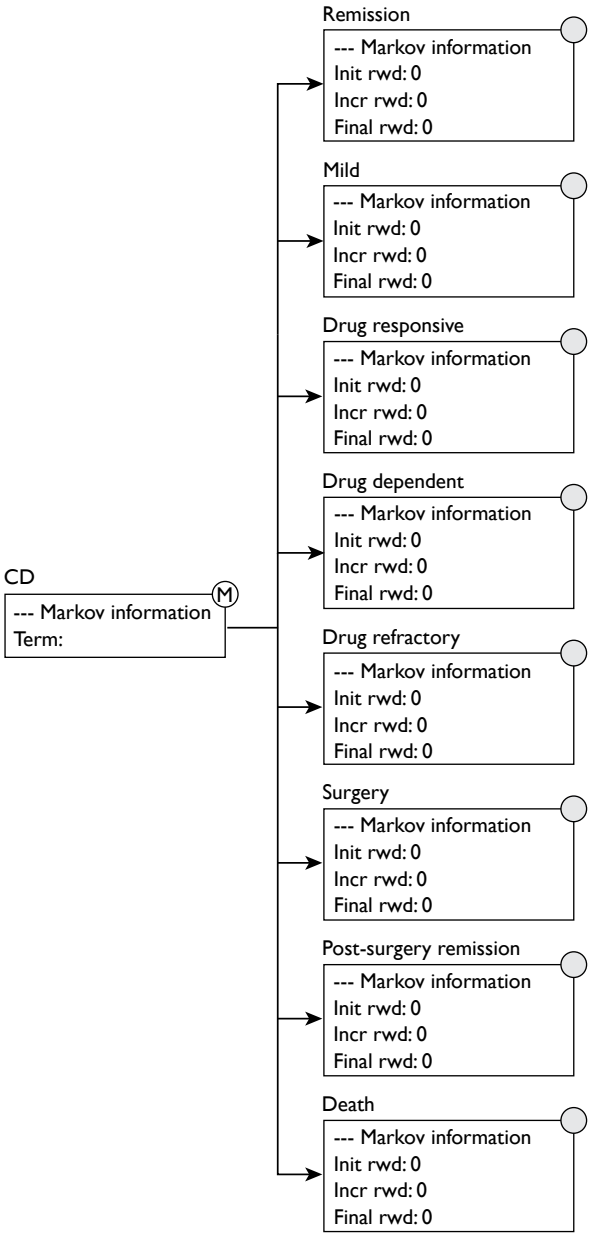

FIGURE 41 Schematic of Silverstein *et al.*'s[26] clinical classification. Incr, incremental; Init, initial; rwd, reward.

and was not responding to SC. It was this group who were candidates for anti-TNF treatment and hence this group was used to form the SC relapse state. The process for removing mild and death states from the Silverstein *et al.*[26] model was slightly more complex and appears below. The four-state matrix: remission, relapse, surgery and post-surgery remission was derived using the following steps.

Begin with the Silverstein *et al.*[26] transition matrix. Reprinted with permission from Elsevier.

Silverstein* et al.[26] *original – 2-month transition probabilities

	Remission	Mild	Drug-responsive	Drug-dependent	Drug-refractory	Surgery	Post-surgery	Death
Remission	0.89688	0.07016	0.00939	0.00639	0.00363	0.00793	0.00395	0.00167
Mild	0.05751	0.90952	0.00829	0.00619	0.00968	0.00585	0.00281	0.00015
Drug-responsive	0.25261	0.2217	0.41262	0.02563	0.00817	0.04569	0.02733	0.00626
Drug-dependent	0.05274	0.03484	0.00193	0.88626	0.00592	0.01071	0.00543	0.00217
Drug-refractory	0.06174	0.05888	0.00392	0.02599	0.74207	0.06435	0.03466	0.00839
Surgery	0.00657	0.06906	0.00801	0.03421	0.02397	0.33714	0.52022	0.00082
Post-surgery	0.00054	0.00849	0.001	0.00152	0.00096	0.00436	0.98126	0.00187
Death	0	0	0	0	0	0	0	0

Step 1: Removing death. It was supposed that death from all states was equally likely. The chance of death in each (t0) state was divided by six and this was added to the six non-mild, non-death states.

Step 1 – Identify and assign increase in probabilities following the removal of the death state

Uses original Silverstein* et al.[26] *matrix, without mild or dead

	Remission	Mild	Drug-responsive	Drug-dependent	Drug-refractory	Surgery	Post-surgery	Death
Remission	0.00028	–	0.00028	0.00028	0.00028	0.00028	0.00028	–
Mild	–	–	–	–	–	–	–	–
Drug-responsive	0.00104	–	0.00104	0.00104	0.00104	0.00104	0.00104	–
Drug-dependent	0.00036	–	0.00036	0.00036	0.00036	0.00036	0.00036	–
Drug-refractory	0.00140	–	0.00140	0.00140	0.00140	0.00140	0.00140	–
Surgery	0.00014	–	0.00014	0.00014	0.00014	0.00014	0.00014	–
Post-surgery	0.00031	–	0.00031	0.00031	0.00031	0.00031	0.00031	–
Death	–	–	–	–	–	–	–	–

Step 2: Removing the mild state. A more complex process was used for the mild state. Here, the issue was not now where one entered the state from, but where one would exit to after leaving mild.

2.1. Each of the non-death transition probabilities out of mild were deflated (subtract?) by the total chance of leaving the mild state (0.090). These probabilities for the exit state for mild were: remission, 0.636; drug-responsive, 0.092; drug-dependent, 0.068; drug-refractory, 0.107; surgery, 0.065; and post-surgery recovery, 0.031.
2.2. These exit probabilities were multiplied by the chance of entering mild from each of the other initial health states (t0) and used to distribute the probabilities. Here, the chance of a person in remission remaining in remission increased by 0.070 (the chance of leaving for mild) × 0.636 (the chance of moving from mild to remission).
2.3. The initial Silverstein *et al.*[26] transition probabilities were increased by the probabilities in (2.1) and (2.2).

Step 2 – Identify and assign increase in probabilities following the removal of the death state, and apply both increases

2.1 Identify transitions out of mild from Silverstein* et al.[26] *matrix excluding death

	Remission	Mild	Drug-responsive	Drug-dependent	Drug-refractory	Surgery	Post-surgery	Death
1. Mild	0.05751	0.90952	0.00829	0.00619	0.00968	0.00585	0.00281	–
2. Mild (excluding mild → mild)	0.63667	–	0.09177	0.06853	0.10716	0.06476	0.03111	–

***2.2 Identify increase in probability using row 2 above, the row-specific transition to mild in Silverstein* et al.[26]**

	Remission	Mild	Drug-responsive	Drug-dependent	Drug-refractory	Surgery	Post-surgery	Death
Remission	0.04467	–	0.00644	0.00481	0.00752	0.00454	0.00218	–
Mild	–	–	–	–	–	–	–	–
Drug-responsive	0.14115	–	0.02035	0.01519	0.02376	0.01436	0.00690	–
Drug-dependent	0.02218	–	0.00320	0.00239	0.00373	0.00226	0.00108	–
Drug-refractory	0.03749	–	0.00540	0.00403	0.00631	0.00381	0.00183	–
Surgery	0.04397	–	0.00634	0.00473	0.00740	0.00447	0.00215	–
Post-surgery	0.00541	–	0.00078	0.00058	0.00091	0.00055	0.00026	–
Death	–	–	–	–	–	–	–	–

2.3 Identify modified Silverstein* et al.[26] *matrix using increases from Step 1 and Step 2.2 matrices

	Remission	Mild	Drug-responsive	Drug-dependent	Drug-refractory	Surgery	Post-surgery	Death
Remission	0.94183	–	0.01611	0.01148	0.01143	0.01275	0.00641	–
Mild	–	–	–	–	–	–	–	–
Drug-responsive	0.39480	–	0.43401	0.04187	0.03297	0.06109	0.03527	–
Drug-dependent	0.07528	–	0.00549	0.88901	0.01002	0.01333	0.00688	–
Drug-refractory	0.10063	–	0.01072	0.03142	0.74978	0.06956	0.03789	–
Surgery	0.05067	–	0.01448	0.03908	0.03151	0.34175	0.52250	–
Post-surgery	0.00626	–	0.00209	0.00241	0.00218	0.00522	0.98184	–
Death	–	–	–	–	–	–	–	–

Step 3. The drug-responsive state has Markov probabilities summing to 1.00001 due to rounding error in the original paper. These have now been corrected.

Step 3 – Correct for summation error in drug-responsive (no changes to five decimal places in matrix)

	Remission	Mild	Drug-responsive	Drug-dependent	Drug-refractory	Surgery	Post-surgery	Death
Remission	0.94183	–	0.01611	0.01148	0.01143	0.01275	0.00641	–
Mild	–	–	–	–	–	–	–	–
Drug-responsive	0.39480	–	0.43401	0.04187	0.03297	0.06109	0.03527	–
Drug-dependent	0.07528	–	0.00549	0.88901	0.01002	0.01333	0.00688	–
Drug-refractory	0.10063	–	0.01072	0.03142	0.74978	0.06956	0.03789	–
Surgery	0.05067	–	0.01448	0.03908	0.03151	0.34175	0.52250	–
Post-surgery	0.00626	–	0.00209	0.00241	0.00218	0.00522	0.98184	–
Death	–	–	–	–	–	–	–	–

Step 4. Steps 1–3 produce a matrix in six states. The states remission, drug-responsive, and drug-dependent were then combined into a single remission state.

4.1. The chance of being in any one of these states was assessed using figures in Silverstein *et al.*[26] Of the three states, there was an 89.1% chance of being in remission, a 2.1% chance of being in a drug-responsive state, and an 8.8% chance of being in a drug-dependent state.
4.2. The chance of remaining in the (broader) remission state was calculated as the average of the chance of moving to any of the three earlier states from the three earlier states, weighted by the 89.1%, 2.1% and 8.8% from (4.1).
4.3. The chance of moving from this (broader) remission state to a relapse, surgical or post-surgery state was also taken as a similar weighted average.
4.4. The chance of transiting to the (broader) remission state was calculated as the sum of the probabilities of the earlier states comprising the (broader) remission state.

Step 4 – Combine states for remission, drug-responsive and drug-dependent into a single state

4.1 Identify chances of being in each state from Silverstein et al.[26]

	Remission	Mild	Drug-responsive	Drug-dependent	Drug-refractory	Surgery	Post-surgery	Death
Time spent in states (total person-years)	737.38	471.35	17.53	72.50	37.37	26.95	570.08	–
Selected states (total person-years)	737.38	–	17.53	72.50		–	–	–
Probability of being in state	89.12%	–	2.12%	8.76%	–	–	–	–

Identify total chances of remaining in any remission-type state

	Remission	Mild	Drug-responsive	Drug-dependent	Drug-refractory	Surgery	Post-surgery	Death
Remission	0.96941	–	–	–	0.01143	0.01275	0.00641	–
Mild	–	–	–	–	–	–	–	–
Drug-responsive	0.87067	–	–	–	0.03297	0.06109	0.03527	–
Drug-dependent	0.96978	–	–	–	0.01002	0.01333	0.00688	–
Drug-refractory	0.14277	–	–	–	0.74978	0.06956	0.03789	–
Surgery	0.10424	–	–	–	0.03151	0.34175	0.52250	–
Post surgery	0.01076	–	–	–	0.00218	0.00522	0.98184	–
Death	–	–	–	–	–	–	–	–

4.2, 4.3, 4.4 Apply chances of being in each state from Silverstein et al.[26] *to weight outcomes*

	Remission	Mild	Drug-responsive	Drug-dependent	Drug-refractory	Surgery	Post-surgery	Death
Remission	0.96735	–	–	–	0.01176	0.01383	0.00706	–
Mild	–	–	–	–	–	–	–	–
Drug-responsive	–	–	–	–	–	–	–	–
Drug-dependent	–	–	–	–	–	–	–	–
Drug-refractory	0.14277	–	–	–	0.74978	0.06956	0.03789	–
Surgery	0.10424	–	–	–	0.03151	0.34175	0.52250	–
Post-surgery	0.01076	–	–	–	0.00218	0.00522	0.98184	–
Death	–	–	–	–	–	–	–	–

Step 5. This gave a matrix in four states (remission, relapse, surgery and post-surgery remission) for 2-monthly cycles. This was modified to form a 4-week transition matrix by halving the figures off the main diagonal and setting the diagonal entries to one minus the remaining values in each row.

Step 5 – Transform to 1-month transition probabilities

	Remission	Mild	Drug-responsive	Drug-dependent	Drug-refractory	Surgery	Post-surgery	Death
Remission	0.98368	–	–	–	0.00588	0.00691	0.00353	–
Mild	–	–	–	–	–	–	–	–
Drug-responsive	–	–	–	–	–	–	–	–
Drug-dependent	–	–	–	–	–	–	–	–
Drug-refractory	0.07139	–	–	–	0.87489	0.03478	0.01894	–
Surgery	0.05212	–	–	–	0.01575	0.67087	0.26125	–
Post-surgery	0.00538	–	–	–	0.00109	0.00261	0.99092	–
Death	–	–	–	–	–	–	–	–

Step 6. Reformat the table and add evidence review group health-state labels to give the final transition matrix used in the evidence review group analysis.

Step 6 – Apply labels and reformat

	SC remission	SC relapse	SC surgery	SC post-surgery remission
SC remission	0.98368	0.00588	0.00691	0.00353
SC relapse	0.07139	0.87489	0.03478	0.01894
SC surgery	0.05212	0.01575	0.67087	0.26125
SC post-surgery remission	0.00538	0.00109	0.00261	0.99092

Steps 1–5 created the transition matrix in *Table 51*, which was used to model SC in both the main SC model and the submodels for maintenance and induction care where patients transit to SC.

These probabilities were used for both severe and moderate disease. The clinical course framework described above did not differentiate between these two states and it was not clear how a mild/moderate division could have been placed upon the active disease patients reported in Silverstein *et al.*[26] The implicit assumption was that SC treatments were equally likely to achieve remission in moderate and severe disease.

Similar to the Silverstein *et al.*[26] analysis, the matrix included transitions to post-surgery remission from relapse and remission states. These transitions were most likely to be an artefact of the maximum likelihood method used to estimate the Silverstein *et al.*[26] transition matrix. Silverstein *et al.*[26] did not report complication rates from surgery and thus it was not included as a state in the model here. As the number of these types of transitions were small, it was not considered here to have substantially weakened the Silverstein *et al.*[26] study as the preferred basis for modelling SC.

Induction transition probabilities

The main difference between the transition matrices for SC and IND was the probability of transiting from relapse to remission. In the SC model, there was a 7.13% chance of a person starting the period in the SC remission state moving to SC relapse at the end of one cycle.

Effectiveness for infliximab and adalimumab treatment were derived from ACCENT I[2,3] and CHARM,[67] respectively. Neither trial reported 4-week outcomes, and 6-week outcomes were used here as highly favourable estimates of efficacy. At 6 weeks, 63/113 patients in the infliximab 5 mg/kg groups (see *Figure 13*) and 96/172 patients in the adalimumab 40-mg e.o.w. groups (see *Figure 22*) were in remission. For both groups, this 6-week effectiveness represented a peak efficacy which fell thereafter. Distributions based on these figures were used to estimate the transition probability from IND relapse to IND remission.

Table 52 shows the IND transition matrix, where the response rate (RESP in the table) is the estimated transition probability for the respective anti-TNF treatment. All individuals started in IND relapse, and those who were to remain in relapse moved to the second relapse state (IND relapse 2). Those who were to remain in relapse for a third 4-week period were deemed non-responders and entered the transitional state. In this state, a patient received SC and had transition probabilities corresponding to the SC relapse state. Following this, the patient remained solely in SC (the SC states).

In the probabilistic sensitivity analysis, the response variables (ACCENT_response, CHARM_response) were modelled using the beta distributions, using the values for the effectiveness estimates outlined in *Table 53*.

Figure 42 shows the effectiveness of infliximab per period under the highly favourable estimates used here, with *Figure 43* showing the equivalent figures for adalimumab. The mean value for both distributions was similar, with slightly less uncertainty in the CHARM[67] data.

Maintenance transition probabilities

Given that the initial doses in trials were identical between induction and maintenance treatment, it would be expected that maintenance would have had the same initial (and subsequent) effectiveness in increasing the relapse to remission rate as induction treatment. Maintenance treatment was expected to have an additional effect, however, in reducing the

TABLE 51 SC transition matrix

	SC remission	SC relapse	SC surgery	SC post-surgery remission
SC remission	0.9837	0.0059	0.0069	0.0035
SC relapse	0.0713	0.8749	0.0348	0.0189
SC surgery	0.0521	0.0158	0.6709	0.2613
SC post-surgery remission	0.0054	0.0011	0.0026	0.9909

probability of an individual relapsing from a remitted state. Ideally, RCT evidence from ACCENT I[2,3] and CHARM[67] would have included separate remission to relapse and relapse to remission rates. In the absence of this information the inverse of the relapse to remission rate was applied to the remission to relapse SC transition probability. Thus, as anti-TNF maintenance therapy was assumed to give about eight times the chance of entering remission from relapse (56% against 7%), the model assumed that there was one-eighth the chance of relapsing among patients in remission. These values changed depending on the precise value of the response variables (ACCENT_response and CHARM_response) in each iteration of the model. Thus, if the response variable was RESP, then the relative effectiveness in obtaining remission was RESP/0.0713, and the expected MNT remission to MNT relapse rate was 0.0059/(RESP/0.0713).

So here, the incremental benefit of maintenance treatment over induction treatment was expected to be a reduction in the probability of relapse from remission states (MNT remission and MNT post-surgery remission). While the chance of relapse from MNT remission was expected to be very small (0.0059 per period) in the base-case analysis, this baseline probability was increased in one-way sensitivity analyses reported below. Barring labelling, the MNT transition matrix (*Table 54*) was identical to the IND transition matrix except in two cells: the probability of relapse from remission and the probability of relapse from post-surgery remission.

TABLE 52 IND transition matrix

	IND remission	IND relapse	IND relapse 2	Transitional	IND surgery	IND post-surgery remission	SC remission	SC relapse	SC surgery	SC post-surgical remission
IND remission	0.9837	0.0059			0.0069	0.0035				
IND relapse	RESP		#		0.0348	0.0189				
IND relapse 2	RESP			#	0.0348	0.0189				
Transitional							0.0713	0.8749	0.0348	0.0189
IND surgery	0.0521	0.0158			0.6709	0.2613				
IND post-surgery remission	0.0054	0.0011			0.0026	#				
SC remission							SC transition matrix – *Table 51*			
SC relapse										
SC surgery										
SC post-surgery remission										

RESP represents either ACCENT_response (infliximab) or CHARM_response (adalimumab).
Shaded cells represent unused transitions.

TABLE 53 Probability distributions for effectiveness estimates

Anti-TNF	Source	Mean	Variable and distribution
Infliximab	Peak (6 weeks) effectiveness from ACCENT I 5 mg/kg arm *Figure 13*	55.7%	ACCENT_response Beta; $\alpha = 63$, $\beta = 50$
Adalimumab	Peak (6 weeks) effectiveness from CHARM 40-mg e.o.w. arm *Figure 22*	55.8%	CHARM_response Beta; $\alpha = 96$, $\beta = 76$

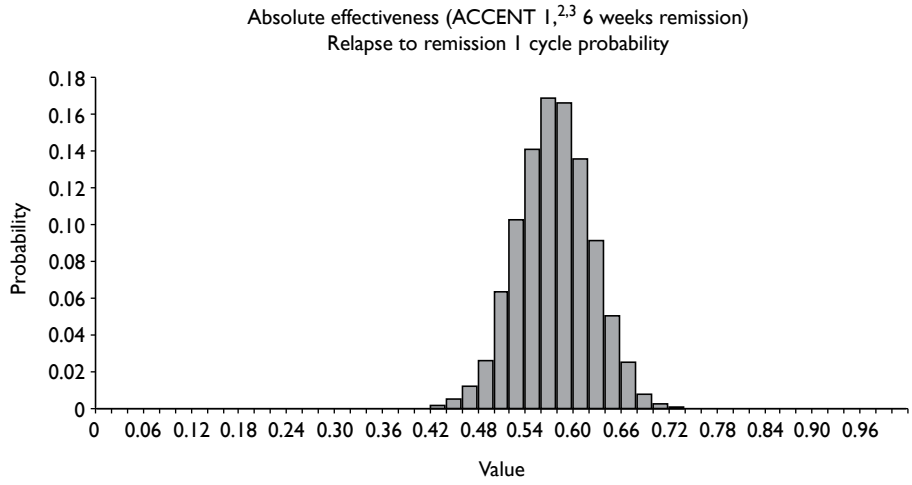

FIGURE 42 Infliximab effectiveness ($n = 113$).

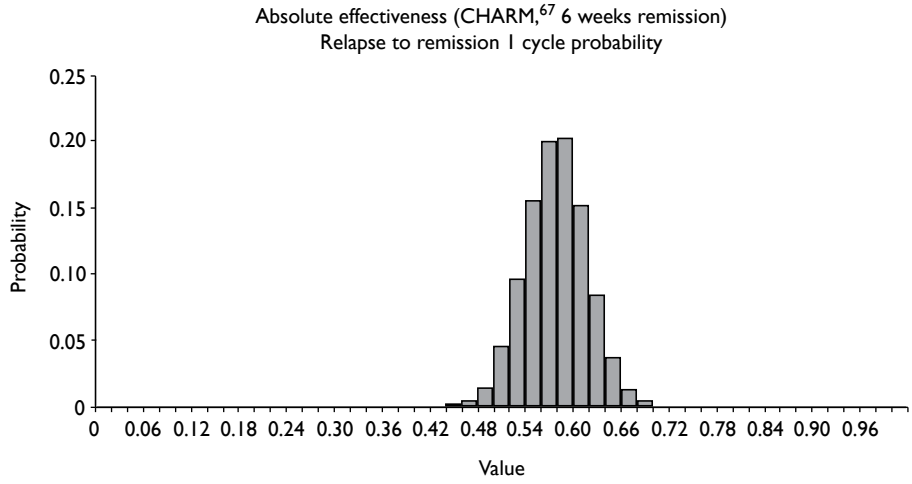

FIGURE 43 Adalimumab effectiveness ($n = 172$).

Utilities

Table 55 shows the utility distributions associated with each modelled state. Most utilities were derived from a widely cited study of HRQoL in CD.[78] While this study did not meet the reference case specification in the NICE methods guide,[93] in the absence of an alternative study that did meet these criteria, it had the desirable characteristics of providing values derived from a choice-based method (time trade-off), being a well-conducted study and providing utility values for differing severities of disease – the type of data required for this analysis. The only states where utility values were not available concerned surgery, and in the absence of published estimates it was assumed that the average utility for individuals in the major surgery state would be equivalent to EQ-5D state 22222 with utility weight of 0.516.

It is possible that the choice of method used to value health states will affect the results of the analysis and increase uncertainty in the results. In this instance, the time trade-off method was selected as this has some methodological consistency with the EQ-5D where EQ-5D results are not available. The difference in the health-state utilities obtained by different methods is a well-known phenomenon and is not, as far as we are aware, a function of the clinical condition

TABLE 54 Maintenance transition matrix

	MNT remission	MNT relapse	MNT relapse 2	Transitional	MNT surgery	MNT post-surgery remission	SC remission	SC relapse	SC surgery	SC post-surgical remission
MNT remission	0.9837	Rel 1			0.0069	0.0035				
MNT relapse	RESP		#		0.0348	0.0189				
MNT relapse 2	RESP			#	0.0348	0.0189				
Transitional							0.0713	0.8749	0.0348	0.0189
MNT surgery	0.0521	0.0158			0.6709	0.2613				
MNT post-surgery remission	0.0054	Rel 2			0.0026	#				
SC remission							SC transition matrix – *Table 51*			
SC relapse										
SC surgery										
SC post-surgery remission										

RESP represents either ACCENT_response (infliximab) or CHARM_response (adalimumab).
Rel 1 = 0.0059/(RESP/0.0713).
Rel 2 = 0.0011/(RESP/0.0713).
Shaded cells represent unused transitions.

under consideration. Rather it reflects methodological uncertainty, not parameter uncertainty. Inflating parameter uncertainty to reflect methodological uncertainty would be methodologically inappropriate and so is not done here. This is not recommended in either the 2004[104] or 2008[93] edition of the NICE methods guide. Indeed, we are not aware of any guide to good practice in economic evaluation that has recommended this, nor are we aware of any methodological paper describing how it might be done if it were deemed to be a desirable thing to do.

Utility values per cycle were calculated by taking the annual utility value and dividing by the number of cycles (13) run by the model. The mean values reported in *Table 55* show the per cycle utility associated with each health state along with the distribution used to capture the uncertainty in these estimates. Although in some cases these values may appear high when taken at face value, it is useful to consider how these should be interpreted. In a standard gamble context, respondents giving this value would accept a one in four chance of death for a procedure that returned them to full health. In a time trade-off context, given a life expectancy of 10 years they would give up slightly over 2.5 years in order to be returned to full health. When looked at from this perspective, these values are not necessarily extremely high or of questionable validity but rather reflect patient views on how this illness, which is not life-threatening, affects their day-to-day life.

Anti-TNF costs

In order to identify the initial (and reinduction) cost of anti-TNF treatments it was necessary to consider the induction drug regimen under each anti-TNF for both induction and maintenance treatments. Where relapse occurred at week 0:

- For infliximab treatment, induction (infliximab IND) involved a loading dose comprising treatment at 0, 2 and 6 weeks at 5 mg/kg (a loading dose) irrespective of response status at 4 weeks.
- Infliximab maintenance treatment (infliximab MNT) also involved the same treatment at 0, 2 and 6 weeks, but with additional doses at weeks 14 and 20 and every subsequent 8 weeks for those entering remission (except in the case of subsequent relapse).
- Adalimumab induction (adalimumab IND) involved a loading dose of 80 mg at week 0 and 40 mg at week 2, with no further treatment.
- Adalimumab maintenance (adalimumab MNT) involved the induction loading doses at weeks 0 and 2, with additional doses of 40 mg at weeks 4 and 6 regardless of response at week 4 (i.e. in either MNT remission or MNT relapse 2).

Infliximab administration costs were taken from a previous HTA report,[99] at £257.50 per treatment. For a single infliximab treatment, total costs were £1936.42 (assuming four 100-mg vials at £419.73 plus administration costs of £257.50). This was received three times in induction, so infliximab IND costs £5809.26 per relapse set against the IND relapse state. There were no anti-TNF costs levied in any other state within the infliximab IND arm.

For infliximab maintenance, each standard dose after induction provided treatment for 8 weeks, so that the standard cost (post induction, pre relapse) was therefore £968.21 each 4 weeks (0.5 × £1936.42). Following induction (or reinduction given relapse), the first treatment post induction occurred at 14 weeks, so that treatment following relapse could be thought of as purchasing 14 weeks' worth of treatment. This was 10 weeks beyond what would normally be purchased in a 4-week period. Hence, the cost of relapse for maintenance was reduced by the equivalent of 2.5 4-weekly charges. MNT relapse infliximab costs were then £3388.74 [£5809.26 – (2.5 × £968.21)]. MNT remission, MNT post-surgery remission and MNT relapse 2 were all allocated the standard 4-week costs, while it was assumed that no infliximab was received in a 4-week period where surgery occurred. If a patient failed to respond within 8 weeks of treatment for a relapse, he or she entered the transitional state. Here, 8 weeks' worth of relapse costs have been previously paid, leaving 6 weeks of unallocated treatment costs (£1452.32) which were set against the transitional state before entering the normal SC states.

For an adalimumab induction arm, three 40-mg doses were assumed to be given, at a cost of £357.50 per dose, so that IND relapse cost £1072.50. No administration costs were included in this value, and no state other than IND relapse incurred an anti-TNF cost. For an adalimumab maintenance arm, all induction doses were incurred within 4 weeks, so that MNT relapse also

TABLE 55 Health-state utility distributions per cycle

Type	States	Variable and distribution
All remission states	SC remission, IND remission, MNT remission, SC post-surgery remission, IND post-surgery remission, MNT post-surgery remission	utility_remission Normal; mean = 0.073, SD = 0.00801
Relapse states (severe disease)	SC relapse, IND relapse, IND relapse 2, MNT relapse, MNT relapse 2, transitional	utility_severe_relapse Normal; mean = 0.056, SD = 0.0012
Relapse states (moderate disease)	SC relapse, IND relapse, IND relapse 2, MNT relapse, MNT relapse 2, transitional	utility_moderate_relapse Normal; mean = 0.068, SD = 0.0012
Surgery states	SC surgery, IND surgery, MNT surgery	utility_surgery Normal; mean = 0.039, SD = 0.0012

Utilities calculated as 1/13 of quality of life values from Gregor *et al.*[78]

incurred £1072.50 in anti-TNF costs. MNT relapse 2, MNT remission and MNT post-surgery remission all required two 40-mg doses of adalimumab (£715). Transitional, MNT surgery, and all SC states involved no anti-TNF costs.

Total health-state costs

The model was developed from an NHS/PSS perspective, as per the NICE reference case.[93] Direct NHS costs were modelled as the sum of anti-TNF costs and type-specific health-state costs; no costs related to PSS were identified as part of the modelling process. Where possible, these health-state costs were taken from the NHS Reference Cost database 2005–6.[105] The reference costs for surgery were modelled as the cost of inpatient IBD interventions, while moderate and severe relapse costs were modelled as the cost of IBD outpatient major and intermediate interventions. Post-surgery remission costs were based on outpatient surgical gastrointestinal follow-up. Relapse costs were based on a gastrointestinal admission to hospital. Remission costs were modelled using Bassi *et al.*[37] and indexed using the PSSRU NHS Pay and Prices Index.[103] The Bassi *et al.*[37] cost for quiescent CD was used as the cost for the remission state.

Distributions for the probabilistic sensitivity analysis were found by identifying the mean and SD of each state. For the database-derived costs, an SD was inferred from the IQR assuming normality. From here, gamma distributions were derived using parameters $\alpha = \frac{\mu^2}{s^2}, \lambda = \frac{\mu}{s^2}$. Mean costs and probabilistic sensitivity analysis distributions for each health state are given in *Table 56*.

Overall, total costs for each state were defined by drug costs (fixed) plus the costs for the corresponding SC state (drawn from the relevant distribution). Non-hospitalisation medical costs were not included in the model except in the administration of infliximab. *Table 57* presents mean total costs for each state to the nearest pound for IND and MNT states, with equivalent costs for SC states given in *Table 56* (note: anti-TNF costs are zero).

Probabilistic sensitivity analysis

Monte Carlo simulation was used to estimate the expected mean costs and effects for SC and each intervention. Each analysis used 10,000 simulations. For each cost-effectiveness analysis the following variables were included in the multivariate probabilistic sensitivity analysis:

- utilities in remission, relapse, surgery and post-surgery remission (see *Table 53*)
- effectiveness of anti-TNF therapy (see *Table 55*)
- direct health-care costs in remission, relapse, surgery and surgical remission (see *Table 56*).

TABLE 56 Type-specific health-state costs

Type	States	Mean cost (£)	Variable and distribution
Remission states	SC remission, IND remission, MNT remission,	52	cost_remission Gamma; $\alpha = 182.43$, $\lambda = 3.51$
Relapse states (severe disease)	SC relapse, IND relapse, IND relapse 2, MNT relapse, MNT relapse 2, transitional	1489	cost_severe_relapse Gamma; $\alpha = 1406.01$, $\lambda = 0.944$
Relapse states (moderate disease)	SC relapse, IND relapse, IND relapse 2, MNT relapse, MNT relapse 2, transitional	474	cost_moderate_relapse Gamma; $\alpha = 1826.81$, $\lambda = 3.85$
Surgery states	SC surgery, IND surgery, MNT surgery	4592	cost_surgery Gamma; $\alpha = 1232.50$, $\lambda = 0.26$
Post-surgery states	SC post-surgery remission, IND post-surgery remission, MNT post-surgery remission	72	cost_surgical_remission Gamma; $\alpha = 349.74$, $\lambda = 4.86$

The probabilistic sensitivity analysis was partial and did not include uncertainties in either the Silverstein *et al.*[26] transition matrix or anti-TNF costs. Additional one-way sensitivity analyses are detailed in *Sensitivity analyses*. CEACs were calculated for induction and maintenance therapies in moderate and severe disease.

Results

Table 58 gives the mean costs and QALYs and expected cost-effectiveness ratios and ICERs for each intervention in induction and maintenance therapy for those suffering from moderate and severe CD.

Cost-effectiveness acceptability curves

For patients with severe disease, infliximab induction treatment was found to be cost-effective relative to maintenance treatment and SC in over 99% of cases at all points up to £100,000 per QALY. Likewise, adalimumab induction treatment was found to be cost-effective relative to maintenance treatment and SC for thresholds up to £100,000 per QALY. Given that these diagrams are relatively uninformative, they are not displayed. *Figures 44* and *45* show the CEACs for induction and maintenance therapies for infliximab and adalimumab respectively in patients with moderate disease.

Sensitivity analyses

The de novo cost-effectiveness model used probabilistic sensitivity analysis to characterise the uncertainty in the clinical and cost data. This is a widely accepted method for addressing uncertainty in decision analysis modelling and is the preferred method according to the NICE reference case.[93] In some cases, insufficient information was available to estimate the uncertainty

TABLE 57 Total costs by health state (all costs in pound sterling)

	Infliximab			Adalimumab		
	State costs	Drug costs	Total costs	State costs	Drug costs	Total costs
IND remission	52	0	52	52	0	52
IND relapse (severe disease)	1489	5809	7298	1489	1073	2562
IND relapse 2 (severe disease)	1489	0	1489	1489	0	1489
Transitional (severe disease)	1489	0	1489	1489	0	1489
IND relapse (moderate disease)	474	5809	6283	474	1073	1547
IND relapse 2 (moderate disease)	474	0	474	474	0	474
Transitional (moderate disease)	474	0	474	474	0	474
IND surgery	4592	0	4592	4592	0	4592
IND post-surgery remission	72	0	72	72	0	72
MNT remission	52	968	1020	52	715	767
MNT relapse (severe disease)	1489	3389	4878	1489	715	2204
MNT relapse 2 (severe disease)	1489	968	2457	1489	715	2204
Transitional (severe disease)	1489	1452	2941	1489	0	1489
MNT relapse (moderate disease)	474	3389	3863	474	715	1189
MNT relapse 2 (moderate disease)	474	968	1442	474	715	1189
Transitional (moderate disease)	474	1452	1926	474	0	474
MNT surgery	4592	0	4592	4592	0	4592
MNT post-surgery remission	72	968	1040	72	715	787

TABLE 58 Cost-effectiveness of anti-TNFs in CD

	Costs (£)		QALYs			
	Mean	SD	Mean	SD	CER vs SC	ICERs
Severe disease						
SC	13,415	278	0.8119	0.0455	–	Dominated
Infliximab IND	12,051	488	0.8943	0.8193	Dominates	Baseline
Infliximab MNT	19,143	187	0.8957	0.0813	£68,315 per QALY	£5.03M per QALY
SC	13,421	283	0.8118	0.0457	–	Dominated
Adalimumab IND	7053	410	0.8942	0.0816	Dominates	Baseline
Adalimumab MNT	14,047	197	0.8956	0.0823	£7749 per QALY	£4.98M per QALY
Moderate disease						
SC	6615	117	0.8926	0.0454	–	Baseline
Infliximab IND	9573	202	0.9240	0.0813	£94,321 per QALY	£94,321 per QALY
Infliximab MNT	16,751	146	0.9245	0.0819	£317,991 per QALY	£13.9M per QALY
SC	6615	117	0.8922	0.0459	–	Dominated
Adalimumab IND	4583	175	0.9231	0.0818	Dominates	Baseline
Adalimumab MNT	11,657	95	0.9236	0.0824	£160,079 per QALY	£13.9M per QALY

CER, cost-effectiveness ratio.

surrounding a parameter value, therefore a series of scenario analyses were also undertaken in order to explore the consequences for the estimates of cost-effectiveness of changes in these values.

Stakeholders who commented on previous draft versions of this report noted that there were aspects of the model that they wished to see changed and, where appropriate, these changes have been made. Given that the focus of the NICE technology appraisal was on severe active CD (because of the licence indication of the drugs) and the cost-effectiveness of treatment in moderate disease is typically poor, these analyses concentrate on severe disease only. The results of all scenarios analyses and other suggested changes are given in the text of the following sections.

The base case was modified in several ways. The SC transition matrix was modified to allow the following:

- incorporation of different relapse rates from remission states
- consideration of the effect of 'implausible' transitions in the SC matrix
- provision of alternative transitions from the surgical states.

A further (fourth) analysis extended the time horizon of analysis up to 20 years. The fifth set of analyses modified the effectiveness estimates used in the base case. In the final set of analyses, infliximab dosages were adjusted according to patient weight in order to provide an analysis that may be relevant to a paediatric population, albeit with caveats as to the applicability of adult data to this population.

Following consultation on the draft report, another request was to consider an analysis of the cost-effectiveness of the anti-TNF agents based on the calculation of dosage using body surface area instead of weight. However, clinical expert advice suggested that there was little evidence

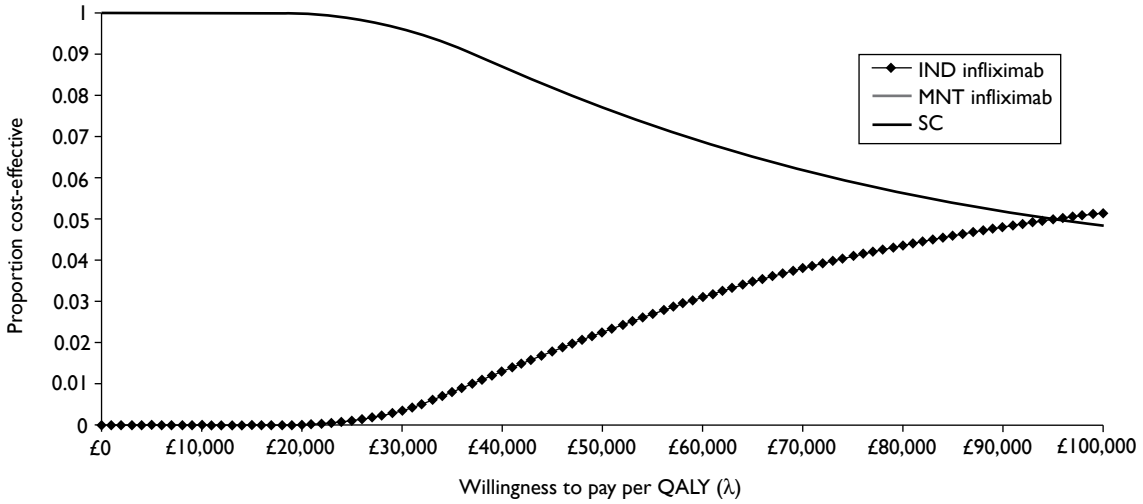

FIGURE 44 Cost-effectiveness acceptability curve for infliximab in moderate disease. Note: the MNT infliximab line runs along the *x*-axis, as at no stage on the scale of the figure is the likelihood of this treatment being cost-effective >0.

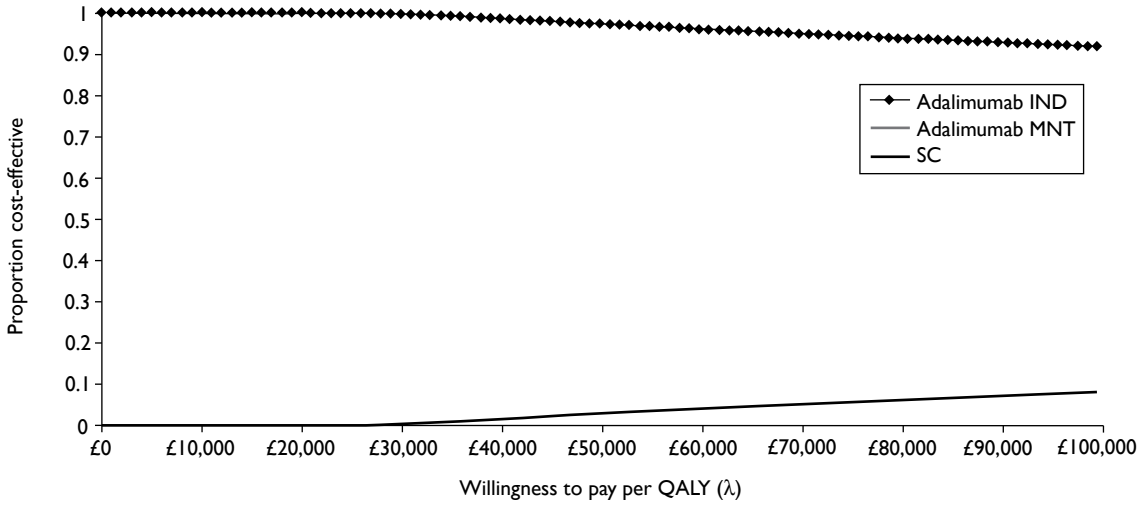

FIGURE 45 Cost-effectiveness acceptability curve for adalimumab in moderate disease. Note: the MNT adalimumab line runs along the *x*-axis, as at no stage on the scale of the figure is the likelihood of this treatment being cost-effective >0.

to suggest that dose scaling based on body surface area is likely to have an impact on the effectiveness of the treatment (Professor C Twelves, Cancer Research UK Leeds, 2008, personal communication). Moreover, because the clinical evidence that was available was based on doses calculated based on weight, there was no suggestion as to what the differential effectiveness would be, making such an analysis speculative at best and misleading at worst. Finally, as the cost-effectiveness estimates were based on a per vial cost, minor adjustments to the dose required would have been unlikely to shift those categories of treatments that were not cost-effective to being cost-effective, for the reasons discussed previously in the report.

Changes to the standard care matrix: relapse rates

The first set of sensitivity tests related to relapse rates in SC and, by extension, the other transition matrices. In the baseline case, there was a relatively small chance of relapse once remission was achieved. In 'standard' remission there was a 0.59% chance of relapse per 4-week period (SC remission to SC relapse) and a 1.6% chance of leaving remission for any reason. Following surgery, there was a 0.11% chance of relapse per 4-week period (SC post-surgery remission to SC relapse) and a 0.81% chance of leaving remission for any reason. These values characterise the risk of an average patient leaving remission within the Silverstein *et al.*[26] cohort.

For groups that had a higher risk of relapse than the Silverstein *et al.*[26] cohort, the transition matrices derived above will not necessarily characterise this risk. As the risk of relapse increases, the time a successfully treated patient spent in remission drops, therefore the general efficacy of anti-TNF treatments against SC would have been expected to fall. As relapse risk increased, the health benefits of maintenance over induction treatments would also have been expected to increase, as the benefit of maintenance was a proportionate reduction in this relapse risk – the higher the risk, the greater would be the absolute benefit of maintenance over induction.

Two different analyses were conducted in order to assess the importance of relapse risk. In the first, the SC remission to SC relapse rate ('sc_relapse') was increased. In the second, sc_relapse was changed and the post-surgery remission rate (SC post-surgery remission to SC relapse, 'ps_relapse') was also changed by the same proportion as sc_relapse (ps_relapse = sc_relapse × 0.0059/0.0011). Changes were made to all the relapse probabilities in all three transition matrices (SC, IND, MNT) for each anti-TNF to explore the impact of such changes.

Supposing that the level of relapse from standard remission was 10 times its original level of 0.59% (0.0059), if sc_relapse had a value = 0.0590, the average length of time in remission would drop from 4.68 years to 1.07 years. *Table 59* presents the cost-effectiveness of anti-TNFs in this analysis. Here, both infliximab and adalimumab induction therapy remained cost-effective versus SC, and neither maintenance therapy was generally cost-effective versus induction/reinduction therapy.

Neither of the maintenance treatments were cost-effective. However, at higher relapse rates – and shorter periods of expected remission – maintenance treatment may become cost-effective. *Table 60* shows the predicted cost-effectiveness of infliximab treatment as relapse rates were increased. The figures shown correspond to the final column of the tables above, identifying both the baseline treatment and the incremental cost-effectiveness of alternative treatments. For treatments that were dominated (directly or through extended dominance), the ICERs are not given but a line displayed.

For groups at relatively little risk of relapse, infliximab induction/reinduction appeared to be a cost-effective strategy. The additional benefit of maintenance was not cost-effective in these cases (ICER > £30,000/QALY).

Standard care became the most cost-effective treatment at the relapse rate between 0.075 and 0.100 (average remission lengths of 314 and 240 days). As the relapse rate increased further, obtaining QALYs with maintenance treatment became less expensive than with induction treatment. However, in none of the cases considered here did the cost-effectiveness ratio for infliximab maintenance fall below £30,000 per QALY. At very high risks of relapse, the ICERs for maintenance treatment even appeared to increase with the relapse rates, suggesting that even higher relapse rates were unlikely to provide clear cost-effectiveness.

TABLE 59 Standard care relapse at 0.0590 – 10 times original level

	Costs (£)		QALYs			
	Mean	SD	Mean	SD	CER vs SC	ICERs
SC	14,271	304	0.8020	0.0414	–	Baseline
Infliximab IND	15,492	405	0.8795	0.0751	£15,755 per QALY	£15,755 per QALY
Infliximab MNT	19,498	218	0.8920	0.0806	£58,078 per QALY	£320,480 per QALY
SC	14,268	300	0.8019	0.0416	–	Dominated
Adalimumab IND	8714	429	0.8799	0.0758	Dominates SC	Baseline
Adalimumab MNT	14,291	218	0.8925	0.0814	£254 per QALY	£442,619 per QALY

CER, cost-effectiveness ratio.

TABLE 60 Infliximab cost-effectiveness with changing relapse rates

		ICERs (£ per QALY)					
		sc_relapse only changing			Both relapse rates changing		
Relapse rate (SC)	Remission length	SC	Infliximab IND	Infliximab MNT	Infliximab SC	Infliximab IND	Infliximab MNT
0.025	2.13 years	–	**Baseline**	1,039,584	–	**Baseline**	1,017,400
0.05	1.24 years	Baseline	**10,041**	412,633	Baseline	**9955**	399,734
0.075	314 days	Baseline	**24,776**	204,973	Baseline	**24,550**	193,601
0.1	240 days	**Baseline**	39,264	101,100	**Baseline**	38,821	91,641
0.125	193 days	**Baseline**	–	49,892	**Baseline**	–	47,232
0.15	161 days	**Baseline**	–	48,137	**Baseline**	–	44,936
0.175	137 days	**Baseline**	–	46,702	**Baseline**	–	43,119
0.2	119 days	**Baseline**	–	45,587	**Baseline**	–	41,629
0.225	105 days	**Baseline**	–	44,793	**Baseline**	–	40,380
0.25	94 days	**Baseline**	–	44,195	**Baseline**	–	39,414
0.275	84 days	**Baseline**	–	43,812	**Baseline**	–	38,587
0.3	76 days	**Baseline**	–	43,621	**Baseline**	–	37,986
0.325	69 days	**Baseline**	–	43,481	**Baseline**	–	37,518
0.35	64 days	**Baseline**	–	43,503	**Baseline**	–	37,135
0.375	59 days	**Baseline**	–	43,634	**Baseline**	–	36,859
0.4	54 days	**Baseline**	–	43,866	**Baseline**	–	36,713
0.425	50 days	**Baseline**	–	44,148	**Baseline**	–	36,587
0.45	47 days	**Baseline**	–	44,559	**Baseline**	–	36,542
0.475	44 days	**Baseline**	–	44,967	**Baseline**	–	36,571
0.5	41 days	**Baseline**	–	45,408	**Baseline**	–	36,668

Bold values indicate cost-effective option at £30,000 per QALY.
– denotes that an option is dominated by one or more options.

In contrast, the similar efficacy and lower costs of adalimumab suggested a lesser role for SC. At all relapse rates, adalimumab IND dominated SC in all cases (up to sc_relapse = 0.500) regardless of whether or not the post-surgery remission rates were also modified. As a result, the relevant comparison was always between induction/reinduction treatment and maintenance treatment. Here, higher relapse rates placed increasing prominence on maintenance over induction treatment.

Table 61 presents the ICERs for the adalimumab treatment options. From standard relapse rates to high relapse rates, the adalimumab induction/reinduction treatment was cost-effective. Above this standard rate, maintenance treatment was first cost-effective and then dominated induction/reinduction. However, the relapse rate cut-off for such treatment appeared very high, and depended only slightly on whether post-surgery relapse rates also increased. Maintenance treatment may have been cost-effective for those who typically suffered severe relapses within 10 or 11 weeks. However, this group was expected to comprise only a very small proportion of CD patients.

Changes to the standard care matrix: removal of implausible transitions

The SC transition matrix presented in *Table 51* included four transitions to remission states that could be considered implausible. Those who have not had surgery (SC remission and SC relapse) would not transit to a post-surgery remission state; equally, those who have had surgery (SC surgery and SC post-surgery remission) would not move to a non-surgical remission state. The analyses were rerun with the SC matrix revised so that these transitions were no longer possible and any probability was reassigned to the expected remission state. For example, the SC surgery state originally had a 0.0521 probability of moving to the SC remission state and a 0.2613 chance of moving to the SC post-surgery remission state. Here, there was a 0.3134 chance (0.0521 + 0.2613) of moving to any remission state. *Table 62* shows the results of removing the implausible transitions (here there is no chance of moving to SC remission from SC surgery) and presents a modified SC matrix with a 0.3134 chance of moving to the (expected) SC post-surgery remission state.

TABLE 61 Adalimumab cost-effectiveness with changing relapse rates

		ICERs (£ per QALY)					
		sc_relapse only changing			Both relapse rates changing		
Relapse rate (SC)	Remission length	SC	Adalimumab IND	Adalimumab MNT	SC	Adalimumab IND	Adalimumab MNT
0.025	2.13 years	–	**Baseline**	1,133,765	–	**Baseline**	1,112,324
0.05	1.24 years	–	**Baseline**	532,789	–	**Baseline**	520,769
0.075	314 days	–	**Baseline**	333,906	–	**Baseline**	322,790
0.1	240 days	–	**Baseline**	234,236	–	**Baseline**	224,302
0.125	193 days	–	**Baseline**	174,035	–	**Baseline**	165,702
0.15	161 days	–	**Baseline**	134,504	–	**Baseline**	122,261
0.175	137 days	–	**Baseline**	106,350	–	**Baseline**	98,714
0.2	119 days	–	**Baseline**	85,136	–	**Baseline**	77,959
0.225	105 days	–	**Baseline**	68,862	–	**Baseline**	61,774
0.25	94 days	–	**Baseline**	55,883	–	**Baseline**	48,849
0.275	84 days	–	**Baseline**	45,445	–	**Baseline**	38,320
0.3	76 days	–	**Baseline**	36,710	–	Baseline	**29,663**
0.325	69 days	–	Baseline	**29,397**	–	Baseline	**22,308**
0.35	64 days	–	Baseline	**23,149**	–	Baseline	**16,007**
0.375	59 days	–	Baseline	**17,807**	–	Baseline	**10,564**
0.4	54 days	–	Baseline	**13,164**	–	Baseline	**5852**
0.425	50 days	–	Baseline	**9121**	–	Baseline	**1692**
0.45	47 days	–	Baseline	**5543**	–	Baseline	**Dominates**
0.475	44 days	–	Baseline	**2385**	–	Baseline	**Dominates**
0.5	41 days	–	–	**Dominates**	–	Baseline	**Dominates**

Bold values indicate cost-effective option at £30,000 per QALY.
– denotes that an option is dominated by one or more options.

Since the IND (see *Table 52*) and MNT matrices (see *Table 54*) were based on the SC matrix, similar changes were also made to these. The revised model was run, and results are given in *Table 63*. The general results were extremely similar to the base case (see *Table 58*), with both induction/reinduction treatments dominating SC. Maintenance treatments cost slightly less per QALY against SC (infliximab £71,000 vs £68,000; adalimumab £8200 vs £7700), and slightly more per QALY against induction (infliximab £4.96M vs £5.03M; adalimumab £4.58M vs £4.98M). As such, any impacts of the implausible transitions in the base-case analysis were very minor.

Changes to the standard care matrix: surgical assumptions

During consultation on the draft report there was discussion about the most appropriate way to incorporate estimates of the probability of having a second surgery following an unsuccessful first surgery into the model. It was argued that the method used in the initial analysis (and for the base-case analysis in this report) overestimated the number of patients who would require repeat surgery. The information as reported in Silverstein *et al.*[26] was based on the probability of requiring repeat surgery within 2 months of the initial surgery. To obtain an estimate of this probability over a 4-week cycle, half of the 2-month value was used to arrive at the base-case values; this method likely led to an overestimate of the number of patients who had repeat surgery over the 1-year model time horizon. In the sensitivity analysis below, the 2-month value is used. This method was likely to result in an underestimate in the number of patients requiring surgery.

As can be seen from *Table 64* when compared with the base case, the largest effect was on the SC arm. This was to be expected – more patients in the SC arm underwent surgery than in any of the treatment arms; reducing the second surgery rate like this lowered the overall cost of the SC arm by more than it lowered the overall cost of the treatment arms.

TABLE 62 Standard care transition matrix

	SC remission	SC relapse	SC surgery	SC post-surgery remission
SC remission	0.9872	0.0059	0.0069	0
SC relapse	0.0902	0.8749	0.0348	0
SC surgery	0	0.0158	0.6709	0.3134
SC post-surgery remission	0	0.0011	0.0026	0.9963

TABLE 63 Implausible transitions removed (severe disease)

	Costs (£)		QALYs			
	Mean	SD	Mean	SD	CER vs SC	ICERs
SC	13,450	285	0.8129	0.0457	–	Dominated
Infliximab IND	12,261	504	0.8925	0.0809	Dominates SC	Baseline
Infliximab MNT	19,209	192	0.8939	0.0815	£71,099 per QALY	£4.96M per QALY
SC	13,450	285	0.8129	0.0457	–	Dominated
Adalimumab IND	7269	427	0.8947	0.0809	Dominates SC	Baseline
Adalimumab MNT	14,137	204	0.8962	0.0816	£8247 per QALY	£4.58M per QALY

CER, cost-effectiveness ratio.

TABLE 64 Cost-effectiveness results with revised probability of repeat surgery

	Costs (£)		QALYs			
Severe disease	Mean	SD	Mean	SD	CER vs SC	ICERs
SC	12,070	274	0.8233	0.0482	–	Dominated
Infliximab IND	11,270	443	0.9004	0.08330	Dominates	Baseline
Infliximab MNT	17,809	150	0.9018	0.0836	£73,108 per QALY	£4.7M per QALY
SC	12,068	269	0.8215	0.0483	–	Dominated
Adalimumab IND	6299	368	0.8991	0.0843	Dominates	Baseline
Adalimumab MNT	12,876	161	0.9004	0.0840	£10,240 per QALY	£5.1M per QALY

CER, cost-effectiveness ratio.

Modelling assumptions: changes to the time horizon

The longer term cost-effectiveness of anti-TNFs was considered and estimates of cost-effectiveness at 5, 10 and 20 years are reported in *Table 65*. Reasons for not adopting a lifetime horizon for this model are discussed in *Model structure*. Estimates of effectiveness in these scenarios have not been changed as no reliable evidence was available to show the effectiveness of either drug at any of the longer term time horizons. As a consequence, these results must be treated with caution. It should also be remembered that no evidence was found to suggest either the direction of change or the magnitude if it were decided to alter the estimates of effectiveness. These results are illustrative only and should be assumed to be sufficiently uncertain as to be unreliable estimates of cost-effectiveness over the time frames modelled.

Modelling assumptions: changes to the effectiveness estimates

In the baseline model, peak clinical effectiveness values (56% remission) were applied every 4 weeks which was highly favourable to the estimated cost-effectiveness of anti-TNF treatments. In this modification, the 4-week effectiveness was reduced in order to provide the peak effectiveness (56%) over 8 weeks. As an example, in order to obtain a 56% effectiveness over 8 weeks, approximately a 34% chance of remission every 4 weeks would be required. Here, 34% of patients achieved remission at 4 weeks (66% remained in relapse) and a further 22% (34% × 66%) achieved remission by 8 weeks. *Table 66* presents the revised cost-effectiveness from this sensitivity analysis.

The effect of these changes highlights the importance of uncertainty in the effectiveness estimates, and particularly in the case of infliximab. In the baseline case, infliximab induction/reinduction treatment dominated SC; in this case, such treatment was no longer cost-effective at a standard £30,000 per QALY threshold. The impact of this assumption on adalimumab was far less critical, as adalimumab IND continued to dominate SC. In neither case would maintenance treatment be justified on cost-effectiveness grounds.

In the absence of specific clinical trial data on the impact of maintenance on relapse probabilities, the model assumed that anti-TNF maintenance impacted on relapse probabilities to approximately the same degree as anti-TNF treatment affected the probability of entering remission. Consequently, where anti-TNF maintenance therapy was assumed to give about eight times the chance of entering remission from relapse, the model assumed there was one-eighth the chance of relapsing among patients in remission.

This assumption was tested by assuming that relapse under maintenance was one-quarter, one-eighth (approximate baseline) or one-sixteenth of the relapse rate under SC and induction

TABLE 65 Cost-effectiveness ratios at different time horizons

	Costs (£)		QALYs			
	Mean	SD	Mean	SD	CER vs SC	ICERs
5 years						
SC	25,631	469	4.5157	0.4277	–	Dominated
Infliximab IND	22,162	759	4.6443	0.4793	Dominates SC	Baseline
Infliximab MNT	69,069	1490	4.6545	0.4838	£1.6M per QALY	£4.6M per QALY
SC	25,670	470	4.5202	0.4217	–	Dominated
Adalimumab IND	16,214	684	4.6374	0.4728	Dominates SC	Baseline
Adalimumab MNT	53,009	804	4.6476	0.4772	£214,592 per QALY	£3.6M per QALY
10 years						
SC	36,822	662	9.1791	0.9364	–	Dominated
Infliximab IND	33,144	942	9.3285	0.9958	Dominates SC	Baseline
Infliximab MNT	129,951	3807	9.3500	0.9963	£544,933 per QALY	£4.5M per QALY
SC	36,823	656	9.2126	0.9287	–	Dominated
Adalimumab IND	26,273	914	9.3453	0.9875	Dominates SC	Baseline
Adalimumab MNT	100,338	2156	9.3653	0.9962	£415,946 per QALY	£3.7M per QALY
20 years						
SC	58,481	1066	18.5560	1.9365	–	Dominated
Infliximab IND	53,991	1374	18.6430	2.0012	Dominates SC	Baseline
Infliximab MNT	250,391	8584	18.7536	2.0259	£971,204 per QALY	£1.8M per QALY
SC	58,486	1071	18.5585	1.9242	–	Dominated
Adalimumab IND	45,716	1377	18.7180	1.9956	Dominates SC	Baseline
Adalimumab MNT	193,840	4928	18.7566	2.0124	£683,261 per QALY	£3.8M per QALY

CER, cost-effectiveness ratio.

TABLE 66 Cost-effectiveness results with peak effectiveness over 8 weeks

	Costs (£)		QALYs			
Severe disease	Mean	SD	Mean	SD	CER vs SC	ICERs
SC	13,417	278	0.8113	0.0460	–	Baseline
Infliximab IND	16,040	544	0.8481	0.0623	£71,315 per QALY	£71,315 per QALY
Infliximab MNT	20,285	242	0.8491	0.0628	£181,475 per QALY	£3.9M per QALY
SC	13,416	279	0.8123	0.0461	–	Dominated
Adalimumab IND	9862	460	0.8637	0.0686	Dominates	Baseline
Adalimumab MNT	15,144	235	0.8650	0.0692	£32,759 per QALY	£4.1M per QALY

CER, cost-effectiveness ratio.

(post-surgery relapse was also changed by the same general amount.) In the standard case, the impact of this assumption was very limited given the low chance of relapse. For the purposes of comparison, higher relapse rates (sc_relapse = 0.05, ps_relapse = $0.05 \times 0.0011/0.0059 = 0.0093$) were therefore used, in order to allow the impact of this assumption to be assessed.

The scenarios in *Table 67* suggest that there may have been some potential for maintenance to be somewhat more cost-effective by modifying these maintenance assumptions, e.g. from £399,000

TABLE 67 Maintenance efficacy assumptions

	Costs (£)		QALYs			
	Mean	SD	Mean	SD	CER vs SC	ICERs
MNT relapse = ¼ cs_relapse						
SC	14,207	301	0.8028	0.0419	–	Baseline
Infliximab IND	15,010	424	0.8824	0.0766	£10,126 per QALY	£10,126 per QALY
Infliximab MNT	19,687	195	0.8911	0.0808	£62,061 per QALY	£537,241 per QALY
SC	14,207	301	0.8028	0.0419	–	Dominates
Adalimumab IND	8492	435	0.8824	0.0765	Dominates	Baseline
Adalimumab MNT	14,401	212	0.8918	0.0806	£2,180 per QALY	£628,617 per QALY
MNT relapse = ⅛ cs_relapse						
SC	14,207	301	0.8028	0.0419	–	Baseline
Infliximab IND	15,010	424	0.8824	0.0766	£10,126 per QALY	£10,126 per QALY
Infliximab MNT	19,438	198	0.8954	0.0820	£57,674 per QALY	£398,649 per QALY
SC	14,207	301	0.8028	0.0419	–	Dominates
Adalimumab IND	8492	435	0.8824	0.0765	Dominates	Baseline
Adalimumab MNT	14,253	210	0.8935	0.812	£507 per QALY	£519,000 per QALY
MNT relapse = 1/16 cs_relapse						
SC	14,207	301	0.8028	0.0419	–	Baseline
Infliximab IND	15,010	424	0.8824	0.0766	£10,126 per QALY	£10,126 per QALY
Infliximab MNT	19,311	200	0.8940	0.0819	£55,119 per QALY	£330,615 per QALY
SC	14,207	301	0.8028	0.0419	–	Dominates
Adalimumab IND	8492	435	0.8824	0.0765	Dominates	Baseline
Adalimumab MNT	14,180	207	0.8938	0.0799	Dominates	£498,947 per QALY

CER, cost-effectiveness ratio.

to £330,000 per QALY in infliximab treatment as the relapse rate moved from one-eighth of the standard rate to one-sixteenth. Here, halving the numbers relapsing per period made some, though relatively little, difference to the cost-effectiveness of treatment. However, doubling those relapsing per period (from one-eight to one-quarter of the standard rate) made a much larger difference – here the infliximab ICER moved from £399,000 to £537,000 per QALY.

While the results of the analysis were sensitive to the assumptions made regarding maintenance efficacy, higher efficacy values are unlikely to affect the ICER much, but lower values may have a much larger effect.

Paediatric Crohn's disease threshold analysis

The review of clinical effectiveness evidence reported found no randomised, placebo-controlled evidence on the effectiveness of infliximab in paediatric CD. An executable model to estimate the cost-effectiveness of infliximab was provided by the manufacturers. However, programming errors in that model prevented validation of the results. A corrected version of the model was eventually provided, but was received outside the accepted time frame for new evidence to be considered as part of the assessment.

A threshold analysis using the de novo cost-effectiveness model based on the adult population effectiveness estimates was undertaken to obtain the estimated required effectiveness of

infliximab in paediatric patients. This analysis must be interpreted with caution as it is often neither straightforward nor advisable to extrapolate the results of research in adults to a paediatric population. It would be a mistake to uncritically accept the notion that research results that apply to adults are applicable to children. In the case of anti-TNF therapy in particular, it is important to consider how the effectiveness of the drugs might differ in a paediatric population, whether or not the same or similar AEs can be expected, the differences in costs of the treatments including both drug costs and the requirement for specialist paediatric services, and finally the potentially different value attached to different aspects of HRQoL in children when compared with adults.

The costs associated with treating children may differ from the costs of treating adults. This may be due to the different costs associated with the drug itself or related to some other factor such as the setting in which care takes place. In these circumstances, given that infliximab doses are according to weight, the costs of treatment may be expected to be lower if a linear relationship between dose and effect is assumed (leaving aside the issue of whether the dose-response relationship holds for the paediatric population as it is assumed to do for the adult population). However, the cost of the drug is only a single factor in establishing the total cost of care for the paediatric population. Often children may need to be seen in specialist paediatric settings, which will attract costs different to those that apply in adult clinics. Generally it would be expected that treatment of paediatric patients will be different to that of adults. An estimate of this cost for the threshold analysis has been made, but given the paucity of available evidence (e.g. on required drug dose, on the model and location of care) the estimate should be viewed with caution.

Owing to a lack of specific evidence, the assumption in this threshold analysis has been made that the utility weights assigned to children for all states in the model were the same as for adults in the same state. But research was clear that it was not necessarily an appropriate assumption. In assessing the HRQoL of children, due consideration was required relating to the domains of life considered important by children (Rosenbaum and Saigal[106]), to the relevant stage of their physiological and mental development (Harris and Butterworth[107]), and to the social context in which they find themselves (Matza *et al.*[108]) which impinges on their social roles (e.g. including aspects of life related their dependence and autonomy) (Fox-Rushby and Parker[109]). Those domains of life that were considered important in an adult population may not necessarily have been appropriate indicators of QoL in children (Petrou and Henderson[110]). It should be clear then that to apply adult utility values to an analysis of paediatric patients was a suboptimal approach to the problem, though the information available permitted no other course of action. After taking into consideration the above arguments, it was difficult to reach a precise conclusion about the effectiveness of infliximab for the treatment of paediatric CD.

In this sensitivity analysis, two key changes to the base case were made. Firstly, it was assumed that the average weight of the paediatric patients would be less than that of the adult patients. Secondly, a change to the administration cost of the drug was made which assumed that this will take place in paediatric gastroenterology service, with a cost of £232.[111] *Table 68* shows the results from analysis of a paediatric population where the weight of the patients was assumed to be between 40 kg and < 60 kg and between 20 kg and < 40 kg. The average weight of the children in the evidence supplied by the manufacturer varied, with a mean of 49.1 kg in Baldassano *et al.*[46] and 43.8 kg in REACH.[45] This analysis was conducted on a per vial basis, as once a vial is opened it must be used or discarded and this represents the true cost to the NHS.

It is clear in the analysis presented in *Table 68* that induction therapy with infliximab for patients with severe disease was the only option that may be cost-effective where two or three vials were used. In neither weight range case is maintenance treatment cost-effective.

TABLE 68 Infliximab paediatric analysis – three vials (children with weight between 40 kg and < 60 kg)

	Costs (£)		QALYs			
	Mean	SD	Mean	SD	CER vs SC	ICERs
40–59 kg (three vials)						
SC	13,418	278	0.8130	0.0462	–	Dominated
Infliximab IND	10,652	497	0.8960	0.0824	Dominates	Baseline
Infliximab MNT	16,918	268	0.8974	0.0830	£41,469 per QALY	£4.5M per QALY
20–39 kg (two vials)						
SC	13,418	280	0.8112	0.0458	–	Dominated
Infliximab IND	9317	490	0.8930	0.0819	Dominates	Baseline
Infliximab MNT	14,813	340	0.8944	0.0825	£16,767 per QALY	£3.9M per QALY

CER, cost-effectiveness ratio.

In the absence of valid estimates of effectiveness in children, a threshold analysis of those scenarios where the initial analysis showed treatments to be cost-ineffective for children with weight between 40 kg and < 60 kg was undertaken. When maintenance therapy is compared with induction therapy the ICER was sufficiently high to preclude the possibility of the former being cost-effective relative to the latter at any estimate of effectiveness. Maintenance therapy in severe disease may be cost-effective compared with SC at the same threshold if the average benefit were equal to 0.93 QALYs.

This threshold analysis demonstrated two things. Firstly, there is the possibility that treatments that were not cost-effective in the base case could become cost-effective if the costs of treatment were significantly lower. Secondly, it highlighted the uncertainty inherent in the model estimates of effectiveness (and in turn the total cost of treatment), given that small changes in estimates of effectiveness can lead to large swings in the estimated cost-effectiveness of treatment.

Discussion

The analyses described in this chapter indicate that infliximab is not likely to be cost-effective, according to the criteria laid out in the NICE Guide to the methods of technology appraisal,[93] in the management of moderate CD. While adalimumab may be cost-effective, there is uncertainty regarding the ICER value. Neither of these therapies is likely to be cost-effective as maintenance therapy for moderate or severe disease. Both treatments are highly cost-effective, with no meaningful uncertainty, as induction therapy in severe disease.

The estimates of cost-effectiveness in maintenance therapy must be viewed as exploratory. This is because of the shortness of the randomised placebo-controlled period of the maintenance trials for these drugs. Essentially these do not provide evidence of the magnitude of effect compared with usual care owing to allowing patients to cross over to 'episodic' treatment relatively quickly after trial commencement. The evidence required to model the cost-effectiveness was the proportion of patients transiting between remission and relapse, and between relapse and remission, with and without treatment at regular time points. Given the absence of this evidence, it has therefore been necessary to postulate a maintenance effect based upon what has been reported in the trials. The implicit assumption for estimating the effect is that anti-TNFs interfere with the underlying biochemical process that causes relapses and that the effectiveness is equivalent whether or not the process has led to symptomatic relapse and whether the patient is in remission or relapse. The Silverstein *et al.*[26] matrix suggested that 82% of patients in remission

were expected to be maintained in remission each year on SC. On average, then, the capacity for additional benefit from anti-TNF maintenance therapy is small, approximately 0.045 QALYs per annum for patients with severe disease. Against this background, it is unlikely that maintenance therapy has sufficient scope for generating health gain to justify its use at current prices.

Another key decision in estimating the cost-effectiveness was to use the Silverstein *et al.*[26] cohort to model usual care for all interventions, and use the Targan *et al.*[57] trial to provide an estimate of absolute effect, but not relative effect. The use of the Silverstein *et al.*[26] data model has some inherent limitations. Expert opinion suggested that the surgery rates were higher than would be seen in practice. Also, the relapse rates were much lower than was likely prevailing in clinical trials. The Silverstein *et al.* model was based upon long-term data on a substantial sample of patients and there was reasonable evidence that, for many patients, the longer term disease course is one of decreasing activity. Thus it would be expected that a model based upon long-term data would predict lower event rates than one based upon shorter term data from patients with highly active disease. However, the scope of the appraisal did not specify a disease activity inclusion criterion, only disease severity and treatment responsiveness criteria. In contrast, the trials applied recent disease activity inclusion criteria. On this basis it was concluded that the Silverstein *et al.* model was more appropriate given the scope of the appraisal than the clinical trial data, while accepting its limitations.

Having chosen to use the Silverstein *et al.*[26] model, the analysis made the assumption that the drug-responsive and drug-dependent states were both effectively managed on standard therapy, and therefore the two states were combined into a single state within the model. This might mean that the costs of the remission state were underestimated as the drug-dependent patients would have been on maintenance therapy to retain a remission status, while drug-responsive patients would have been managed with induction therapy. The effect of this will be to overstate the cost saving associated with achieving remission and thereby improve the cost-effectiveness of anti-TNFs because of their higher remission rate.

The relative effect seen in the Targan *et al.*[57] trial was an outlier due to the very low rate of remission at 4 weeks in the control arm. However, the absolute magnitude of effect was consistent with the remission rate seen in the pre-randomisation phase of the ACCENT I[2,3] trial of infliximab.

An important difference between this model and others was the use of a 1-year time horizon and the exclusion of death from the model. Silverstein *et al.*[26] reported a small risk of death in each state. The mean risk of death varied between states, i.e. between 0.00015 and 0.00839. The greatest risks were for the 'drug-responsive' and 'drug-refractory' states (0.00626 and 0.00839 respectively). If these results had been used as the basis for incorporating mortality into the model and therefore adopting a lifetime horizon, the effectiveness of the drug in inducing remission would have produced an apparent mortality gain for treatment of approximately 0.00213 per additional remissions created – i.e. slightly over two lives in a cohort of 1000 patients. As the total QALYs produced by induction therapy were in the region of seven QALYs per year, this would have completely swamped the direct effectiveness, and made the treatments appear highly cost-effective, even though the evidence did not support a *causal* link between status in the Silverstein *et al.*[26] framework and mortality, and there was no direct evidence of a mortality benefit from anti-TNF treatment.

The analysis of uncertainty was probabilistic but not comprehensively so. Notably, the SC transition probabilities were entered into the model deterministically. The effect of this was to understate the uncertainty regarding the costs and outcomes from standard therapy, and, by extension, the uncertainty around the cost-effectiveness of the anti-TNFs in both induction/

episodic and maintenance therapy. The primary effect of incorporating additional uncertainty was to increase the model's prediction of expected value of subsequent research.

It was useful to consider briefly the implications on the cost-effectiveness of treatment for patients who were outside the four-vial analysis owing to their weight. The model effectively assumed that all patients were likely to fall somewhere between 60 kg and < 80 kg, when the clinical reality was that many patients would be either above or below this range. There was no evidence to suggest that weight had a direct effect on the efficacy of treatment – an assumption supported by a weight-based dosing regimen. Therefore the only difference that should have been expected would be in the costs of the treatment – the smaller the patient, the fewer vials required, the lower the cost, and vice versa. From an empirical standpoint, the paediatric sensitivity analysis can be extrapolated (see *Table 68*) to test how changes in the number of vials required affected the cost-effectiveness. It is worth noting that the administration costs in the paediatric analysis were slightly lower than in the adult analysis, but this did not matter greatly for the purposes of this argument.

From that analysis, it was clear that there was only one change to the relative cost-effectiveness when compared with the base case. In this case, when only two vials were required, the use of infliximab for patients with moderate disease could be considered cost-effective, whereas in the base case it would not be. Based on the three-vial paediatric analysis, the decisions would likely be the same as in the base case. Mindful that a very small number of adults with CD may have a weight of less than 40 kg, it seemed unlikely that treatment for patients who fell below the average weight would be cost-effective. Similarly, given the assumption that effectiveness was unaltered by weight and that costs would only increase for patients with a weight above 80 kg, it followed that the treatment was unlikely to be cost-effective for patients above the average weight.

The empirical evidence was only one of two parts of the argument. The second point at issue was whether or not it would be appropriate to discriminate against patients based on their weight when this was unrelated to the effectiveness of the treatment but changed the cost of treatment and therefore the relative cost-effectiveness of the treatment. This form of subgroup discrimination is not permitted by the NICE reference case.[93] Therefore it would have been inappropriate to suggest that one group of people with weight less than some critical level received treatment while those with weight above this level were denied it, where there is no demonstrable difference in health outcomes as a result of the difference in weight.

A further important consideration was the focus of this analysis on the cost-effectiveness of these treatments in the induction of remission. The trials reported response rates for remission, and CDAI response 70 and response 100. CDAI response rates cannot be converted into improvements in health without knowing the baseline CDAI for each patient. Although Gregor *et al.*[92] demonstrated a linear relationship between CDAI scores and utility values, they also found that the relationship was only modestly correlated, with increasing levels of uncertainty in utility scores as CDAI score increased. It was not considered possible here, therefore, to attach a utility gain to a 70- or 100-point gain on the CDAI without knowledge of the pre-treatment CDAI status.

As discussed above, it was chosen to construct a model based upon health state (remission, relapse, requiring surgery and remission following surgery) rather than CDAI score. This decision was guided by the desire to quantify the cost-effectiveness of treatments in producing health rather than their cost-effectiveness in shifting the clinical pathway. The results from the Gregor *et al.*[92] study suggested that when patients were grouped as per the Silverstein *et al.*[26] framework, the differences in mean HRQoL were extremely small, and much smaller than those used in the structure of health states adopted in this analysis.

A simple model of CD was constructed which focused on the cost-effectiveness of anti-TNF therapies in achieving or maintaining remission. The assumptions made here regarding cost of care and utilities gains from treatment favoured the anti-TNFs over usual care. The analyses drew out the much larger health benefit for patients with severe disease compared with moderate disease and how this fed through to ICERs that were likely to be acceptable for severe disease but not moderate disease. The analysis also highlighted the important variations in effectiveness and cost between the therapies. Perhaps most importantly, the analysis reflected the assumption that a substantial number of patients would achieve remission under SC and that the incidence of relapse among those in remission was such that maintenance therapy would have to be much less costly for it to be a cost-effective option.

Budget impact assessment

The NICE guidance on infliximab from 2002[1] estimated that 31,000 patients in England and 1800 in Wales had CD, that 2% had very severe disease and that between 1050 and 4200 patients would have been eligible for treatment. These estimates were made in the absence of good-quality CD prevalence studies. There is now more information on the UK prevalence of CD but not as much on the typical spread of severity.

It was estimated from the incidence/prevalence section in this report that the prevalence of CD in the UK is approximately 150 per 100,000 but could be between 50 and 400 per 100,000. The incidence of new cases of CD has been estimated to be approximately 5 per 100,000 per year but could be between 3.8 and 10 per 100,000 per year. The incidence and prevalence estimates from both industry submissions are shown in *Table 69*.

These incidence and prevalence estimates are for all CD patients rather than those with moderate-to-severe CD or severe CD. A large cross-sectional survey of CD patients with CDAI scores used to indicate the percentage with mild, moderate and severe CD was not found.

In a UK study[37] of 172 CD patients attending a university hospital during a 6-month period, 7% were in remission, 33% had mild disease, 42% had severe disease, 8% had surgery and 10% were in post-surgery remission. Severity was judged by treatments being used rather than on CDAI score so severe CD patients were those being treated with corticosteroids or immunosuppressive regimens.

In a Canadian QoL study,[92] 180 consecutive CD patients referred to a tertiary care hospital had CDAI scores measured. The overall mean CDAI score was 182 (95% CI 166 to 199). There were 52 patients classified as 'chronically active therapy resistant' with mean CDAI of 246 (95% CI 220 to 272), 34 patients classified as 'chronically active therapy responsive' with CDAI 72 (95% CI 60 to 84), 45 patients classified as 'acute disease exacerbation' with CDAI 249 (95% CI 217 to 281) and 49 patients in remission with CDAI 129 (95% CI 110 to 148). This equates to 54% with severe

TABLE 69 Incidence and prevalence estimates of CD in industry submissions

	Incidence	Prevalence
Adalimumab submission[4]	10/100,000 per year used in budget impact section (derived from NICE guidance)	50–100/100,000 'however this is likely to be an underestimation'
		62.5/100,000 used in budget impact section (derived from NICE guidance)
Infliximab submission[96]	14/100,000 per year	50–100/100,000, 145/100,000

disease (CDAI > 220) and 46% with mild disease (CDAI < 220). These 46% of patients with mild disease would also be categorised as in remission (CDAI < 150).

In a regional cohort of 373 CD patients from Denmark, in the first year 80% had highly active disease (defined as more than four stools daily, blood or pus daily, severe or daily abdominal pains and systemic symptoms such as fever or weight loss).[25] In the second year 40% had high activity, 22% had low activity and 38% were in remission. In subsequent years the proportions were approximately 30%, 20% and 50% respectively.

From the three studies mentioned above it can be estimated that approximately 40% of CD patients will have moderate-to-severe disease and may be considered eligible for treatment according to the inclusion criteria for the RCTs.

In the Olmstead County cohort study of 174 CD patients,[26] follow-up information for up to 10 years was used in a Markov model to estimate the probability of future clinical course. From this it was estimated that 1.77% of CD patients might be in a severe, drug-refractory disease state. As this was based on a model, it may be much less reliable than actual cohort study results.

With a prevalence of 150/100,000 and a total population of approximately 50 million in England and 3 million in Wales, there would be approximately 79,500 CD patients – 75,000 in England and 4500 in Wales. If 40% had moderate-to-severe disease, this would be 31,800 CD patients. There is no information on the proportion of patients with severe CD as defined by CDAI > 300 within the moderate-to-severe category. However, it is noticeable that the mean CDAI score for all of the induction trials included in the clinical effectiveness review was approximately 300. These RCTs included patients described as having moderate-to-severe CD.[57,63,64] From this it can be estimated that if there is a roughly normal distribution, approximately 50% of patients with moderate-to-severe CD will have a CDAI score of more than 300 (*Table 70*).

The cost of treatment with the new interventions (induction and maintenance) for adults (non-fistulising CD) with both drugs is shown in *Table 71*. This includes the cost of administration in hospital or clinic in the case of infliximab. The administration cost would include the presence of a health professional during the 2 hours of infusion and for a period of time afterwards. As there is a (small) risk of acute allergic reactions, emergency equipment should be available. No administration costs were given for adalimumab on the grounds that it can be given subcutaneously. However, training must be given before this can occur which will incur a cost.

For infliximab, the estimated three vials per person is likely to be an underestimate, as the mean weight of patients from the four large trials included in the clinical effectiveness review that gave this information (CHARM,[67] CLASSIC I,[63] GAIN,[64] Targan *et al.*[57]) suggested that the mean weight of CD patients was approximately 71.5 kg so a dose of 5 mg/kg would require four

TABLE 70 Estimated prevalence of CD severity

CD severity	Number in England and Wales	Percentage of total CD population
All CD	79,500	100%
Moderate-to-severe CD	31,800	40%
Severe CD	15,900	20%
Severe and drug-resistant CD (estimate from a Silverstein *et al.*[26] study Markov model only)	1590	2%[a]

a Rounded from 1.77%.

TABLE 71 Estimated costs of new intervention from industry submissions

	From industry submission	Induction	Maintenance for 1 year
Adalimumab	Cost per 40-mg vial – £357.50, no administration cost given	80 mg at week 0 then 40 mg at week 2 (two doses) = £1072.50 (+ administration)	40 mg e.o.w. (26 doses) = £9295 (+ admin)
Infliximab	Cost per 100-mg vial – £419.73. Total cost per infusion – £1355.19 (Assumes 60-kg person so at 5 mg/kg would need three vials, plus administration cost of £96)	One dose at weeks 0, 2 and 6 (three doses) = £4065.57	5 mg/kg every 8 weeks (6.5 doses) = £8808.74

vials per person. Also, it was unclear how the administration cost of £96 taken from an HTA report on psoriatic arthritis (Woolacott *et al.*[99]) was actually derived. In that HTA report, the annual administration cost for treatment (every 8 weeks so – 6.5 treatments) was estimated to be £1673.75, which equates to £257.50 per treatment. Taking these revised costs into account would give the induction dose estimate as £5809.26 $\{[(4\times419.73)+257.50]\times3\}$ and the annual maintenance cost (not including the initial induction dose) estimate as £12,586.73 $\{[(4\times419.73)+257.50]\times6.5\}$ gives the cost per treatment, of which 6.5 are required per year.

If 31,800 CD patients in England and Wales with moderate-to-severe CD received treatment, this equates to a total budget impact for both drugs that can be seen in *Table 72*. If only CD patients with a CDAI score > 300 are treated (a much more likely scenario), this equates to a total budget impact for both drugs that can be seen in *Table 73*. The current NICE guidance on infliximab states that it should be used in patients with severe active CD whose condition is refractory to other treatment, who are intolerant to or experience toxicity from these treatments, and for whom surgery is inappropriate.[112] It is unclear how many people would be in this category so the precise budget impact if the current NICE guidance is maintained is unclear. The estimates in *Tables 72* and *73* will be an overestimation (compare with *Table 74*).

Fistulising disease occurs in 17%–43% of people with CD (ACCENT II[65]). In two trials of moderate-to-severe CD that also gave details on fistulising patients, the proportions were 14% (GAIN[64]) and 15% (CHARM[67]). Therefore it is possible that more people with fistulas have mild CD as measured by CDAI scores. If approximately 30% of all CD patients (23,850 in England and Wales) have fistulas then the estimated budget impact is shown in *Table 75*. Note that the prevalence used in these estimates does not include children. It is estimated that the incidence of CD in children is 5.3 per 100,000 per year (Jenkins[11]) and that 20%–30% of all new cases of CD are in people aged < 20 years (infliximab industry submission[96]).

Estimations of the budget impact do not include changes to potential costs arising from two situations. The first is the need for retreatment for patients who initially respond to treatment and then relapse. These patients will require a second induction dose of treatment, increasing the likely cost of treatment, resulting in a likely underestimate of the total budget impact. The budget impact estimates also do not account for people who are responding to treatment but choose to discontinue treatment. This will lead to an overestimate of the cost of the total budget impact.

To put the above calculations into perspective, the total NHS drug bill for 2004–5 was £9,965,000,000.[113] The mean annual cost of treating CD per patient (data collection in 2000, when infliximab was not being widely used) was approximately £3300 (see *Table 3*), so if 31,800 patients were treated at that time this would have amounted to a cost of approximately £105,067,000.

TABLE 72 Budget impact of new intervention for moderate-to-severe CD

	Induction	Maintenance for 1 year
Adalimumab from industry submission	£34,105,500	£295,581,000
Infliximab from industry submission	£129,285,126	£280,117,932
Infliximab from recalculation	£184,734,468	£400,258,014

TABLE 73 Budget impact of new intervention for severe CD

	Induction	Maintenance for 1 year
Adalimumab from industry submission	£17,052,750	£147,790,500
Infliximab from industry submission	£64,642,563	£140,058,966
Infliximab from recalculation	£92,367,234	£200,129,007

TABLE 74 Budget impact of new intervention for severe, drug-resistant CD if Silverstein *et al.*[26] model accurate

	Induction	Maintenance for 1 year
Adalimumab from industry submission	£1,705,275	£14,779,050
Infliximab from industry submission	£6,464,256	£14,005,897
Infliximab from recalculation	£9,236,723	£20,012,901

TABLE 75 Budget impact of new intervention for fistulising CD

	Induction	Maintenance for 1 year
Adalimumab from industry submission	£25,579,125	£221,685,750
Infliximab from industry submission	£96,963,844	£210,088,449
Infliximab from recalculation	£138,550,851	£300,193,510

As a comparison, the industry submission for adalimumab used the 2002 NICE guidance[1] on infliximab to estimate that there would be a prevalence of 27,811, of whom 1112 would be eligible for treatment with adalimumab. Combined with the incidence estimates for CD they estimated that 1287 CD patients would be eligible for adalimumab treatment in 2007, rising to 2000 patients in 2011. This would cost £11,971,784 in 2007, rising to £18,604,165 in 2011. They compared this with the budget impact of treating these patients with infliximab of £19,211,660 in 2007 to £29,854,950 in 2011.

The industry submission for infliximab estimated that the total cost of infliximab to the NHS per year would be £24,165,283 in the first year, rising to £38,916,321 in the fifth year. This assumed that 2744 people would be eligible for treatment in the first year, rising to 4419 people in the fifth year. They estimated that 28% of all patients with CD would be eligible for treatment with infliximab.

Mortality rates

No excess mortality rates with adalimumab or infliximab were found in any of the RCTs included in the clinical effectiveness review. However, there are reports in the medical press of relatively high rates of serious AEs with disease-modifying antirheumatic drugs. In a report of the serious

adverse drug events reported to the US FDA between 1998 and 2005, infliximab was the seventh most frequently suspected drug for deaths and the third most frequently suspected drug for disability and other serious outcomes. Adalimumab was also listed as having 2389 serious adverse drug events.[114] It is not known how many people were taking these drugs.

In the UK, the drug analysis prints compiled from suspected adverse drug reactions are reported through the Yellow Card Scheme. Fatal reactions reported up to 26 May 2006 are summarised in *Table 76*. The highest number of deaths was due to infections but it is surprising that the category of diseases of the circulatory system, particularly including myocardial infarctions, was relatively high for both adalimumab and infliximab. Tuberculosis was not linked to many deaths. It is known that the Yellow Card Scheme tends to have an under-reporting of AEs. It has been calculated that £50,390,200 was spent on infliximab in 2006 (for all indications).[115] Given that infliximab costs £419.73 per vial, this would suggest that the NHS used 120,052 vials in 2006. If three vials were used per person, ~40,000 people would have received infliximab, suggesting a very approximate overall mortality rate of 0.5%. It is unclear from this information whether there is an excess mortality in patients receiving infliximab. There is no information on the number of people taking infliximab for CD or the mortality rate in this patient group.

TABLE 76 Yellow Card Scheme reported deaths for adalimumab and infliximab

	Number of reported deaths	
Cause of death	**Adalimumab**	**Infliximab**
Infections (not TB)	31	70
TB	2	6
Neoplasms	9	28
Mental and behavioural disorders	0	1
Diseases of the circulatory system	31	40
Diseases of the respiratory system	9	32
Diseases of the digestive system	0	4
Death/sudden death	11	23
Other	3	10
Total fatal outcome	**96**	**214**
Total number of reports	**693**	**1949**

TB, tuberculosis.

Chapter 5

Discussion

Statement of principal findings

Clinical effectiveness review

Eleven RCTs were identified that had at least one study arm that included some participants within the UK licensed indication for adalimumab or infliximab.[2,3,45,46,57,58,62–67] The results from these are summarised below. Results for other trial arms that used adalimumab and infliximab outside licence dose regimens are presented in *Appendix 10*.

For adalimumab, two induction trials (CLASSIC I[63] and GAIN[64]) and two maintenance trials (CLASSIC II[66] and CHARM[67]) in adults with moderate-to-severe CD were identified.

For infliximab, one induction trial (Targan *et al.*[57]) and two maintenance trials in adults with moderate-to-severe CD (ACCENT I[2,3] and Rutgeerts *et al.*[58]), one induction (Present *et al.*[62]) and one maintenance trial (ACCENT II[65]) in adults with fistulising CD, and one induction (Baldassano *et al.*[46]) and one maintenance trial (REACH[45]) in children with moderate-to-severe CD were identified.

All were placebo-controlled trials, with the exception of the paediatric trials which compared different doses of infliximab, and there were no head-to-head comparisons of the two drugs.

There was no information on the relative effectiveness of treatments depending on ethnicity or other similar groups.

There were concerns regarding the trial design and study quality, particularly for the maintenance trials. These concerns related to the division of patients into subgroups (responders and non-responders) at different time points, the high proportions of scheduled crossovers resulting in the lack of a true placebo group, uncertainties regarding the handling and number of missing binary and continuous data, and the occasional dose escalation beyond licensed indication.

Particular concerns related to the ACCENT I[2,3] trial. The comparison between 'episodic' and 'scheduled' treatment described in the publication by Rutgeerts *et al.*[3] is not a valid comparison. The 'placebo' arm changed to 'episodic treatment' after 14 weeks and the scheduled maintenance arm participants could switch to episodic increased treatment. There was no randomisation to episodic and scheduled maintenance arms at the beginning of the trial.

Statistically significant effect sizes in favour of anti-TNF therapy compared with placebo were found in all induction trials by week 4 for both CDAI response rates and remission (for CLASSIC I[63] this was only at the highest induction dose regimen of adalimumab); effect sizes in Targan *et al.*[57] (infliximab) were greater than those for adalimumab but were associated with greater uncertainty.

High and varied placebo response rates observed in the induction trials are thought to result from a tendency of CDAI scores to regress to the mean, from a placebo effect and possibly from differences in concomitant treatment in the trials.

There was statistically significant evidence from both large maintenance trials (CHARM,[67] adalimumab and ACCENT I,[3] infliximab[2]) that for the subgroups defined as 'responders', anti-TNF therapy was more beneficial than placebo with respect to remission or response rates at reported follow-up times. However, it appeared that point prevalence rather than sustained response (remission) was reported and so the results represented group rather than individual response (remission) and did not inform on persistence of the response (remission) state in the individual.

Indirect comparisons between adalimumab and infliximab were not made because they were judged unlikely to be valid because of the heterogeneity between the trials caused by variation in placebo rates, the apparently arbitrary selection of responders only in the maintenance trials and the varied definition of responder status.

The practice of dichotomising patients into responders and non-responders was considered to be clinically useful only if 'responders' were more likely to benefit from maintenance of treatment. There was no evidence available from the identified trials to confirm or refute this.

There was evidence from both the induction and maintenance trials that infliximab promotes fistula closure to a greater extent than placebo (which was statistically significant for maintenance treatment). However, it is possible that fistula closure may not always be the most desirable outcome as it may result in increased development of abscesses.

In the paediatric infliximab trials, no reliable quantitative estimate of the effectiveness of infliximab was possible as the placebo or SC response rates were not measured. In REACH[45] there was an improved response with higher dosage of infliximab which implied a possible beneficial effect of infliximab, should a comparison ever be made with a control with zero dosage of infliximab.

Patient-related QoL was measured by the IBDQ in seven trials (induction and maintenance).[2,3,57,58,63,64,66,67] Overall there was a beneficial effect (statistically significant at some time points) of anti-TNF therapy, shown by greater improvement (or less deterioration over time) in IBDQ scores in the treatment arms.

Cost-effectiveness review

A review and quality assessment of existing published literature on cost-effectiveness identified four papers for inclusion into the review.[5–7,90] All concerned infliximab; no published studies on the cost-effectiveness of adalimumab were identified.

The four published infliximab cost-effectiveness studies were all independently funded and the results suggested that single use or 'episodic' treatment (various definitions) with infliximab had a relatively high cost-effectiveness ratio for both non-fistulising and fistulising disease (all above £50,000/QALY for non-fistulising disease and all above £100,000/QALY for fistulising disease).

The results of both industry submissions (adalimumab and infliximab) typically showed ICERs of under £30,000 for both anti-TNFs versus SC.

For the adalimumab industry submission model there was a lack of clarity over the source and interpretation of data used in the industry model, and key elements of the model could not be verified. Corrected results for both severe CD and moderate and severe (combined) CD were substantially higher than in the industry submitted model; in the severe subgroup of patients the corrected ICER approached cost-effectiveness (at a threshold of £30,000).

For infliximab, errors were identified in the industry model (active CD), some of which could not be corrected. The revised model was suggestive of infliximab being cost-effective for 'episodic' (clinician discretion) treatment, though the exact nature of this intervention remained unclear. Scheduled maintenance treatment with infliximab was unlikely to be cost-effective. The industry model for fistulising CD revised here also suggested that infliximab was unlikely to be cost-effective. No functioning model was provided for paediatric CD within the time frame of the project, so no conclusions could be made from the reported findings.

De novo economic model

A simple Markov model was developed from the NHS/PSS perspective to estimate the incremental cost per QALY for both drugs compared with SC in (a) induction/episodic therapy (as defined for the purposes of the economic model) for moderate and severe disease; and (b) maintenance therapy for moderate and severe disease. The model had a 1-year time horizon and was constructed and analysed in TREEAGE PRO 2008.

The findings were that for induction/episodic treatment, both adalimumab and infliximab were cost-effective (dominant relative to SC) in the management of severe CD and that adalimumab (but not infliximab) was cost-effective for moderate CD, according to the criteria laid out in the NICE *Guide to the methods of technology appraisal*.[93] Neither drug was cost-effective as maintenance therapy for moderate or severe disease.

Budget impact assessment

A simple budget impact assessment was conducted using information from prevalence data and the industry submissions. It suggested that the total cost to the NHS in England and Wales for induction in severe disease only could range between £17M and £92M and for maintenance for 1 year between £140M and £200M. These totals would be less only if those CD patients whose condition is refractory to other treatment, who are intolerant to or experience toxicity from these treatments and for whom surgery is inappropriate were treated. It is unclear how many people would be in this category, so the precise budget impact if the current NICE guidance is maintained was unclear.

Strengths and limitations of the assessment

- Well-established systematic review techniques were used for this technology assessment, which lends considerable strength to its validity and reliability.
- Searches for RCTs were conducted systematically. Using a sensitive search strategy was likely to have identified all of the relevant evidence; checking industry submissions did not yield additional RCTs.
- Both the licence indications (for adalimumab and infliximab) and current NICE guidance[112] on infliximab specify the use of the drugs in 'severe' CD but the NICE scope for this work specified 'moderate-to-severe' CD. The identified induction RCTs (or induction phases of maintenance RCTs) included patients with moderate-to-severe CD or a CDAI score between 220 and 400 or 450. This means that none of the included trials matched the NICE guidance or licence indications with reference to the severity of CD. Subgroup results for patients with an initial CDAI score of ≥ 300 have been presented here if they were available from the trials. However, none of the trials were planned for this specific subgroup so did not stratify by whether patients were above or below the 300 CDAI threshold. Furthermore, there were no consensus guidelines in the literature on what CDAI score constitutes 'severe' CD. Both the licence indications and the NICE guidance specify that adalimumab and infliximab should be used in patients who are resistant and/or intolerant to conventional treatment. While many or most of the patients in the included studies were likely to meet this criterion,

some may not have done. Only one study (Rutgeerts *et al.*[58] in infliximab) had an inclusion criterion that patients should be treatment resistant.

- Considerable efforts were made to try to understand the flow of patients through the trials. Several of the included trials had very complicated structures where patients could take several different pathways with different treatments, and one of these has been diagrammed to illustrate patient flow as clearly as possible (see *Appendix 9*).
- The assessment of relative effectiveness of adalimumab and infliximab was limited by the fact that no head-to-head comparisons were available. A formal indirect comparison was inappropriate owing to clinical heterogeneity between trials, indicated by variation in placebo rates, and the variable subgroup selection of responders and non-responders.
- For dichotomous outcomes, variable placebo rates can influence the effect size values depending on the outcome measure used. In order to gain accurate estimates of effect sizes, both placebo and intervention rates and both risk differences and risk ratios are presented in the clinical effectiveness section (see *Chapter 3*).
- Trial designs for the maintenance trials were unusual, so trial quality and any potential impact on the validity of results were investigated in detail.
- The systematic appraisal of both the published papers and industry models facilitated a comprehensive review of the cost-effectiveness evidence in this area. However, the evidence is limited; only four published economic studies met the review inclusion criteria,[5–7,90] of which all considered infliximab, and none considered adalimumab. One paper was not quality assessed because of a lack of detail,[5] and the remaining three papers were of variable quality.[6,7,90]
- The assessments of the industry models were hampered by inconsistent use of data, lack of clarity over the source and interpretation of data and, in one case, unclear details of treatment, which meant that it was not possible to satisfactorily verify or interpret the model.
- The strength of the new economic model presented here is its simple and transparent structure and inputs. However, CD is a very complex disease so it could be argued that the simple model presented here does not take account of all of the nuances of the disease. On the other hand, the more complicated a model becomes, the harder it is to establish accurate inputs to populate the model. Given that there was much uncertainty around a number of model parameters, not least the effectiveness estimates and relapse rates, on balance it was felt to be more appropriate to have a simpler model.

Uncertainties

All of the included trials in the clinical effectiveness review were funded by the relevant drug companies. It is uncertain whether independently funded research in this area would yield different results; it may, however, have much more simple designs, which would aid interpretation of the results considerably.

CD is a lifelong condition with sometimes relatively long cycles of relapse and remission. The trials were mostly of 1 year's duration or less. It is uncertain whether the effect of the drugs would gradually wear off over time, and whether this might be associated with an increase in antibodies to the drug.

The way the included trials were conducted and reported has provided considerable uncertainty as to the effectiveness of the drugs. Aspects of this are discussed in detail in *Chapter 3, Discussion of results and assessment of effectiveness*, and, for the maintenance trials, include:

- How the relatively large proportions who crossed over or were lost to follow-up were counted.

- The use of point prevalence, rather than number of patients remaining in remission or as responders.
- Different or unclear handling of missing binary and continuous data.
- The division of patients into subgroups of responders and non-responders at different time points.

One area of considerable uncertainty is regarding the division of patients as 'responders' and 'non-responders' on the basis of initial response to a single dose or up to three or four doses only. Where trials did give maintenance treatment to 'non-responders', separate results have not been published. It may be that in the 'non-responder' group there are CD patients who will respond to treatment but take longer to do so. The finding regarding the division of patients into responders and non-responders at specific time points has implications for the licence indications. The current licence indication for infliximab mentions that if patients have not responded to induction treatment within 2 weeks, there is no evidence to support further treatment. No evidence was identified to support this statement, so it is unclear whether this part of the licence indication is evidence-based. It may be that the some of the so-called non-responders are taking longer to respond because of drug–drug interactions that have not yet been evaluated.

The patients included in most of the trials had varying levels of severity of CD. They were mostly described as having moderate-to-severe CD or a CDAI score between 220 and 400 or 450. The trials were all multicentre and there is no indication whether patients from different countries had different mean levels of severity. Patients in the USA may have been enrolled at a level of less severity than UK or European patients because of the different health systems in the different countries. Also there is no information on the ethnic group of participants. There is no information on whether the drugs were found to be more effective in one country than another or in one ethnic group than another. Therefore it is unclear how generalisable the results of these trials are to the UK.

Applicability to individual patients is also uncertain. Although patients within the categories of 'moderate-to-severe' CD and fistulising CD may appear to be fairly homogeneous populations, this is unlikely to be the case in practice. Owing to the variable nature of the disease, these are actually likely to be very heterogeneous populations in terms of manifestation of disease, severity of disease, treatment (including surgical) history or concomitant medications, and impact of disease on patients' lives. Therefore the effect of a drug on a specific type of patient is also unclear, and it is not known if there are subgroups of patients who would benefit more or less from these drugs.

The main outcome measures used in the trials are based on the CDAI, which may not be an adequate measure for capturing clinically meaningful changes in disease severity (see *Chapter 3, Discussion of results and assessment of effectiveness* for further detail) or capturing aspects of QoL such as psychological, social and occupational functioning. The disease-specific QoL measure IBDQ was reported in a number of trials but a generic QoL measure such as EQ-5D may have been more useful.

There was very little information from any of the included trials about hospitalisation rates. This is a key cost driver in the industry economic models and the economic model presented here. Also, some hospitalisations are for relatively minor procedures, such as fistula drainage in someone who is relatively well, and can just be an overnight stay whereas others are because patients are seriously ill and have to stay in hospital for weeks. Therefore simple counts of hospitalisations will not take into account all relevant information.

There was considerable uncertainty as to whether treatment might affect mortality rates.

The comparison of AE rates was affected by the design of the maintenance trials, as all patients initially received the study drug before being randomised to drug or placebo and, additionally, patients in most maintenance trials had the opportunity to cross over from placebo to drug treatment if specified criteria were met. Therefore, there is uncertainty around AEs due to the study drug.

The uncertainties in the clinical data (as outlined above) have complicated the economic analysis. It is difficult to define comparators where the details of treatment are uncertain. In such cases, the interpretation of economic models within the published papers becomes problematical.

The published economic models relied heavily on a small body of data, primarily 24 years of data from Olmstead County, USA. A Markov analysis of these data has been widely used. Similarly, in part, the industry models relied on data from small samples.

Both the published cost-effectiveness studies and the industry submission models lacked long-term data.

The analyses within all of the economic models typically used a Markov model. Markov models assume zero memory; how long a patient has been in a health state and how they got there may impact on resources. This could be important in a CD patient group.

Other relevant factors

It was outside the remit of this assessment to look at the effectiveness of adalimumab or infliximab as first-line or 'top-down' therapy. It has been suggested that there may be advantages to this approach in terms of avoiding complications such as surgery and hospitalisations.[61,116]

Chapter 6

Conclusions

Implications for service provision

Adalimumab and infliximab gave statistically significant effect sizes in favour of anti-TNF therapy compared with placebo in all induction trials for moderate-to-severe CD patients [between 6% and 24% (adalimumab) and 21% and 44% (infliximab) more patients in remission with anti-TNFs than with placebo]. There was statistically significant evidence from one large maintenance trial for adalimumab and one large maintenance trial for infliximab that, for the subgroups defined as 'responders', anti-TNF therapy was more beneficial than placebo with respect to remission or response rates at reported follow-up times [between 24% and 29% (adalimumab) and 14% and 24% (infliximab) more patients achieved remission with anti-TNFs].

The findings of the economic model were that for induction, both adalimumab and infliximab were cost-effective (dominant relative to SC) in the management of severe CD and adalimumab was cost-effective for moderate CD (dominant relative to SC), according to the criteria laid out in the NICE *Guide to the methods of technology appraisal*.[93] Induction therapy with infliximab was not cost-effective for moderate CD (ICER of £94,321). Neither drug was cost-effective as maintenance therapy for moderate or severe disease (ICERs around £14M and £5M respectively for both drugs).

The cost-effectiveness analysis highlights important variations in effectiveness and cost between the two therapies. Perhaps most importantly, the analysis reflects the fact that a substantial number of patients will achieve remission under SC and that the incidence of relapse among those in remission is such that maintenance therapy with the anti-TNF drugs assessed here would have to be much less costly for it to be a cost-effective option.

Suggested research priorities

Independently funded RCT research on effectiveness of treatment

- If the licence indication for both drugs remains for patients with severe active CD who are resistant and/or intolerant to other CD treatments, trials for anti-TNF drugs should be conducted in these patients separately.
- In order to take into account natural fluctuations in relapse and remission in CD, any future trials should be conducted for a period of at least 1 year.
- Any future trials in children should include a placebo (SC) arm, as there is currently no evidence of the benefit of anti-TNF therapy compared with SC.
- As there is currently no evidence that the subgroup of 'responders' is more likely to benefit than the whole group of eligible CD patients ('responders' and 'non-responders'), any future maintenance trials should be undertaken in the whole patient group; subgroup analysis of 'responders and 'non-responders' can be undertaken as part of the analysis, providing the trial has sufficiently high patient numbers.
- The potential benefit of 'episodic' treatment (treatment as required/deemed clinically necessary) compared with scheduled treatment should be investigated in an appropriately

designed RCT, randomised to three treatment arms (placebo or SC, 'episodic' treatment and scheduled treatment) after appropriate induction.

- CD is a relapsing and remitting condition. Each individual will have episodes of varying length and severity and periods of remission of varying length and mildness. Some patients will go into remission without the use of additional drug treatment. Therefore it is vital that this is taken into account when planning RCTs to assess accurately the added benefit of a particular drug treatment.
- There should be no scheduled crossovers in RCTs as this means that there is no true placebo arm and results become difficult to interpret, particularly where high proportions of patients cross over. Where patients need to use alternative treatment during the course of a trial, they should be considered as withdrawals.
- Any future trials should measure QoL (using a generic QoL measure, e.g. EQ-5D) and should also record number and type of hospitalisations (including length of stay in hospital), as this information is important when considering the cost-effectiveness of treatments. If CDAI continues to be used as the main outcome measure there needs to be much more work on how this translates to the effect of the disease on the person. Does a change of 50 points from 150 to 200 have a similar magnitude of impact as a change from 350 to 400?
- Reporting of trial results needs to be clear, with results reported for all patients, and responders and non-responders separately if appropriate, and numbers of withdrawals at each time point clearly stated.

Research into the natural history of Crohn's disease

There is currently little information on the natural history of the disease in individual patients. A cohort study following individual patients over several years would provide information on mortality rates, and the length of time patients have mild, moderate or severe disease or are in remission; this information in turn would facilitate the interpretation of trial results. This cohort study must include a variety of patient attributes including ethnicity.

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Contributions of authors

The protocol was written by J Dretzke, C Meads and M Connock, with comments from all coauthors. Literature searching was carried out by A Fry-Smith. Study selection, data extraction and quality assessment clinical effectiveness were carried out by J Dretzke, M Connock, J Czeczot and C Meads. M Connock performed the clinical effectiveness analysis, with comments from all coauthors. Systematic review cost-effectiveness was carried out by R Edlin, C Hulme and C McCabe. R Edlin, C Hulme and C McCabe did the appraisal of industry models with comments from all coauthors. C McCabe, R Edlin and J Round ran the de novo economic model. J Dretzke, R Edlin, J Round, M Connock, C Meads, C Hulme and C McCabe wrote this report, with contributions from all coauthors. C Meads was the project manager.

About 'home unit'

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively undertake research synthesis to produce health technology assessments. Most of the members are based in the Department of Public Health & Epidemiology, University of Birmingham, Birmingham, UK; however, other members are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility, University of Birmingham, Birmingham, UK.

The WMHTAC produce systematic reviews, health technology assessments and economic evaluations for the NHS R&D HTA programme (NCCHTA), NICE, and for the health service in the West Midlands. The WMHTAC also undertakes methodological research on research synthesis, and provides training in systematic reviews and health technology assessment.

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Appendix 1

Calculation of Crohn's Disease Activity Index (adapted from Best *et al.*[39])

Variable	Description	Scoring	Multiplier
Number of liquid stools	Sum of 7 days		×2
Abdominal pain	Sum of 7 days' ratings	0 = none	×5
		1 = mild	
		2 = moderate	
		3 = severe	
General well-being	Sum of 7 days' ratings	0 = generally well	×7
		1 = slightly under par	
		2 = poor	
		3 = very poor	
		4 = terrible	
Extraintestinal complications	Number of complications listed	Arthritis/arthralgia, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, aphtous stomatitis, anal fissure/fistula/abscess, fever >37.8 °C	×20
Antidiarrhoeal drugs	Use in the previous 7 days	0 = no	×30
		1 = yes	
Abdominal mass		0 = no	×10
		2 = questionable	
		5 = definite	
Haematocrit	Expected–observed haematocrit	Men: 47 observed	×6
		Women: 42 observed	
Body weight	Ideal/observed ratio	[1 – (ideal/observed)] × 100	×1 (not < –10)

Appendix 2

Guidelines on the medical management of Crohn's disease

From: Carter* et al.[9] *on behalf of the British Society of Gastroenterology

The severity of CD is more difficult to assess than ulcerative colitis. The general principles are to consider the site (ileal, ileocolic, colonic, other), pattern (inflammatory, stricturing, fistulising) and activity of the disease before treatment decisions are made in conjunction with the patient.

An alternative explanation for symptoms other than active disease should be considered (such as bacterial overgrowth, bile salt malabsorption, fibrotic strictures, dysmotility, gall stones) and disease activity confirmed (usually by CRP or erythrocyte sedimentation rate) before starting steroids. Individuals with CD have many investigations over their lifetime, and imaging (colonoscopy, small bowel radiology) should not be repeated unless it will alter management or a surgical decision depends on the result.

1.1 Active ileal/ileocolonic/colonic disease

Patients should be encouraged to participate actively in the decision to treat with high dose aminosalicylates, different corticosteroids, nutritional therapy, antibiotics, new biological agents, or surgery. Infliximab is considered in section 1.5.

In mild ileocolonic CD, high-dose mesalazine (4 g/day) may be sufficient initial therapy (grade A).

For patients with moderate to severe disease, or those with mild to moderate ileocolonic CD that has failed to respond to oral mesalazine, oral corticosteroids such as prednisolone 40-mg daily is appropriate (grade A).

Prednisolone should be reduced gradually according to severity and patient response, generally over 8 weeks. More rapid reduction is associated with early relapse (grade C).

Budesonide 9-mg daily is appropriate for patients with isolated ileo-caecal disease with moderate disease activity, but marginally less effective than prednisolone (grade A).

Intravenous steroids (hydrocortisone 400 mg/day or methylprednisolone 60 mg/day) are appropriate for patients with severe disease (grade B). Concomitant IV metronidazole is often advisable, because it may be difficult to distinguish between active disease and a septic complication.

Elemental or polymeric diets are less effective than corticosteroids, but may be used to induce remission in selected patients with active CD who have a contraindication to corticosteroid therapy, or who would themselves prefer to avoid such therapy (grade A).

Elemental or polymeric diets are appropriate adjunctive therapy (grade C).

Total parenteral nutrition is appropriate adjunctive therapy in complex, fistulising disease (grade B).

Sulphasalazine 4-g daily is effective for active colonic disease, but cannot be recommended as first line therapy in view of a high incidence of side effects. It may be appropriate in selected patients (grade A).

Metronidazole 10–20 mg/kg/day, although effective, is not usually recommended as first line therapy for CD in view of the potential for side effects (grade A). It has a role in selected patients with colonic or treatment-resistant disease, or those who wish to avoid steroids.

Topical mesalazine may be effective in left-sided colonic CD of mild to moderate activity (grade B).

Azathioprine 1.5–2.5 mg/kg/day or mercaptopurine 0.75–1.50 mg/kg/day may be used in active CD as adjunctive therapy and as a steroid sparing agent. However, its slow onset of action precludes its use as a sole therapy (grade A).

Infliximab 5 mg/kg is effective (grade A), but is best avoided in patients with obstructive symptoms (see section 1.5).

Surgery should be considered for those who have failed medical therapy, and may be appropriate as primary therapy in patients with limited ileal or ileo-caecal disease (grade C).

Recommendations

1.1.1 Initial treatment of active ileal or ileocolonic CD with high dose mesalazine, corticosteroids, nutritional therapy or surgery should be tailored to the severity of disease and take the views of the patient into account.

1.1.2 There is insufficient evidence to recommend the use of other agents outside trials or specialist centres.

1.2 Fistulising and perianal disease

Active perianal disease or fistulas are often associated with active CD elsewhere in the gastrointestinal tract. The initial aim should be to treat active disease and sepsis. For more complex, fistulising disease, the approach involves defining the anatomy, supporting nutrition and potential surgery. For perianal disease, magnetic resonance imaging and examination under anaesthetic are particularly helpful.

Metronidazole 400-mg three times daily (grade A) and/or ciprofloxacin 500-mg twice daily (grade B) are appropriate first line treatments for simple perianal fistulas.

Azathioprine 1.5–2.5 mg/kg/day or mercaptopurine 0.75–1.50 mg/kg/day are potentially effective for simple perianal fistulas or enterocutaneous fistulas where distal obstruction and abscess have been excluded (grade A).

Infliximab (three infusions of 5 mg/kg at 0, 2 and 6 weeks) should be reserved for patients whose perianal or enterocutaneous fistulas are refractory to other treatment, and should be used as part of a strategy that includes immunomodulation and surgery (grade A).

Surgery (see section 7 of the guidelines), including seton drainage, fistulectomy and the use of advancement flaps, is appropriate for persistent or complex fistulas in combination with medical treatment (grade C).

Elemental diets or parenteral nutrition have a role as adjunctive therapy, but not as sole therapy (grade B).

There is insufficient evidence to recommend other agents outside clinical trials or specialist centres.

Recommendation

1.2.1 Controlled therapeutic trials combining medical and surgical therapy in perianal CD should be conducted.

1.3 Other sites

The same general principles apply, although there are no RCTs in the treatment of gastroduodenal or diffuse small bowel disease.

Oral CD. This is best managed in conjunction with a specialist in oral medicine. Topical steroids, topical tacrolimus, intralesional steroid injections, enteral nutrition and infliximab may have a role in management but there are no RCTs.

Gastroduodenal disease. Symptoms are often relieved by proton pump inhibitors. Surgery is difficult and may be complicated by fistulation.

Diffuse small bowel disease. Stricture dilatation or strictureplasty with or without triamcinolone injection should be considered. Nutritional support before and after surgery is usually essential. Other approaches, including the combination of infliximab with surgery for residual strictures, are evolving.

1.4 Maintenance of remission

The efficacy of drug therapy appears to depend on whether remission was achieved with medical or surgical therapy, on the risk of relapse and on the site of disease. Smoking cessation is probably the most important factor in maintaining remission.

To reduce the risk of relapse in CD, all smokers should be strongly advised to stop (grade A), with help (counselling, nicotine patches or substitutes) offered to achieve this.

Mesalazine has limited benefit and is ineffective at doses < 2 g/day or for those who have needed steroids to induce remission (grade A).

Azathioprine 1.5–2.5 mg/kg/day and mercaptopurine 0.75–1.5 mg/kg are effective, but reserved as second line therapy because of potential toxicity (grade A).

Methotrexate (15- to 25-mg intramuscular weekly) is effective for patients whose active disease has responded to intramuscular methotrexate (grade A). It is appropriate for those intolerant of, or who have failed, azathioprine/mercaptopurine therapy (grade B) once potential toxicity and other options, including surgery, have been discussed with the patient. Folic acid 5 mg once a week, taken 3 days after methotrexate, may reduce side effects. Subcutaneous or oral therapy may be effective (grade B).

Infliximab is effective at a dose of 5–10 mg/kg every 8 weeks in patients who have responded to an initial infusion 12 weeks earlier, for up to 44 weeks (grade A). It is best used as part of treatment strategy including immunomodulation once other options, including surgery, have been discussed with the patient (grade B).

Sulphasalazine cannot be recommended (grade A).

Corticosteroids, including budesonide, are not effective (grade A), although some patients have chronic active disease who appear steroid dependent (below).

Recommendations

1.4.1 Patients with CD who smoke should be offered help to stop.

1.4.2 Immunomodulation with azathioprine, mercaptopurine or methotrexate is usually appropriate if patients relapse more than once per year as steroids are withdrawn.

1.5 Chronic active and steroid-dependent disease

Long-term treatment with steroids is undesirable. Patients who have a poor response to steroids can be divided into steroid refractory and steroid dependent. *Steroid-refractory disease* may be defined as active disease in spite of an adequate dose and duration of prednisolone (20 mg/day for 2 weeks) and *steroid dependence* as a relapse when the steroid dose is reduced below 20 mg/day, or within 6 weeks of stopping steroids. Such patients should be considered for treatment with immunomodulators if surgery is not an immediate consideration.

Azathioprine 1.5–2.5 mg/kg/day, or mercaptopurine 0.75–1.25 mg/kg/day are the first line agents of choice for steroid-dependent disease (grade A).

Monitoring the full blood count to detect neutropenia is advisable, although there is no evidence that this is effective because profound neutropenia and sepsis can develop rapidly. The full blood count is best checked within 4 weeks of starting therapy and every 6–12 weeks thereafter, although may be done more frequently. Routine measurement of thiopurine methyltransferase activity before treatment, which may identify some (but not all) patients at risk of neutropenia, cannot yet be recommended but is debated. Large published series report safe use of azathioprine without thiopurine methyltransferase assay.

Methotrexate intramuscular 25-mg weekly for up to 16 weeks followed by 15-mg weekly is effective for chronic active disease (grade A). Oral dosing is effective for many patients (grade B).

Infliximab (5 mg/kg) should be reserved for patients with moderate to severe CD who are refractory to or intolerant of treatment with steroids, mesalazine, azathioprine/mercaptopurine and methotrexate, and for whom surgery is considered inappropriate (grade A).

Recommendation

1.5.1 Immunomodulation with azathioprine, mercaptopurine or methotrexate should be tried if steroids cannot be withdrawn without deterioration in disease activity.

Appendix 3

Search strategy clinical effectiveness

Clinical effectiveness searches

Note: certolizumab pegol and natalizumab were originally part of this appraisal; they were subsequently excluded after searching had been completed.

Source – MEDLINE (Ovid), 1950 to week 4 May 2007

1. (adalimumab or humira).mp., (540)
2. (certolizumab or cimzia).mp. (19)
3. (infliximab or remicade).mp. (3096)
4. (natalizumab or tysabri).mp.(208)
5. or/1-4 (3473)
6. Crohn Disease/ (21,624)
7. crohn$.mp. (25,626)
8. or/6-7 (25,626)
9. 5 and 8 (1046)
10. randomized controlled trial.pt. (235,561)
11. controlled clinical trial.pt. (74,973)
12. randomized controlled trials.sh. (48,808)
13. random allocation.sh. (57,966)
14. double blind method.sh. (91,410)
15. single blind method.sh. (10,959)
16. or/10-15 (399,453)
17. (animals not human).sh. (4,090,275)
18. 16 not 17 (365,869)
19. clinical trial.pt. (436,028)
20. exp clinical trials/ (191,534)
21. (clin$adj25 trial$).ti,ab. (130,375)
22. ((singl$or doubl$or trebl$or tripl$) adj25 (blind$or mask$)).ti,ab. (90,759)
23. placebo$.ti,ab. (102,414)
24. random$.ti,ab. (372,182)
25. placebos.sh. (26,175)
26. research design.sh. (47,543)
27. or/19-26 (846,379)
28. 27 not 17 (743,134)
29. 28 not 18 (394,326)
30. 18 or 29 (760,195)
31. 9 and 30 (276)
32. limit 31 to yr="2000 - 2007" (258)

Source – MEDLINE (Ovid), 1950 to week 2 June 2007*

1. ca2.mp. (105,839)
2. d2e7.mp. (23)
3. cdp870.mp. (26)
4. pha-738144.mp. (0)
5. pha 738144.mp. (0)
6. (anti adj2 4 integrin).mp. (45)

7. anti alpha4 integrin.mp. (49)
8. anti alpha 4 integrin.mp. (32)
9. or/1-8 (105,978)
10. crohn disease/ (21,691)
11. crohn$.mp. (25,715)
12. or/10-11 (25,715)
13. 9 and 12 (66)
14. randomized controlled trial.pt. (236,980)
15. controlled clinical trial.pt. (75,195)
16. randomized controlled trials.sh. (49,205)
17. random allocation.sh. (58,180)
18. double blind method.sh. (91,776)
19. single blind method.sh. (11,028)
20. or/14-19 (401,708)
21. (animals not human).sh. (4,106,179)
22. 20 not 21 (367,711)
23. clinical trial.pt. (436,884)
24. exp clinical trials/(192,444)
25. (clin$adj25 trial$).ti,ab. (131,452)
26. ((singl$or doubl$or trebl$or tripl$) adj25 (blind$or mask$)).ti,ab. (91,157)
27. placebo$.ti,ab. (102,972)
28. random$.ti,ab. (374,725)
29. placebos.sh. (26,255)
30. research design.sh. (47,827)
31. or/23-30 (851,045)
32. not 21 (747,002)
33. 32 not 22 (396,637)
34. 22 or 33 (764,348)
35. 13 and 34 (26)
36. limit 35 to yr="2000 - 2007" (22)

*Additional search to account for alternative terminology used for the drugs.

Source – EMBASE (Ovid), 1980 to week 22 2007

1. (adalimumab or humira).mp. (2036)
2. (certolizumab or cimzia).mp., (230)
3. (infliximab or remicade).mp., (7811)
4. (natalizumab or tysabri).mp. (843)
5. or/1-4 (8685)
6. Crohn Disease/ (20,817)
7. crohn$.mp. (23,756)
8. or/6-7 (23,756)
9. 5 and 8 (2554)
10. limit 9 to "treatment (2 or more terms min difference)" (506)
11. limit 10 to yr="2000 - 2007" (492)

Source – EMBASE (Ovid), 1980 to week 25* 2007

1. ca2.mp. (115,879)
2. d2e7.mp. (65)
3. cdp870.mp. (16)
4. pha-738144.mp. (1)

5. pha 738144.mp. (1)
6. (anti adj2 4 integrin).mp. (9)
7. anti alpha4 integrin.mp. (37)
8. anti alpha 4 integrin.mp. (2)
9. or/1-8 (116,001)
10. crohn$.mp. (23,876)
11. crohn disease/ (20,928)
12. or/10-11 (23,876)
13. 9 and 12 (72)
14. limit 13 to ("treatment (2 or more terms min difference)" and yr="2000 - 2007") (17)

*Additional search to account for alternative terminology used for the drugs.

Cochrane Library (CENTRAL), 2007, issue 2

#1 adalimumab OR humira
#2 certolizumab OR cimzia
#3 infliximab OR remicade
#4 natalizumab OR tysabri
#5 (#1 OR #2 OR #3 OR #4)
#6 crohn*
#7 MeSH descriptor Crohn Disease explode all trees
#8 (#6 OR #7)
#9 (#5 AND #8)

Cochrane Library (CENTRAL), 2007, issue 2*

#1 ca2
#2 d2e7
#3 cdp870
#4 pha-738144
#5 pha next 738144
#6 antegren
#7 integrin
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 crohn*
#10 MeSH descriptor Crohn Disease explode all trees
#11 (#9 OR #10)
#12 (#8 AND #11)

*Additional search to account for alternative terminology used for the drugs.

Source – MEDLINE (Ovid) In-Process & Other Non-Indexed Citations, 4 June 2007

1. (adalimumab or humira).mp (71)
2. (certolizumab or cimzia).mp (10)
3. (infliximab or remicade).mp (209)
4. (natalizumab or tysabri).mp. (14)
5. or/1-4 (249)
6. crohn$.mp. (549)
7. 5 and 6 (77)
8. limit 7 to yr="2000 - 2007" (76)

Source – MEDLINE (Ovid) In-Process & Other Non-Indexed Citations, 26 June 2007*

1. ca2.mp. (1007)
2. d2e7.mp. (0)
3. cdp870.mp. (0)
4. pha-738144.mp. (0)
5. pha 738144.mp. (0)
6. (anti adj2 4 integrin).mp. (0)
7. anti alpha4 integrin.mp. (2)
8. anti alpha 4 integrin.mp. (0)
9. or/1-8 (1009)
10. crohn$.mp. (602)
11. 9 and 10 (0)

*Additional search to account for alternative terminology used for the drugs.

Ongoing studies

Source – National Research Register (2007 Issue 2)

See above *Cochrane Library* clinical effectiveness search strategy.

Sources – Current Controlled Trials and ClinicalTrials.gov

Search terms: adalimumab OR humira; certolizumab OR cimzia; infliximab OR remicade; natalizumab OR tysabri; ca2 OR d2e7; cdp870 OR pha-738144; pha 738144 OR anti 4 integrin; anti alpha4 integrin OR anti alpha 4 integrin

References were selected where they also included CD.

Appendix 4

Data extraction form

Reviewer: Date:

Study author, year: Reference: Geographical location of the study

Baseline characteristics	Placebo *n*=	Drug 1 *n*=	Drug 2 *n*=	Drug 3 *n*=
Mean age ± SD				
Sex				
Ethnicity				
Mean weight (kg) ± SD				
Mean height ± SD				
Number smokers				
Mean duration of Crohn's disease (years) ± SD				
Intestinal area involved				
Ileum only				
Colon only				
Ileum/colon				
Jejunal only				
Perianal only				
Other				
% with fistulas				
Where all with fistulising disease:				
Number of (draining) fistulas				
Location of fistulas				
Mean PDAI score				
Previous surgery for Crohn's				
Mean baseline CDAI ± SD				
Mean baseline IBDQ median (range)				
Other disease activity index or measure of disease severity (e.g. Harvey–Bradshaw)				
Mean C-reactive protein ± SD				
Previous or concurrent biologic agent (state which)				
(% of patients previously received/receiving agent, % naive)				
Other concurrent medication				
Corticosteroids (e.g. prednisone or budesonide) state which				
Immunosuppressive agent (e.g. mercaptopurine, methotrexate, azathioprine) state which				
Oral aminosalicylate				
Antibiotic				
Other: specify				

Notes: (identify any statistically significant differences)

Study design/methodology – see flow chart

List all outcomes:

Do not extract data on laboratory parameters

Outcomes: state which type of analysis (e.g. efficacy, ITT, safety, etc.)

Outcome 1)

	Placebo *n*=	Drug 1 *n*=	Drug 2 *n*=	Drug 3 *n*=
Baseline				
First time point				
p-value vs placebo				
Second time point				
p-value vs placebo				
Third time point				
p-value vs placebo				

List number of patients for each study arm at each time point
Repeat table for all relevant outcomes

Subgroup analyses (if applicable):

Safety

Adverse event		Placebo *n*=	Drug 1 *n*=	Drug 2 *n*=	Drug 3 *n*=
Average follow-up					
Any adverse event (%)					
Death					
Adverse event leading to withdrawal					
GI	Nausea				
	Vomiting				
	Abdominal pain				
CNS	Headache				
	Pain				
	Fatigue				
Infection	URTI				
	Other infection				
	Serious infection				
	TB				
Haematological					
Cardiovascular	Chest pain				
	Hypotension				
	Hypertension				
	Heart failure				
Skin	Pruritus				
	Injection site reaction				
	(give details)				
Hypersensitivity	Acute				
	Delayed				

Adverse event		Placebo *n*=	Drug 1 *n*=	Drug 2 *n*=	Drug 3 *n*=
Respiratory	Dyspnoea				
MS	MS or symptoms of MS (e.g. demyelination)				
Bone marrow					
Other	Myalgia				
	Fever				
	Abscess				
	Antibodies to DNA				
	Human anti-TNF agent				
	Lupus arthritis				
	AE during or within 2 hours of infusion				
	Other				
	Other				

Inclusion/exclusion criteria

Inclusion criteria:

Age/sex
Duration of CD
Severity of CD
Surgical history
Concurrent treatment (non biologics)
Concurrent treatment (biologics)
Previous treatment (non biologics)
Previous treatment (biologics)
Concurrent disease
Female patients of child bearing potential included?

Exclusion criteria:

Concurrent treatment (non biologics)
Concurrent treatment (biologics)
Previous treatment (non biologics)
Previous treatment (biologics)
Previous/imminent surgery
Concurrent disease

Are patients within UK licence in terms of severity of disease and resistance/intolerance to conventional treatment?

Follow-up of patients through trial

Number of patients enrolled:
Number of patients excluded (state main reasons)
Number of patients randomised:
Number of patients at each time point and reasons for withdrawal

	Placebo	Drug 1	Drug 2	Drug 3	Drug 4
Time point 1					
Time point 2					
Time point 3					
Time point 4					
Number completed					

Duration of study:

Number of infusions:
(how administered/where administered)

Number of assessments:

Additional notes on trial design (if applicable):

Funding source:

Quality assessment

Randomisation	Details on method of randomisation
	If described, was the method adequate?
Concealment	Details of method of allocation concealment
	If described, was the method adequate?
Blinding	Details on placebo (indistinguishable from intervention?)
	Details of blinding: patients
	Details of blinding: study investigators
	Details of blinding: study co-ordinators
	Details of blinding: data analysts
	Details of blinding: other
Comparability of groups	Were groups comparable at baseline?
	For a) baseline scores
	For b) demographics
	Were groups treated the same throughout the trial, with the exception of the intervention?
	For a) assessments
	For b) other care

Analysis	Were all trial participants accounted for throughout trial?	
	Was loss to follow-up >20%?	
	(state actual loss to follow-up for each time point)	
	Was it stated that an ITT analysis was performed?	
ITT: data from all assessments used regardless of compliance with allocated treatment	Was an ITT analysis performed for all relevant outcomes (according to the reported data), or was a sensitivity analysis performed?	
Sensitivity analysis should be performed where assessment data missing	If other analysis (e.g. including open-label patients, describe)	
	Was a sample size calculation performed?	
	Was there any selective reporting of outcome measures?	

Description of which patients were included in which analysis: (primary, secondary, efficacy, ITT, open label, safety, etc.)

Appendix 5

Extraction of data from published graphs

Scans of published graphs were overlayed with a grid, printed, enlarged to A3 and then used to extract data. The data were used to redraw the graph and compare with the original. Examples are shown below.

Scan of published graph with grid overlay

(CiC information has been removed.)

Scan of published graph with grid overlay

(CiC information has been removed.)

Scans of published graphs overlayed with graphs redrawn using data extracted from grid-overlayed originals

(CiC information has been removed.)

Appendix 6

Consistency of trials with licence indications

TABLE 77 Consistency of trials with licence indications

Licence indication	Study	Population/study characteristics
Adalimumab		
■ For treatment of severe, active CD (note: *severe* is not further defined) ■ In patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies ■ Recommended induction dose regimen is 80 mg at week 0 followed by 40 mg at week 2; in case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0, 80 mg at week 2 can be used ■ After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection; patients who experience decrease in their response may benefit from an increase in dose intensity to 40 mg every week	Hanauer *et al.*, 2006 CLASSIC I[63] INDUCTION	■ Moderate-to-severe CD (CDAI 220–450) 'despite conventional therapy' ■ Concomitant steroids and immunosuppressants permitted (unclear if all patients resistant or intolerant) ■ Three dose regimens used: 40 mg/20 mg, 80 mg/40 mg, 160 mg/80 mg at weeks 0 and 2 respectively
	Sandborn *et al.*, 2007 GAIN[64] INDUCTION	■ Moderate-to-severe CD (CDAI 220–450) ■ Concomitant steroids and immunosuppressants permitted (unclear if all patients resistant or intolerant) ■ All patients resistant/intolerant to infliximab ■ Higher induction dose regimen used (160 mg at week 0, 80 mg at week 2)
	Colombel *et al.*, 2007 CHARM[67] MAINTENANCE	■ Moderate-to-severe CD (CDAI 220–450) ■ Concomitant corticosteroids and immunosuppressants permitted; unclear if all patients resistant or intolerant ■ 40 mg weekly or every other week compared with placebo
	Sandborn *et al.*, 2007 CLASSIC II[66] MAINTENANCE	■ See CLASSIC I[63] for patient characteristics ■ 40 mg weekly or e.o.w. compared with placebo

Licence indication	Study	Population/study characteristics
Infliximab – adults		
■ For treatment of severe, active CD (note: *severe* is not further defined) ■ In patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies ■ 5 mg/kg given as an intravenous infusion over a 2-hour period; available data do not support further treatment in patients not responding within 2 weeks ■ Maintenance: additional infusions of 5 mg/kg at 2 and 6 weeks after the initial dose, followed by infusion every 8 weeks ■ Readministration: infusion of 5 mg/kg (within 16 weeks following the last infusion) if signs and symptoms of the disease recur	Targan *et al.*, 1997[57] INDUCTION	■ Moderate-to-severe CD, CDAI score between 220 and 450 ■ Patients eligible if receiving mesalamine or oral corticosteroids or mercaptopurine or azathioprine (unclear if all patients resistant or intolerant) ■ Single intravenous infusion over 2 hours of 5 mg/kg, 10 mg/kg or 20 mg/kg infliximab
	Hanauer *et al.*, 2002[3] and Rutgeerts *et al.*, 2004[2] ACCENT I[2,3] MAINTENANCE	■ Moderate-to-severe CD, CDAI score between 220–450 ■ Patients receiving corticosteroids, immunosuppressive agents, aminosalicylates or antibiotics eligible (unclear if all patients resistant or intolerant) ■ Infusions at week 2 and 6 after the initial dose, then every 8 weeks of 5 mg/kg or 10 mg/kg infliximab
	Rutgeerts *et al.*, 1999[58] (follow-on from Targan *et al.*[57] trial) MAINTENANCE	■ Moderate-to-severe CD, CDAI score between 220 and 400 ■ Concomitant corticosteroids or immunosuppressive agents allowed, patients who had not responded to aminosalicylates eligible ■ States that all patients treatment resistant (not specified which treatment(s) specifically) ■ 10 mg/kg infliximab every 8 weeks
Infliximab – fistulising CD		
■ Treatment of fistulising, active CD in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy) ■ An initial 5 mg/kg infusion given over a 2-hour period is to be followed with additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion; if a patient does not respond after these three doses, no additional treatment with infliximab should be given ■ In responding patients, the strategies for continued treatment are: additional infusions of 5 mg/kg every 8 weeks or readministration if signs or symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks	Present *et al.*, 1999[62] INDUCTION	■ Single or multiple draining fistulas ■ Concomitant aminosalicylates, corticosteroids, mercaptopurine, azathioprine or antibiotics permitted (unclear if all patients resistant or intolerant) ■ 5 mg/kg or 10 mg/kg infliximab at weeks 0, 2 and 6
	Sands *et al.*, 2004 ACCENT II[65] MAINTENANCE	■ Single or multiple draining fistulas ■ Concomitant aminosalicylates, corticosteroids, mercaptopurine, azathioprine, methotrexate or antibiotics permitted (unclear if all patients resistant or intolerant) ■ 5 mg/kg or 10 mg/kg infliximab at weeks 0, 2 and 6 (all patients), then 5 mg/kg infliximab every 8 weeks

Licence indication	Study	Population/study characteristics
Infliximab – children		
■ For treatment of severe, active Crohn's disease (note *severe* is not further defined) ■ In paediatric patients aged 6–17 years ■ Who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant or have contraindications to such therapies; Remicade has been studied only in combination with conventional immunosuppressive therapy ■ 5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter; some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient Available data do not support further infliximab treatment in paediatric patients not responding within the first 10 weeks of treatment	Baldassano *et al.*, 2003[46] INDUCTION	■ Moderate-to-severe, PCDAI ≥ 30 or modified CDAI ≥ 200 ■ Active disease despite prior treatment with one or more of: corticosteroids, mercaptopurine or azathioprine, methotrexate, ciclosporin, tacrolimus ■ Single 2-hour infusion of 1 mg/kg, 5 mg/kg or 10 mg/kg infliximab
	Hyams *et al.*, 2007 REACH[45] MAINTENANCE	■ Moderate-to-severe, PCDAI ≥ 30 ■ Required concomitant treatment with azathioprine, mercaptopurine or methotrexate; permitted: aminosalicylates, oral corticosteroids, antibiotics or enteral nutrition (unclear if all patients resistant or intolerant) ■ 5 mg/kg infliximab at weeks 0, 2 and 6; followed by 5 mg/kg infliximab every 8 or 12 weeks

Appendix 7

Publications not obtained

Infliximab. A last resort for Crohn's disease after failure of steroids and azathioprine. *Prescrire Int* 2000;**9**:163–5.

Abramowitz L. Treatments of anoperineal localized Crohn's disease. [French]. *Acta Endoscopica* 2005;**35**:748–50.

Bayes M, Rabasseda X, Prous JR. Gateways to clinical trials: November 2006. *Methods Find Exp Clin Pharmacol* 2006;**28**:657–78.

Bayes M, Rabasseda X, Prous JR. Gateways to clinical trials: January/February 2007. *Methods Find Exp Clin Pharmacol* 2007;**29**:53–71.

Dotan I, Yeshurun D, Hallak A, Horowitz N, Tiomny E, Reif S, *et al.* [Treatment of Crohn's disease with anti TNF alpha antibodies--the experience in the Tel Aviv Medical Center]. [Hebrew]. *Harefuah* 2001;**140**:289–93.

Escher JC, van-den BG, Kate FT, te VA, van DS. Mucosal healing and down-regulation of inflammation with anti-tumor necrosis factor a (Infliximab) in children with refractory Crohn's disease. *J Pediatr Gastroenterol Nutr* 2000;**31**:S19.

Isaacs KL. Adalimumab induction therapy in Crohn disease. *Evid Base Gastroenterol* 2006;**7**:67–8.

Koltun WA. A Paradigm for the Management of Complex Perineal Crohn's Disease in the Anti-TNF Era. *Semin Colon Rectal Surg* 2006;**17**:61–7.

Mahadevan U. TNF-alpha antagonists: Benefits beyond remission. *Rev Gastroenterol Disord* 2007;**7**(Suppl. 1):S13–S19.

Mealy NE, Bayes M. Treatment of gastrointestinal disorders: Certolizumab pegol. *Drugs Future* 2005;**30**:600–1.

Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, *et al.* A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology* 2005;**129**:807–18. [Erratum published in *Gastroenterology* 2005;**129**:1808.]

Appendix 8

Ongoing trials

TABLE 78 Ongoing trials likely to meet inclusion criteria

Study/source	Country	Study design	Population	Treatment	Trial start/likely completion
Study M04–729 NCT00445939 Clinicaltrials.gov Information provided by Abbott	Japan	Multicentre, randomised, double-blind, placebo-controlled study of adalimumab for the induction of clinical remission in Japanese subjects with CD	Japanese subjects with CD, CDAI score of ≥ 220 and ≤ 450; if previously received infliximab, subjects who discontinued owing to a loss of response or intolerance	Adalimumab	Study start March 2007; recruitment stage (information verified March 2007)
Study M06–837 NCT00445432 Clinicaltrials.gov Information provided by Abbott	Japan	Multicentre, randomised, double-blind, placebo-controlled study of adalimumab for the maintenance of clinical remission in Japanese subjects with CD	Japanese subjects with CD enrolled in and completed study M04–729	Adalimumab	Study start March 2007; recruitment stage (information verified March 2007)
Study M05–769 NCT00348283 Clinicaltrials.gov Information provided by Abbott	Multicentre (USA, Canada, Europe)	Multicentre, randomised, double-blind, placebo-controlled study of the human anti-TNF monoclonal antibody adalimumab endoscopy trial to evaluate the effects on mucosal healing in subjects with CD involving the colon	Patients with moderate-to-severe ileocolonic CD	Adalimumab	Study start August 2006; recruitment stage (information verified April 2007)
Study M06–806 NCT00409682 Clinicaltrials.gov Information provided by Abbott	Multicentre (USA, Canada, Europe)	Multicentre, randomised, double-blind, placebo-controlled study to evaluate the safety, efficacy and pharmacokinetics of the human anti-TNF monoclonal antibody adalimumab in paediatric subjects with moderate-to-severe CD	Children aged 6–17 years with moderate-to-severe CD	Adalimumab	Study start March 2007; recruitment stage or not yet recruiting (information verified April 2007)

Since the writing of this report three of the above trails have completed, with one (NCT00445432) still ongoing (checked November 2010).

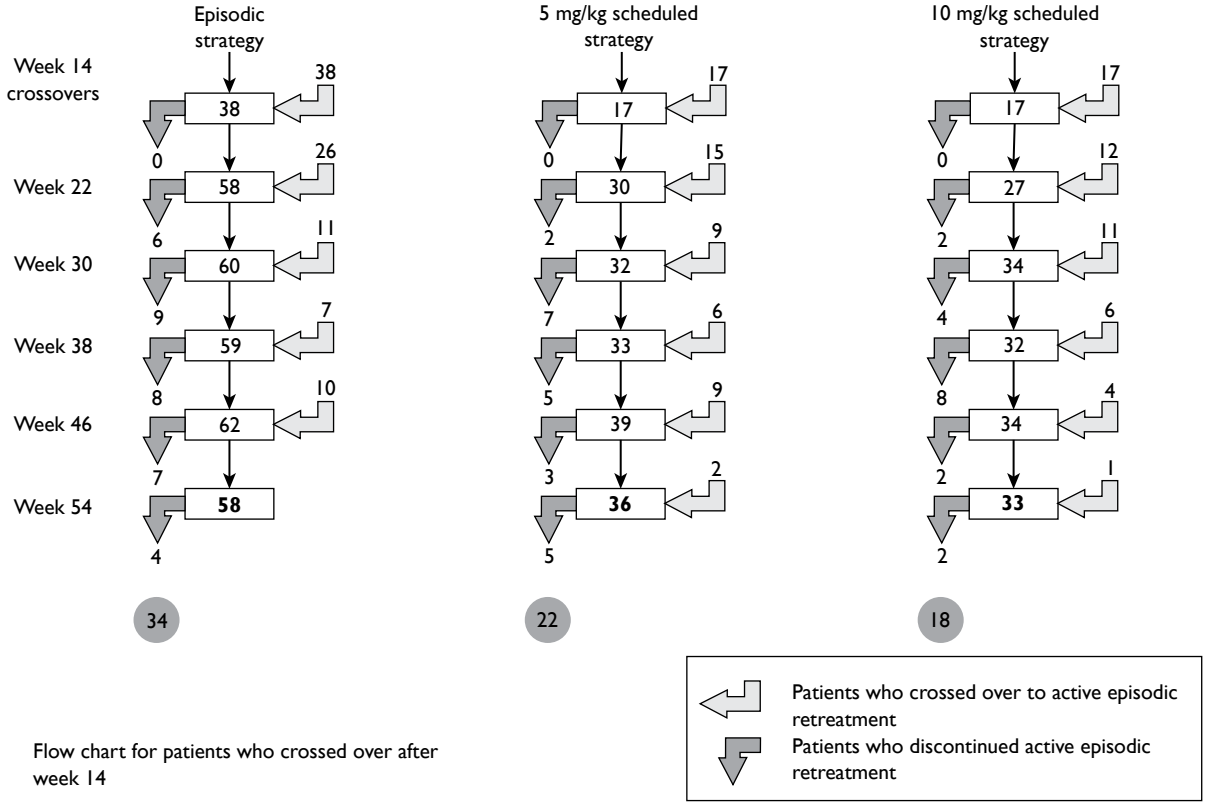
TABLE 79 Ongoing trials not meeting inclusion criteria

Study/source	Country	Study design	Population	Treatment	Trial start/likely completion
RP0401 NCT00132899 Information provided by Robarts Research Institute, Schering-Plough	Canada	A phase III randomised, placebo-controlled, double-blind, parallel group, multicentre study to evaluate the safety and efficacy of infliximab with methotrexate for the long-term treatment of CD	Patients with symptoms that are persistent enough to require corticosteroid therapy	Infliximab (vs infliximab plus methotrexate)	Study start December 2005, expected completion December 2007 (information verified December 2005)
CR004804 NCT00094458 Information provided by Centocor, Inc., Schering-Plough	Multicentre (USA, Canada, Europe)	Multicentre, randomised, double-blind, active controlled trial comparing Remicade (Infliximab) and Remicade plus azathioprine in the treatment of patients with CD naive to both immunomodulators and biologic therapy (SONIC trial)	Patients with CDAI score of >220 to <450	Infliximab (vs infliximab plus azathioprine)	Study start March 2005; recruitment stage or no longer recruiting (information verified May 2007)

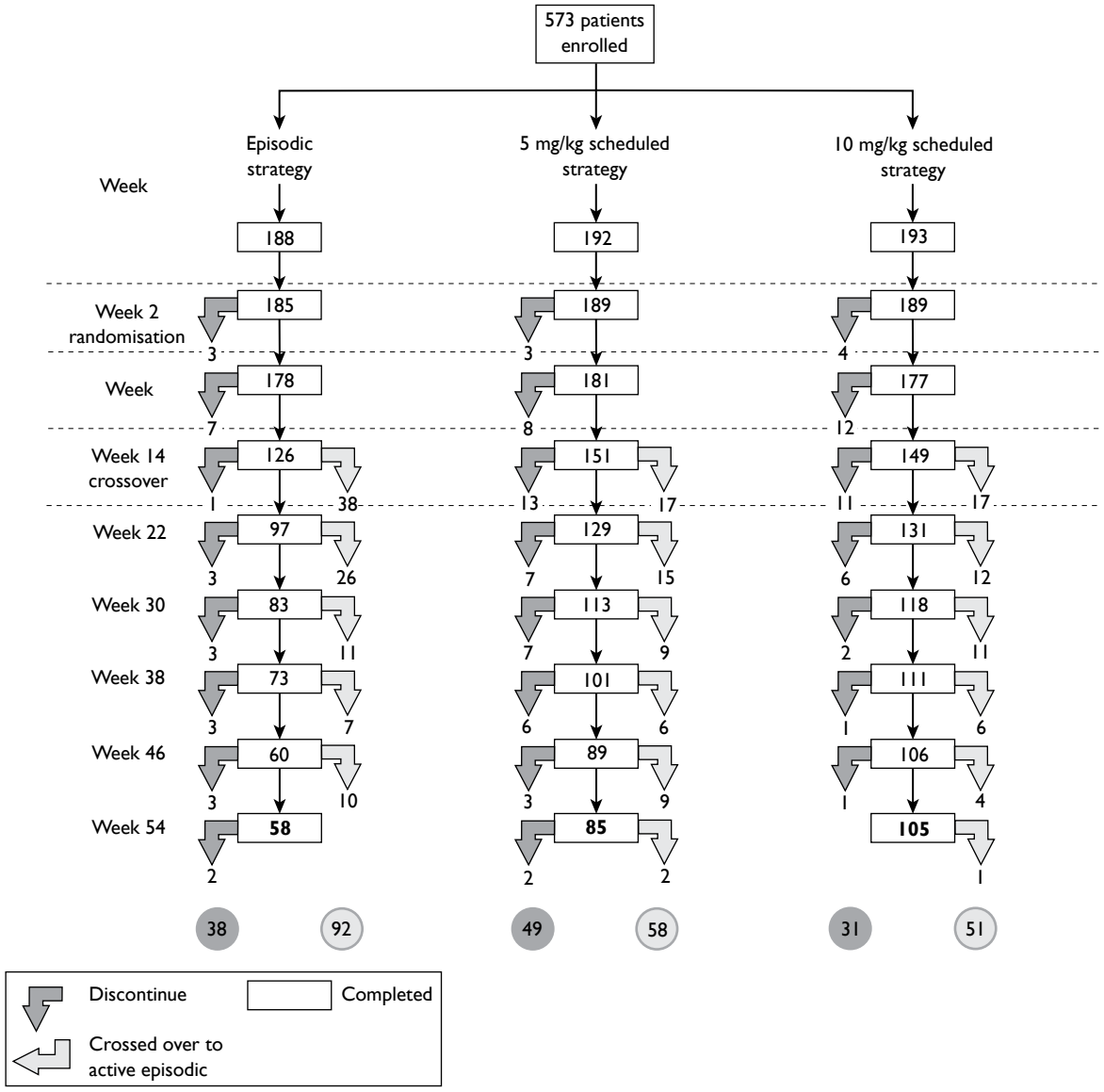
SONIC, Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease.
Since the writing of this report both of the above trials have completed (checked November 2010).

Appendix 9

Flow of patients through ACCENT I[2,3] trial



Flow chart for patients who crossed over after week 14


573 patients enrolled
Episodic strategy
5 mg/kg scheduled strategy
10 mg/kg scheduled strategy
Week
188
192
193
Week 2 randomisation
185
189
189
3
3
4
Week
178
181
177
7
8
12
Week 14 crossover
126
151
149
1
38
13
17
11
17
Week 22
97
129
131
3
26
7
15
6
12
Week 30
83
113
118
3
11
7
9
2
11
Week 38
73
101
111
3
7
6
6
1
6
Week 46
60
89
106
3
10
3
9
1
4
Week 54
58
85
105
2
2
2
1
38
92
49
58
31
51
Discontinue
Completed
Crossed over to active episodic

Appendix 10

Results for all included studies irrespective of licence indication

This appendix presents the results from the included trials by outcome measure in the form of forest plots.

Induction trials

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RR
Targan *et al.*[57]	52	1	Inflix	5	0	4.64
Targan *et al.*[57]	52	2	Inflix	5	0	10.19
Targan *et al.*[57]	52	3	Inflix	5	0	11.11
Targan *et al.*[57]	52	4	Inflix	5	0	12.04
Targan *et al.*[57]	53	1	Inflix	10	0	2.679
Targan *et al.*[57]	53	2	Inflix	10	0	5.357
Targan *et al.*[57]	53	3	Inflix	10	0	5.357
Targan *et al.*[57]	53	4	Inflix	10	0	6.25
Targan *et al.*[57]	53	1	Inflix	20	0	2.679
Targan *et al.*[57]	53	2	Inflix	20	0	5.357
Targan *et al.*[57]	53	3	Inflix	20	0	5.357
Targan *et al.*[57]	53	4	Inflix	20	0	6.25
CLASSIC I[63]	148	1	Ada	40/20	0 and 2	2.4
CLASSIC I[63]	148	2	Ada	40/20	0 and 2	1
CLASSIC I[63]	148	4	Ada	40/20	0 and 2	1.444
CLASSIC I[63]	149	1	Ada	80/40	0 and 2	1.973
CLASSIC I[63]	149	2	Ada	80/40	0 and 2	1.48
CLASSIC I[63]	149	4	Ada	80/40	0 and 2	1.973
CLASSIC I[63]	150	1	Ada	160/80	0 and 2	2.337
CLASSIC I[63]	150	2	Ada	160/80	0 and 2	1.753
CLASSIC I[63]	150	4	Ada	160/80	0 and 2	2.921
GAIN[64]	325	1	Ada	160/80	0 and 2	1.74
GAIN[64]	325	2	Ada	160/80	0 and 2	3.55
GAIN[64]	325	4	Ada	160/80	0 and 2	2.958

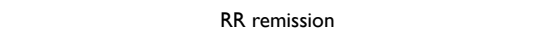


FIGURE 46 Induction trials – risk ratio of remission. Ada, adalimumab; Inflix, infliximab; RR, risk ratio.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RD
Targan *et al.*[57]	52	1	Inflix	5	0	0.15
Targan *et al.*[57]	52	2	Inflix	5	0	0.37
Targan *et al.*[57]	52	3	Inflix	5	0	0.40
Targan *et al.*[57]	52	4	Inflix	5	0	0.44
Targan *et al.*[57]	53	1	Inflix	10	0	0.07
Targan *et al.*[57]	53	2	Inflix	10	0	0.17
Targan *et al.*[57]	53	3	Inflix	10	0	0.17
Targan *et al.*[57]	53	4	Inflix	10	0	0.21
Targan *et al.*[57]	53	1	Inflix	20	0	0.07
Targan *et al.*[57]	53	2	Inflix	20	0	0.17
Targan *et al.*[57]	53	3	Inflix	20	0	0.17
Targan *et al.*[57]	53	4	Inflix	20	0	0.21
CLASSIC I[63]	148	1	Ada	40/20	0 and 2	0.09
CLASSIC I[63]	148	2	Ada	40/20	0 and 2	0.00
CLASSIC I[63]	148	4	Ada	40/20	0 and 2	0.05
CLASSIC I[63]	149	1	Ada	80/40	0 and 2	0.07
CLASSIC I[63]	149	2	Ada	80/40	0 and 2	0.06
CLASSIC I[63]	149	4	Ada	80/40	0 and 2	0.12
CLASSIC I[63]	150	1	Ada	160/80	0 and 2	0.09
CLASSIC I[63]	150	2	Ada	160/80	0 and 2	0.10
CLASSIC I[63]	150	4	Ada	160/80	0 and 2	0.23
GAIN[64]	325	1	Ada	160/80	0 and 2	0.03
GAIN[64]	325	2	Ada	160/80	0 and 2	0.15
GAIN[64]	325	4	Ada	160/80	0 and 2	0.14

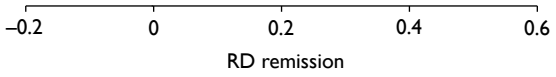


FIGURE 47 Induction trials – risk difference of remission. Ada, adalimumab; Inflix, infliximab; RD, risk difference.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RR
CLASSIC I[63]	148	1	Adal	40/20	0 and 2	1.42
CLASSIC I[63]	148	2	Adal	40/20	0 and 2	1.45
CLASSIC I[63]	148	4	Adal	40/20	0 and 2	1.32
CLASSIC I[63]	149	1	Adal	80/40	0 and 2	1.56
CLASSIC I[63]	149	2	Adal	80/40	0 and 2	2.51
CLASSIC I[63]	149	4	Adal	80/40	0 and 2	1.56
CLASSIC I[63]	150	1	Adal	160/80	0 and 2	1.30
CLASSIC I[63]	150	2	Adal	160/80	0 and 2	2.12
CLASSIC I[63]	150	4	Adal	160/80	0 and 2	1.95
GAIN[64]	325	1	Adal	160/80	0 and 2	1.62
GAIN[64]	325	2	Adal	160/80	0 and 2	2.02
GAIN[64]	325	4	Adal	160/80	0 and 2	1.55

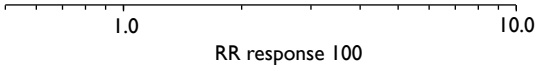


FIGURE 48 Induction trials – risk ratio of response 100. Adal, adalimumab; RR, risk ratio.

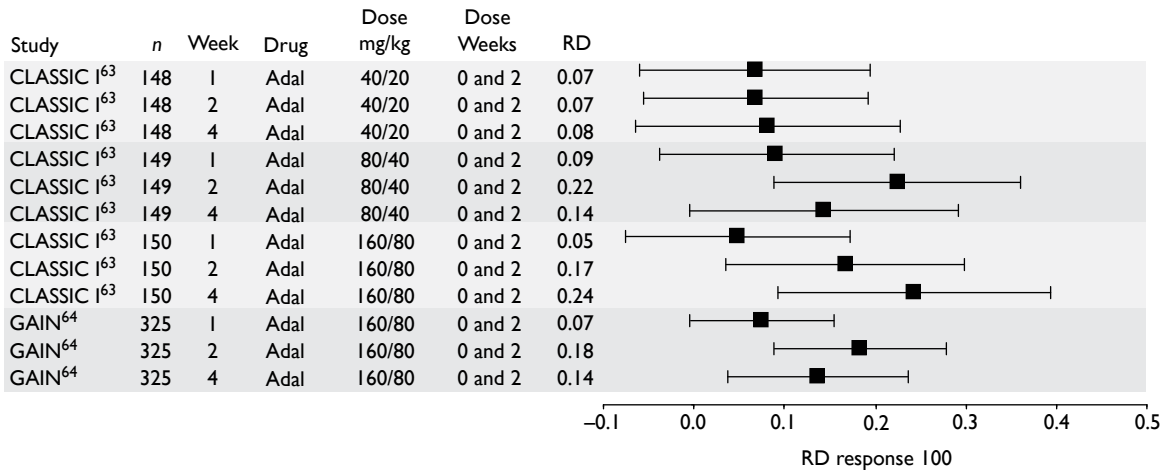


FIGURE 49 Induction trials – risk difference of response 100. Adal, adalimumab; RD, risk difference.

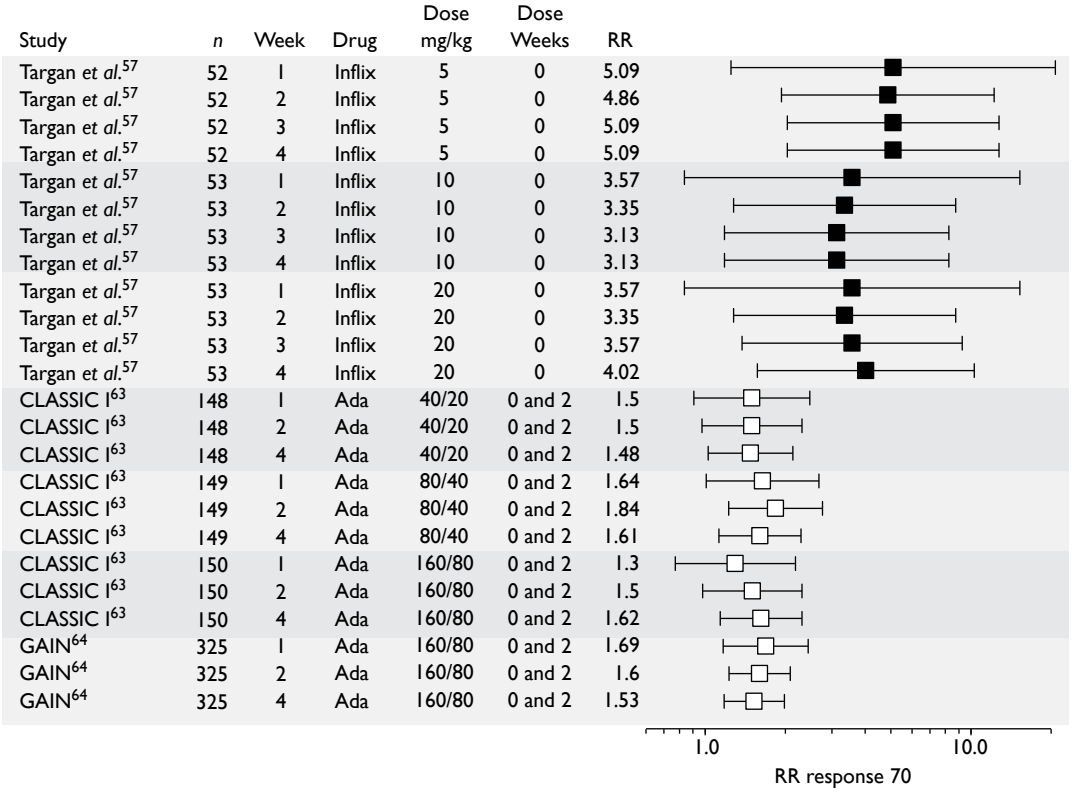


FIGURE 50 Induction trials – risk ratio response 70. Ada, adalimumab; Inflix, infliximab; RR, risk ratio.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RD
Targan *et al.*[57]	52	1	Inflix	5	0	0.33
Targan *et al.*[57]	52	2	Inflix	5	0	0.62
Targan *et al.*[57]	52	3	Inflix	5	0	0.65
Targan *et al.*[57]	52	4	Inflix	5	0	0.65
Targan *et al.*[57]	53	1	Inflix	10	0	0.21
Targan *et al.*[57]	53	2	Inflix	10	0	0.38
Targan *et al.*[57]	53	3	Inflix	10	0	0.34
Targan *et al.*[57]	53	4	Inflix	10	0	0.34
Targan *et al.*[57]	53	1	Inflix	20	0	0.21
Targan *et al.*[57]	53	2	Inflix	20	0	0.38
Targan *et al.*[57]	53	3	Inflix	20	0	0.41
Targan *et al.*[57]	53	4	Inflix	20	0	0.48
CLASSIC I[63]	148	1	Ada	40/20	0 and 2	0.12
CLASSIC I[63]	148	2	Ada	40/20	0 and 2	0.15
CLASSIC I[63]	148	4	Ada	40/20	0 and 2	0.18
CLASSIC I[63]	149	1	Ada	80/40	0 and 2	0.16
CLASSIC I[63]	149	2	Ada	80/40	0 and 2	0.25
CLASSIC I[63]	149	4	Ada	80/40	0 and 2	0.22
CLASSIC I[63]	150	1	Ada	160/80	0 and 2	0.07
CLASSIC I[63]	150	2	Ada	160/80	0 and 2	0.15
CLASSIC I[63]	150	4	Ada	160/80	0 and 2	0.23
GAIN[64]	325	1	Ada	160/80	0 and 2	0.14
GAIN[64]	325	2	Ada	160/80	0 and 2	0.2
GAIN[64]	325	4	Ada	160/80	0 and 2	0.18

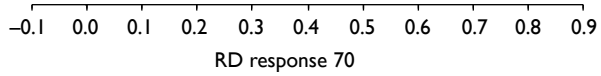


FIGURE 51 Induction trials – risk difference response 70. Ada, adalimumab; Infl, infliximab; RD, risk difference.

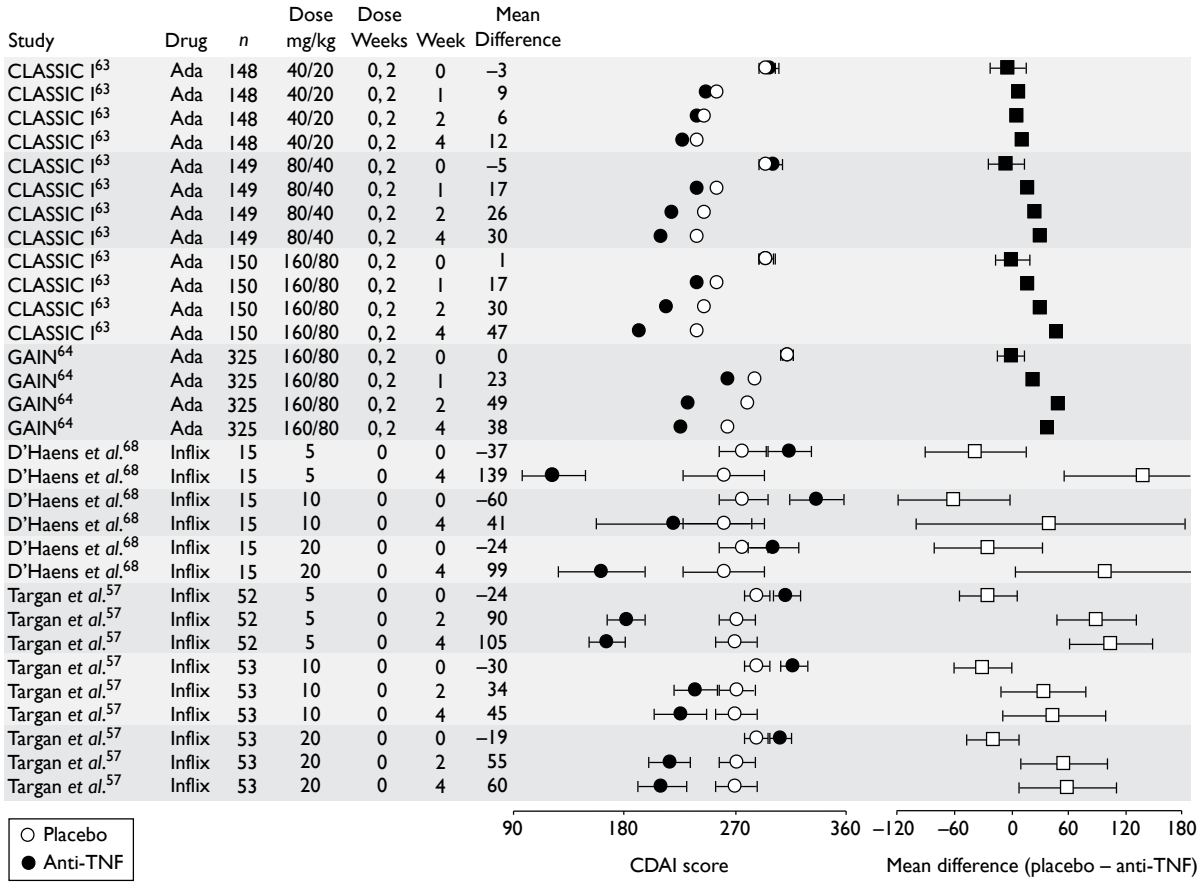


FIGURE 52 Induction trials – CDAI scores (mean scores). Ada, adalimumab; Inflix, infliximab.

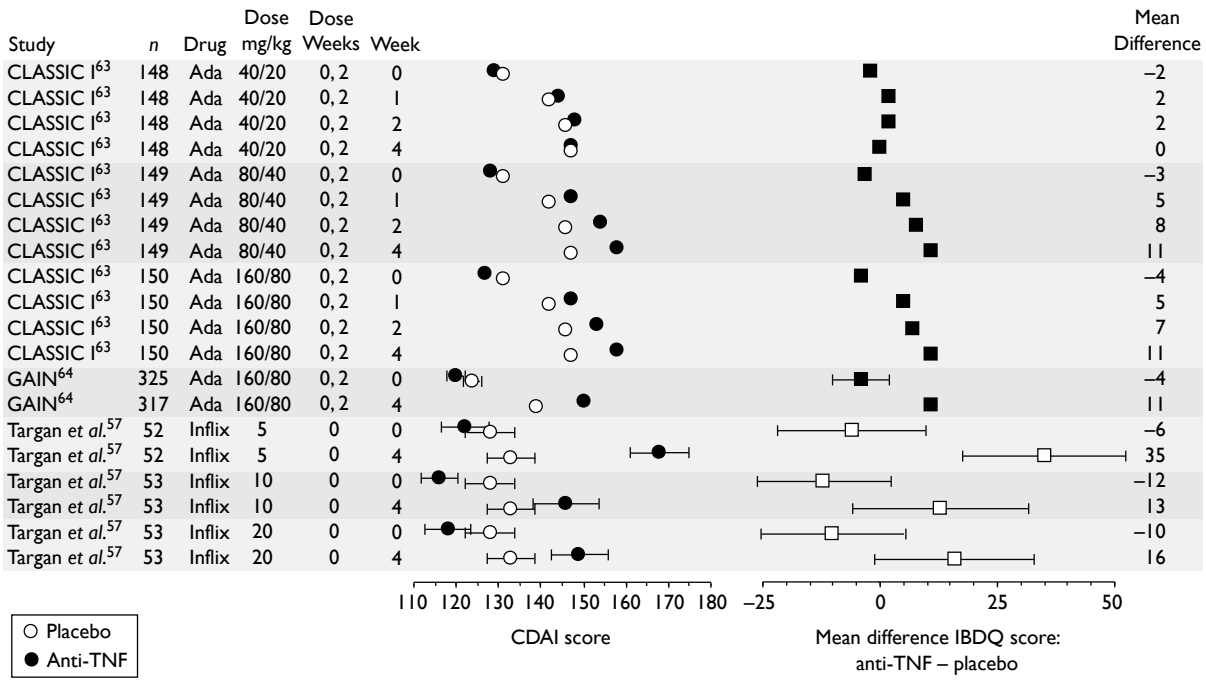


FIGURE 53 Induction trials – IBDQ scores. Ada, adalimumab; Inflix, infliximab.

Maintenance trials (unless stated 'dose weeks' refers to post-randomisation doses)

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RR
ACCENT I[2,3]	222	30	Inflix	5	2, 6: every 8	1.86
ACCENT I[2,3]	222	54	Inflix	5	2, 6: every 8	2.08
ACCENT I[2,3]	223	30	Inflix	10	2, 6: every 8	2.14
ACCENT I[2,3]	223	54	Inflix	10	2, 6: every 8	2.82
Rutgeerts *et al.*[58]	73	2	Inflix	10	0, 8, 16, 24 (?)	1.75
Rutgeerts *et al.*[58]	73	4	Inflix	10	0, 8, 16, 24 (?)	1.14
Rutgeerts *et al.*[58]	73	8	Inflix	10	0, 8, 16, 24 (?)	0.97
Rutgeerts *et al.*[58]	73	12	Inflix	10	0, 8, 16, 24 (?)	0.85
Rutgeerts *et al.*[58]	73	16	Inflix	10	0, 8, 16, 24 (?)	1.46
Rutgeerts *et al.*[58]	73	20	Inflix	10	0, 8, 16, 24 (?)	1.86
Rutgeerts *et al.*[58]	73	24	Inflix	10	0, 8, 16, 24 (?)	1.60
Rutgeerts *et al.*[58]	73	28	Inflix	10	0, 8, 16, 24 (?)	1.95
Rutgeerts *et al.*[58]	73	32	Inflix	10	0, 8, 16, 24 (?)	1.78
Rutgeerts *et al.*[58]	73	36	Inflix	10	0, 8, 16, 24 (?)	1.57
Rutgeerts *et al.*[58]	73	40	Inflix	10	0, 8, 16, 24 (?)	1.86
Rutgeerts *et al.*[58]	73	44	Inflix	10	0, 8, 16, 24 (?)	2.78
Rutgeerts *et al.*[58]	73	48	Inflix	10	0, 8, 16, 24 (?)	1.81
CHARM[67]	342	4	Ada	40	4–55 e.o.w.	1.10
CHARM[67]	342	6	Ada	40	4–55 e.o.w.	1.69
CHARM[67]	342	8	Ada	40	4–55 e.o.w.	1.54
CHARM[67]	342	12	Ada	40	4–55 e.o.w.	1.91
CHARM[67]	342	16	Ada	40	4–55 e.o.w.	2.17
CHARM[67]	342	20	Ada	40	4–55 e.o.w.	1.98
CHARM[67]	342	26	Ada	40	4–55 e.o.w.	2.35
CHARM[67]	342	32	Ada	40	4–55 e.o.w.	2.11
CHARM[67]	342	40	Ada	40	4–55 e.o.w.	2.47
CHARM[67]	342	48	Ada	40	4–55 e.o.w.	2.92
CHARM[67]	342	56	Ada	40	4–55 e.o.w.	3.06
CHARM[67]	327	4	Ada	40	4–55 weekly	0.90
CHARM[67]	327	6	Ada	40	4–55 weekly	1.31
CHARM[67]	327	8	Ada	40	4–55 weekly	1.46
CHARM[67]	327	12	Ada	40	4–55 weekly	1.81
CHARM[67]	327	16	Ada	40	4–55 weekly	2.47
CHARM[67]	327	20	Ada	40	4–55 weekly	2.08
CHARM[67]	327	26	Ada	40	4–55 weekly	2.76
CHARM[67]	327	32	Ada	40	4–55 weekly	2.69
CHARM[67]	327	40	Ada	40	4–55 weekly	3.00
CHARM[67]	327	48	Ada	40	4–55 weekly	3.49
CHARM[67]	327	56	Ada	40	4–55 weekly	3.46
CLASSIC II[66]	37	4	Ada	40	4–55 e.o.w.	1.07
CLASSIC II[66]	37	8	Ada	40	4–55 e.o.w.	1.52
CLASSIC II[66]	37	12	Ada	40	4–55 e.o.w.	1.61
CLASSIC II[66]	37	16	Ada	40	4–55 e.o.w.	1.38
CLASSIC II[66]	37	20	Ada	40	4–55 e.o.w.	1.79
CLASSIC II[66]	37	24	Ada	40	4–55 e.o.w.	1.68
CLASSIC II[66]	37	32	Ada	40	4–55 e.o.w.	2.17
CLASSIC II[66]	37	40	Ada	40	4–55 e.o.w.	1.89
CLASSIC II[66]	37	48	Ada	40	4–55 e.o.w.	1.54
CLASSIC II[66]	37	56	Ada	40	4–55 e.o.w.	1.78
CLASSIC II[66]	36	4	Ada	40	4–55 weekly	1.13
CLASSIC II[66]	36	8	Ada	40	4–55 weekly	1.60
CLASSIC II[66]	36	12	Ada	40	4–55 weekly	1.60
CLASSIC II[66]	36	16	Ada	40	4–55 weekly	1.27
CLASSIC II[66]	36	20	Ada	40	4–55 weekly	1.67
CLASSIC II[66]	36	24	Ada	40	4–55 weekly	1.89
CLASSIC II[66]	36	32	Ada	40	4–55 weekly	2.57
CLASSIC II[66]	36	40	Ada	40	4–55 weekly	2.13
CLASSIC II[66]	36	48	Ada	40	4–55 weekly	2.13
CLASSIC II[66]	36	56	Ada	40	4–55 weekly	1.88

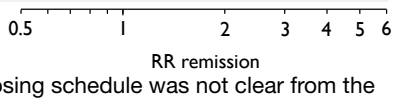


FIGURE 54 Maintenance trials – risk ratio remission (responders). ?, the dosing schedule was not clear from the published papers; Ada, adalimumab; Inflix, infliximab; RR, risk ratio.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RD
ACCENT I[2,3]	222	30	Inflix	5	2, 6: every 8	0.18
ACCENT I[2,3]	222	54	Inflix	5	2, 6: every 8	0.15
ACCENT I[2,3]	223	30	Inflix	10	2, 6: every 8	0.24
ACCENT I[2,3]	223	54	Inflix	10	2, 6: every 8	0.25
Rutgeerts *et al.*[58]	73	2	Inflix	10	0, 8, 16, 24 (?)	0.21
Rutgeerts *et al.*[58]	73	4	Inflix	10	0, 8, 16, 24 (?)	0.07
Rutgeerts *et al.*[58]	73	8	Inflix	10	0, 8, 16, 24 (?)	–0.02
Rutgeerts *et al.*[58]	73	12	Inflix	10	0, 8, 16, 24 (?)	–0.07
Rutgeerts *et al.*[58]	73	16	Inflix	10	0, 8, 16, 24 (?)	0.18
Rutgeerts *et al.*[58]	73	20	Inflix	10	0, 8, 16, 24 (?)	0.26
Rutgeerts *et al.*[58]	73	24	Inflix	10	0, 8, 16, 24 (?)	0.23
Rutgeerts *et al.*[58]	73	28	Inflix	10	0, 8, 16, 24 (?)	0.29
Rutgeerts *et al.*[58]	73	32	Inflix	10	0, 8, 16, 24 (?)	0.26
Rutgeerts *et al.*[58]	73	36	Inflix	10	0, 8, 16, 24 (?)	0.21
Rutgeerts *et al.*[58]	73	40	Inflix	10	0, 8, 16, 24 (?)	0.29
Rutgeerts *et al.*[58]	73	44	Inflix	10	0, 8, 16, 24 (?)	0.35
Rutgeerts *et al.*[58]	73	48	Inflix	10	0, 8, 16, 24 (?)	0.16
CHARM[67]	327	4	Ada	40	4–55 weekly	–0.04
CHARM[67]	327	6	Ada	40	4–55 weekly	0.10
CHARM[67]	327	8	Ada	40	4–55 weekly	0.16
CHARM[67]	327	12	Ada	40	4–55 weekly	0.22
CHARM[67]	327	16	Ada	40	4–55 weekly	0.31
CHARM[67]	327	20	Ada	40	4–55 weekly	0.23
CHARM[67]	327	26	Ada	40	4–55 weekly	0.30
CHARM[67]	327	32	Ada	40	4–55 weekly	0.29
CHARM[67]	327	40	Ada	40	4–55 weekly	0.31
CHARM[67]	327	48	Ada	40	4–55 weekly	0.32
CHARM[67]	327	56	Ada	40	4–55 weekly	0.29
CHARM[67]	342	4	Ada	40	4–55 e.o.w.	0.04
CHARM[67]	342	6	Ada	40	4–55 e.o.w.	0.23
CHARM[67]	342	8	Ada	40	4–55 e.o.w.	0.18
CHARM[67]	342	12	Ada	40	4–55 e.o.w.	0.25
CHARM[67]	342	16	Ada	40	4–55 e.o.w.	0.25
CHARM[67]	342	20	Ada	40	4–55 e.o.w.	0.21
CHARM[67]	342	26	Ada	40	4–55 e.o.w.	0.23
CHARM[67]	342	32	Ada	40	4–55 e.o.w.	0.19
CHARM[67]	342	40	Ada	40	4–55 e.o.w.	0.22
CHARM[67]	342	48	Ada	40	4–55 e.o.w.	0.25
CHARM[67]	342	56	Ada	40	4–55 e.o.w.	0.24
CLASSIC II[66]	36	4	Ada	40	4–55 weekly	0.11
CLASSIC II[66]	36	8	Ada	40	4–55 weekly	0.33
CLASSIC II[66]	36	12	Ada	40	4–55 weekly	0.33
CLASSIC II[66]	36	16	Ada	40	4–55 weekly	0.17
CLASSIC II[66]	36	20	Ada	40	4–55 weekly	0.33
CLASSIC II[66]	36	24	Ada	40	4–55 weekly	0.44
CLASSIC II[66]	36	32	Ada	40	4–55 weekly	0.61
CLASSIC II[66]	36	40	Ada	40	4–55 weekly	0.50
CLASSIC II[66]	36	48	Ada	40	4–55 weekly	0.50
CLASSIC II[66]	36	56	Ada	40	4–55 weekly	0.39
CLASSIC II[66]	37	4	Ada	40	4–55 e.o.w.	0.06
CLASSIC II[66]	37	8	Ada	40	4–55 e.o.w.	0.29
CLASSIC II[66]	37	12	Ada	40	4–55 e.o.w.	0.34
CLASSIC II[66]	37	16	Ada	40	4–55 e.o.w.	0.23
CLASSIC II[66]	37	20	Ada	40	4–55 e.o.w.	0.39
CLASSIC II[66]	37	24	Ada	40	4–55 e.o.w.	0.34
CLASSIC II[66]	37	32	Ada	40	4–55 e.o.w.	0.45
CLASSIC II[66]	37	40	Ada	40	4–55 e.o.w.	0.40
CLASSIC II[66]	37	48	Ada	40	4–55 e.o.w.	0.24
CLASSIC II[66]	37	56	Ada	40	4–55 e.o.w.	0.35

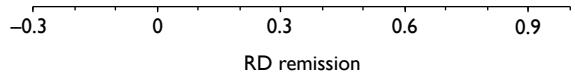


FIGURE 55 Maintenance trials – risk difference remission (responders). ?, the dosing schedule was not clear from the published papers; Ada, adalimumab; Inflix, infliximab; RD, risk difference.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RR
ACCENT I[2,3]	380	2	Inflix	5	2, 6: every 8	0.94
ACCENT I[2,3]	380	6	Inflix	5	2, 6: every 8	1.28
ACCENT I[2,3]	380	10	Inflix	5	2, 6: every 8	1.29
ACCENT I[2,3]	380	14	Inflix	5	2, 6: every 8	1.47
ACCENT I[2,3]	380	22	Inflix	5	2, 6: every 8	1.35
ACCENT I[2,3]	380	30	Inflix	5	2, 6: every 8	1.20
ACCENT I[2,3]	380	38	Inflix	5	2, 6: every 8	1.10
ACCENT I[2,3]	380	46	Inflix	5	2, 6: every 8	1.17
ACCENT I[2,3]	380	54	Inflix	5	2, 6: every 8	1.14
ACCENT I[2,3]	381	2	Inflix	10	2, 6: every 8	1.05
ACCENT I[2,3]	381	6	Inflix	10	2, 6: every 8	1.21
ACCENT I[2,3]	381	10	Inflix	10	2, 6: every 8	1.35
ACCENT I[2,3]	381	14	Inflix	10	2, 6: every 8	1.52
ACCENT I[2,3]	381	22	Inflix	10	2, 6: every 8	1.62
ACCENT I[2,3]	381	30	Inflix	10	2, 6: every 8	1.28
ACCENT I[2,3]	381	38	Inflix	10	2, 6: every 8	1.28
ACCENT I[2,3]	381	46	Inflix	10	2, 6: every 8	1.44
ACCENT I[2,3]	381	54	Inflix	10	2, 6: every 8	1.27

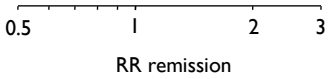


FIGURE 56 Maintenance trials – risk ratio remission, all patients. Inflix, infliximab; RR, risk ratio.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RD
ACCENT I[2,3]	380	2	Inflix	5	2, 6: every 8	–0.02
ACCENT I[2,3]	380	6	Inflix	5	2, 6: every 8	0.09
ACCENT I[2,3]	380	10	Inflix	5	2, 6: every 8	0.09
ACCENT I[2,3]	380	14	Inflix	5	2, 6: every 8	0.12
ACCENT I[2,3]	380	22	Inflix	5	2, 6: every 8	0.09
ACCENT I[2,3]	380	30	Inflix	5	2, 6: every 8	0.07
ACCENT I[2,3]	380	38	Inflix	5	2, 6: every 8	0.03
ACCENT I[2,3]	380	46	Inflix	5	2, 6: every 8	0.05
ACCENT I[2,3]	380	54	Inflix	5	2, 6: every 8	0.05
ACCENT I[2,3]	381	2	Inflix	10	2, 6: every 8	0.01
ACCENT I[2,3]	381	6	Inflix	10	2, 6: every 8	0.06
ACCENT I[2,3]	381	10	Inflix	10	2, 6: every 8	0.11
ACCENT I[2,3]	381	14	Inflix	10	2, 6: every 8	0.13
ACCENT I[2,3]	381	22	Inflix	10	2, 6: every 8	0.16
ACCENT I[2,3]	381	30	Inflix	10	2, 6: every 8	0.09
ACCENT I[2,3]	381	38	Inflix	10	2, 6: every 8	0.09
ACCENT I[2,3]	381	46	Inflix	10	2, 6: every 8	0.13
ACCENT I[2,3]	381	54	Inflix	10	2, 6: every 8	0.09

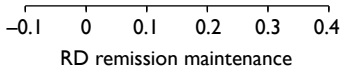


FIGURE 57 Maintenance trials – risk difference remission, all patients. Inflix, infliximab; RD, risk difference.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RR
CHARM[67]	327	26	Ada	40	4–55 weekly	1.97
CHARM[67]	327	56	Ada	40	4–55 weekly	2.90
CHARM[67]	342	26	Ada	40	4–55 e.o.w.	1.95
CHARM[67]	342	56	Ada	40	4–55 e.o.w.	2.51
CLASSIC II[66]	36	4	Ada	40	4–55 weekly	1.13
CLASSIC II[66]	36	8	Ada	40	4–55 weekly	1.33
CLASSIC II[66]	36	12	Ada	40	4–55 weekly	1.70
CLASSIC II[66]	36	16	Ada	40	4–55 weekly	1.23
CLASSIC II[66]	36	20	Ada	40	4–55 weekly	1.36
CLASSIC II[66]	36	24	Ada	40	4–55 weekly	1.55
CLASSIC II[66]	36	32	Ada	40	4–55 weekly	2.00
CLASSIC II[66]	36	40	Ada	40	4–55 weekly	1.70
CLASSIC II[66]	36	48	Ada	40	4–55 weekly	1.50
CLASSIC II[66]	36	56	Ada	40	4–55 weekly	1.60
CLASSIC II[66]	37	4	Ada	40	4–55 e.o.w.	1.01
CLASSIC II[66]	37	8	Ada	40	4–55 e.o.w.	1.18
CLASSIC II[66]	37	12	Ada	40	4–55 e.o.w.	1.71
CLASSIC II[66]	37	16	Ada	40	4–55 e.o.w.	1.24
CLASSIC II[66]	37	20	Ada	40	4–55 e.o.w.	1.55
CLASSIC II[66]	37	24	Ada	40	4–55 e.o.w.	1.38
CLASSIC II[66]	37	32	Ada	40	4–55 e.o.w.	1.58
CLASSIC II[66]	37	40	Ada	40	4–55 e.o.w.	1.52
CLASSIC II[66]	37	48	Ada	40	4–55 e.o.w.	1.33
CLASSIC II[66]	37	56	Ada	40	4–55 e.o.w.	1.42

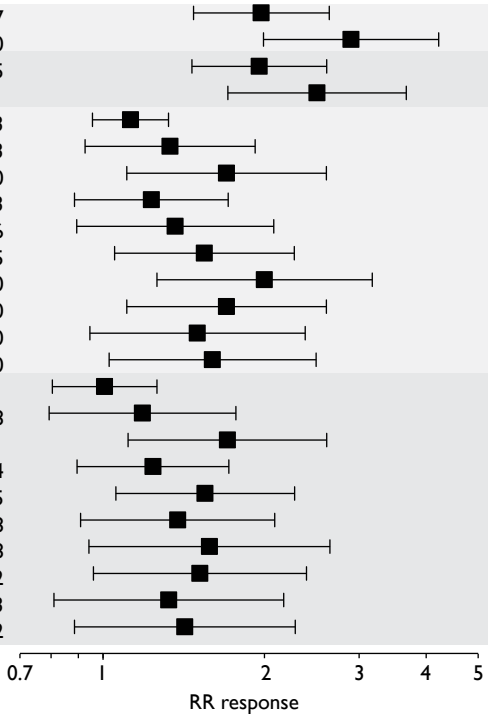


FIGURE 58 Maintenance trials – risk ratio response 100. Ada, adalimumab; RR, risk ratio.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RD
CHARM[67]	327	26	Ada	40	4–55 weekly	0.26
CHARM[67]	327	56	Ada	40	4–55 weekly	0.31
CHARM[67]	342	26	Ada	40	4–55 e.o.w.	0.25
CHARM[67]	342	56	Ada	40	4–55 e.o.w.	0.25
CLASSIC II[66]	36	4	Ada	40	4–55 weekly	0.11
CLASSIC II[66]	36	8	Ada	40	4–55 weekly	0.22
CLASSIC II[66]	36	12	Ada	40	4–55 weekly	0.39
CLASSIC II[66]	36	16	Ada	40	4–55 weekly	0.17
CLASSIC II[66]	36	20	Ada	40	4–55 weekly	0.22
CLASSIC II[66]	36	24	Ada	40	4–55 weekly	0.33
CLASSIC II[66]	36	32	Ada	40	4–55 weekly	0.50
CLASSIC II[66]	36	40	Ada	40	4–55 weekly	0.39
CLASSIC II[66]	36	48	Ada	40	4–55 weekly	0.28
CLASSIC II[66]	36	56	Ada	40	4–55 weekly	0.33
CLASSIC II[66]	37	4	Ada	40	4–55 e.o.w.	0.01
CLASSIC II[66]	37	8	Ada	40	4–55 e.o.w.	0.12
CLASSIC II[66]	37	12	Ada	40	4–55 e.o.w.	0.39
CLASSIC II[66]	37	16	Ada	40	4–55 e.o.w.	0.17
CLASSIC II[66]	37	20	Ada	40	4–55 e.o.w.	0.34
CLASSIC II[66]	37	24	Ada	40	4–55 e.o.w.	0.23
CLASSIC II[66]	37	32	Ada	40	4–55 e.o.w.	0.29
CLASSIC II[66]	37	40	Ada	40	4–55 e.o.w.	0.29
CLASSIC II[66]	37	48	Ada	40	4–55 e.o.w.	0.18
CLASSIC II[66]	37	56	Ada	40	4–55 e.o.w.	0.23

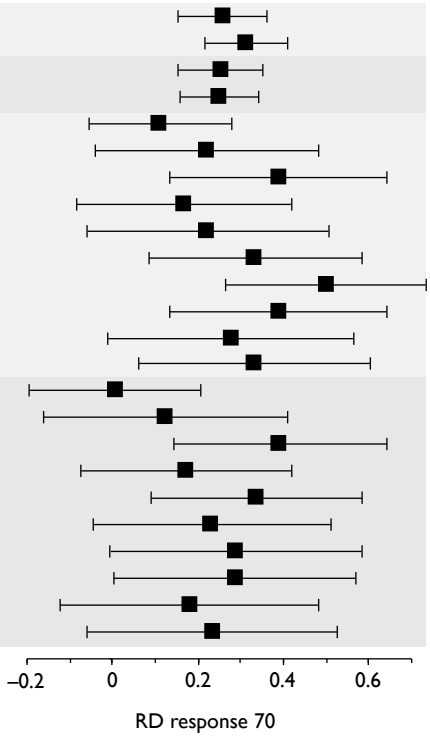


FIGURE 59 Maintenance trials – risk difference response 100. Ada, adalimumab; RD, risk difference.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RR
ACCENT I[2,3]	222	30	Inflix	5	2, 6: every 8	1.88
ACCENT I[2,3]	222	54	Inflix	5	2, 6: every 8	2.46
ACCENT I[2,3]	223	30	Inflix	10	2, 6: every 8	2.16
ACCENT I[2,3]	223	54	Inflix	10	2, 6: every 8	3.06
Rutgeerts *et al.*[58]	73	2	Inflix	10	0, 8, 16, 24 (?)	1.22
Rutgeerts *et al.*[58]	73	4	Inflix	10	0, 8, 16, 24 (?)	1.00
Rutgeerts *et al.*[58]	73	8	Inflix	10	0, 8, 16, 24 (?)	1.00
Rutgeerts *et al.*[58]	73	12	Inflix	10	0, 8, 16, 24 (?)	0.97
Rutgeerts *et al.*[58]	73	16	Inflix	10	0, 8, 16, 24 (?)	1.08
Rutgeerts *et al.*[58]	73	20	Inflix	10	0, 8, 16, 24 (?)	1.18
Rutgeerts *et al.*[58]	73	24	Inflix	10	0, 8, 16, 24 (?)	1.27
Rutgeerts *et al.*[58]	73	28	Inflix	10	0, 8, 16, 24 (?)	1.30
Rutgeerts *et al.*[58]	73	32	Inflix	10	0, 8, 16, 24 (?)	1.26
Rutgeerts *et al.*[58]	73	36	Inflix	10	0, 8, 16, 24 (?)	1.64
Rutgeerts *et al.*[58]	73	40	Inflix	10	0, 8, 16, 24 (?)	1.49
Rutgeerts *et al.*[58]	73	44	Inflix	10	0, 8, 16, 24 (?)	1.72
Rutgeerts *et al.*[58]	73	48	Inflix	10	0, 8, 16, 24 (?)	1.70
CHARM[67]	342	26	Ada	40	4–55 e.o.w.	1.91
CHARM[67]	342	56	Ada	40	4–55 e.o.w.	2.44
CHARM[67]	327	26	Ada	40	4–55 weekly	1.99
CHARM[67]	327	56	Ada	40	4–55 weekly	2.78
CLASSIC II[66]	37	4	Ada	40	4–55 e.o.w.	0.95
CLASSIC II[66]	37	8	Ada	40	4–55 e.o.w.	0.89
CLASSIC II[66]	37	12	Ada	40	4–55 e.o.w.	1.07
CLASSIC II[66]	37	16	Ada	40	4–55 e.o.w.	1.01
CLASSIC II[66]	37	20	Ada	40	4–55 e.o.w.	1.14
CLASSIC II[66]	37	24	Ada	40	4–55 e.o.w.	1.14
CLASSIC II[66]	37	32	Ada	40	4–55 e.o.w.	1.31
CLASSIC II[66]	37	40	Ada	40	4–55 e.o.w.	1.08
CLASSIC II[66]	37	48	Ada	40	4–55 e.o.w.	1.17
CLASSIC II[66]	37	56	Ada	40	4–55 e.o.w.	1.09
CLASSIC II[66]	36	8	Ada	40	4–55 weekly	0.89
CLASSIC II[66]	36	12	Ada	40	4–55 weekly	1.13
CLASSIC II[66]	36	16	Ada	40	4–55 weekly	1.06
CLASSIC II[66]	36	20	Ada	40	4–55 weekly	1.13
CLASSIC II[66]	36	24	Ada	40	4–55 weekly	1.13
CLASSIC II[66]	36	32	Ada	40	4–55 weekly	1.38
CLASSIC II[66]	36	40	Ada	40	4–55 weekly	1.29
CLASSIC II[66]	36	48	Ada	40	4–55 weekly	1.31
CLASSIC II[66]	36	56	Ada	40	4–55 weekly	1.23

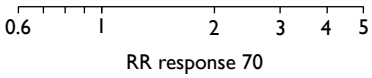


FIGURE 60 Maintenance trials – risk ratio response 70 (responders). ('Dose weeks' for Rutgeerts *et al*.[58] refers to all scheduled dose weeks including those prior to randomisation.) ?, the dosing schedule was not clear from the published papers; Ada, adalimumab; Inflix, infliximab; RR, risk ratio.

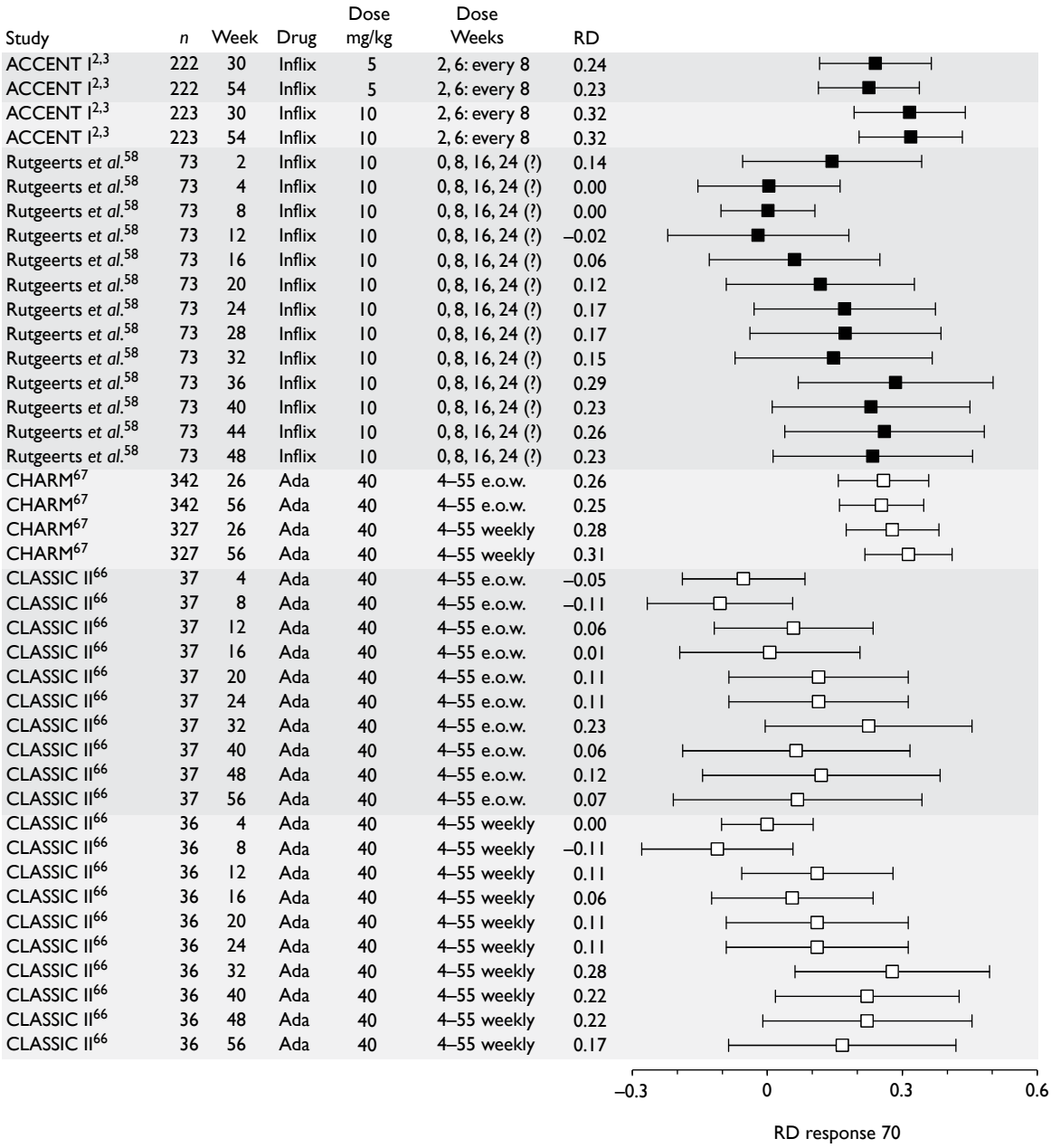


FIGURE 61 Maintenance trials – risk difference response 70 (responders). ('Dose weeks' for Rutgeerts *et al*.[58] refers to all scheduled dose weeks including those prior to randomisation.) ?, the dosing schedule was not clear from the published papers; Ada, adalimumab; Inflix, infliximab; RD, risk difference.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RR
ACCENT I[2,3]	380	2	Inflix	5	2, 6: every 8	0.98
ACCENT I[2,3]	380	6	Inflix	5	2, 6: every 8	1.21
ACCENT I[2,3]	380	10	Inflix	5	2, 6: every 8	1.19
ACCENT I[2,3]	380	14	Inflix	5	2, 6: every 8	1.28
ACCENT I[2,3]	380	22	Inflix	5	2, 6: every 8	1.11
ACCENT I[2,3]	380	30	Inflix	5	2, 6: every 8	1.16
ACCENT I[2,3]	380	38	Inflix	5	2, 6: every 8	1.10
ACCENT I[2,3]	380	46	Inflix	5	2, 6: every 8	1.13
ACCENT I[2,3]	380	54	Inflix	5	2, 6: every 8	1.10
ACCENT I[2,3]	381	2	Inflix	10	2, 6: every 8	0.98
ACCENT I[2,3]	381	6	Inflix	10	2, 6: every 8	1.14
ACCENT I[2,3]	381	10	Inflix	10	2, 6: every 8	1.16
ACCENT I[2,3]	381	14	Inflix	10	2, 6: every 8	1.31
ACCENT I[2,3]	381	22	Inflix	10	2, 6: every 8	1.22
ACCENT I[2,3]	381	30	Inflix	10	2, 6: every 8	1.24
ACCENT I[2,3]	381	38	Inflix	10	2, 6: every 8	1.16
ACCENT I[2,3]	381	46	Inflix	10	2, 6: every 8	1.20
ACCENT I[2,3]	381	54	Inflix	10	2, 6: every 8	1.08

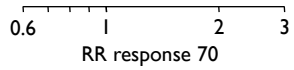


FIGURE 62 Maintenance trials – risk ratio response 70 all patients. Inflix, infliximab; RR, risk ratio.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	RD
ACCENT I[2,3]	380	2	Inflix	5	2, 6: every 8	–0.01
ACCENT I[2,3]	380	6	Inflix	5	2, 6: every 8	0.12
ACCENT I[2,3]	380	10	Inflix	5	2, 6: every 8	0.11
ACCENT I[2,3]	380	14	Inflix	5	2, 6: every 8	0.14
ACCENT I[2,3]	380	22	Inflix	5	2, 6: every 8	0.06
ACCENT I[2,3]	380	30	Inflix	5	2, 6: every 8	0.08
ACCENT I[2,3]	380	38	Inflix	5	2, 6: every 8	0.06
ACCENT I[2,3]	380	46	Inflix	5	2, 6: every 8	0.07
ACCENT I[2,3]	380	54	Inflix	5	2, 6: every 8	0.06
ACCENT I[2,3]	381	2	Inflix	10	2, 6: every 8	–0.01
ACCENT I[2,3]	381	6	Inflix	10	2, 6: every 8	0.08
ACCENT I[2,3]	381	10	Inflix	10	2, 6: every 8	0.09
ACCENT I[2,3]	381	14	Inflix	10	2, 6: every 8	0.15
ACCENT I[2,3]	381	22	Inflix	10	2, 6: every 8	0.12
ACCENT I[2,3]	381	30	Inflix	10	2, 6: every 8	0.12
ACCENT I[2,3]	381	38	Inflix	10	2, 6: every 8	0.09
ACCENT I[2,3]	381	46	Inflix	10	2, 6: every 8	0.11
ACCENT I[2,3]	381	54	Inflix	10	2, 6: every 8	0.05

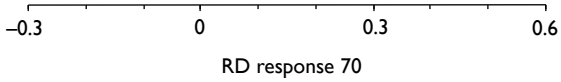


FIGURE 63 Maintenance trials – risk difference response 70 all patients. Inflix, infliximab; RD, risk difference.

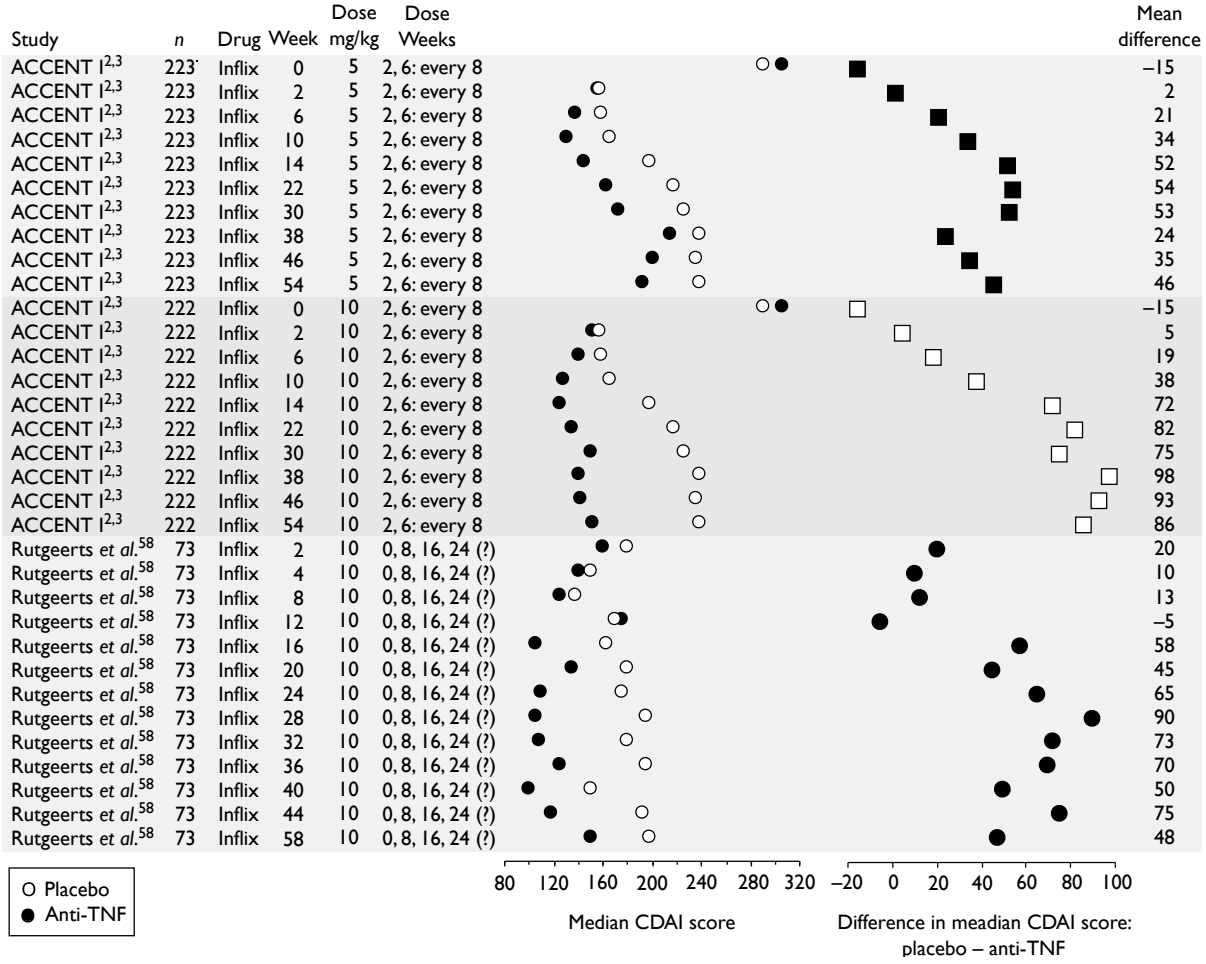


FIGURE 64 Maintenance trials – CDAI scores for trials reporting median scores (results for responders). ?, the dosing schedule was not clear from the published papers; Inflix, infliximab.

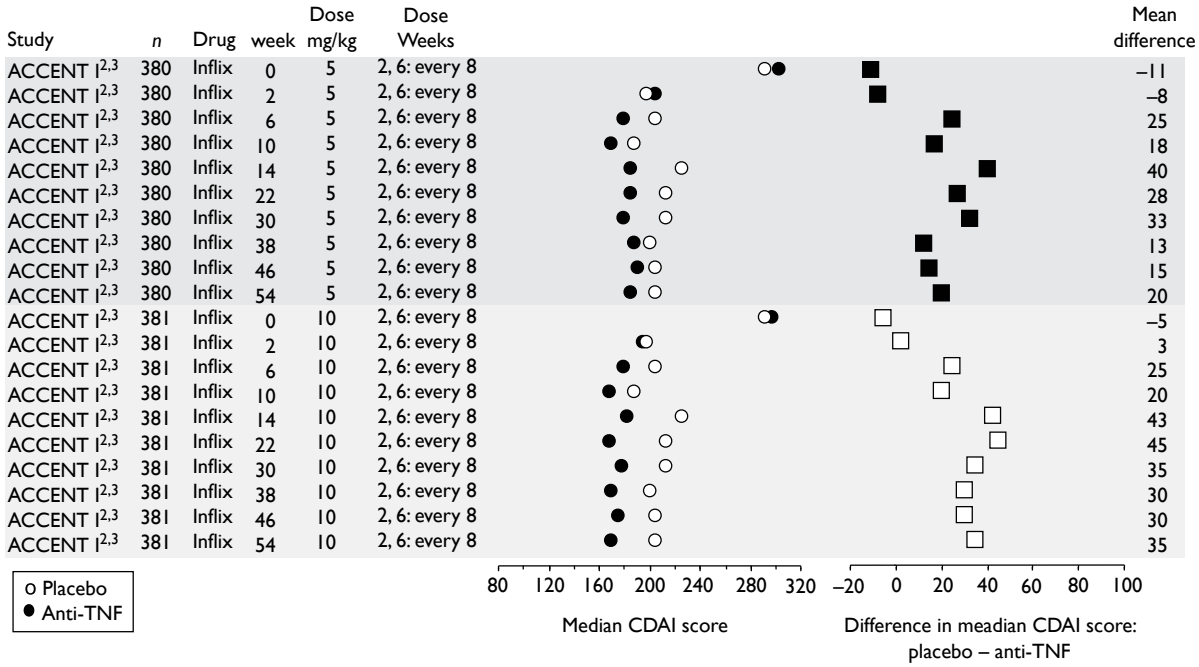


FIGURE 65 Maintenance trials – CDAI scores for trials reporting median scores (results for all patients). Inflix, infliximab.

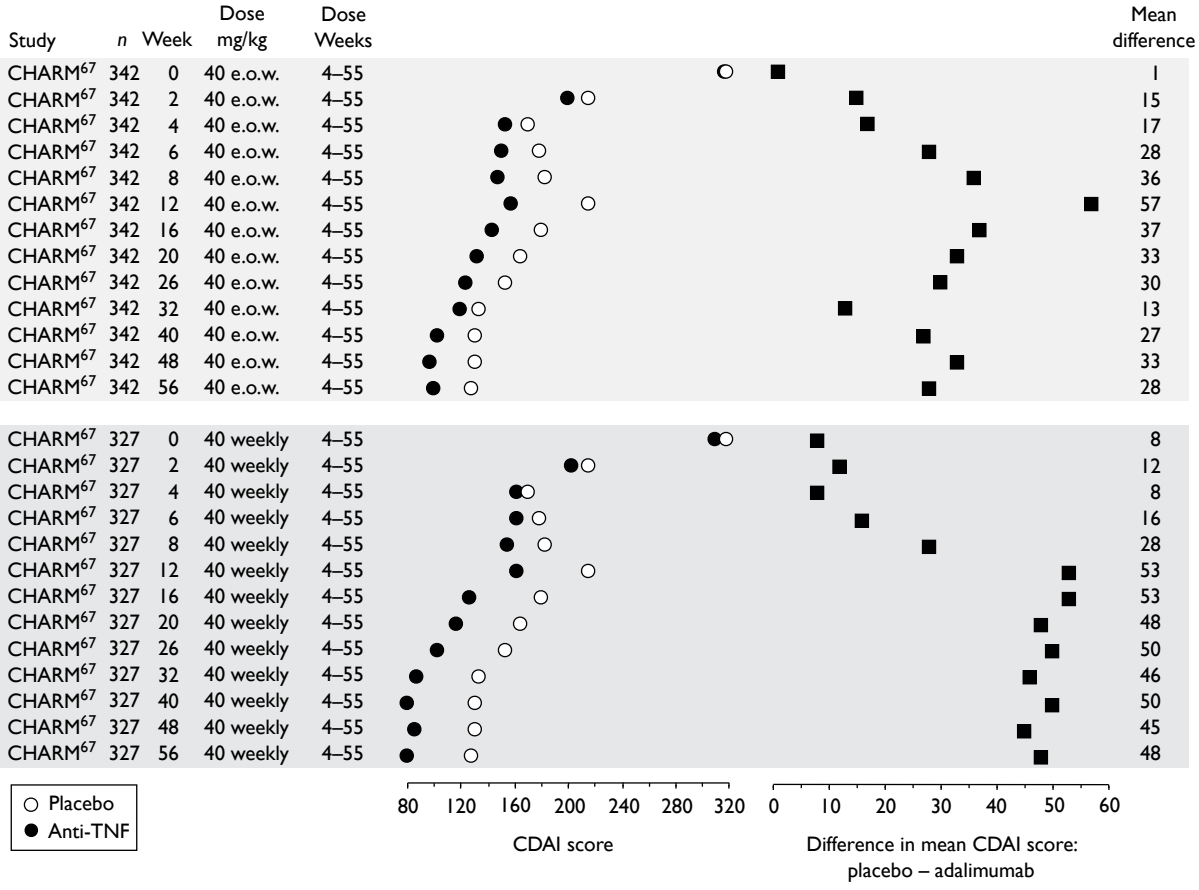


FIGURE 66 Maintenance trials – CDAI scores for trials reporting mean scores.

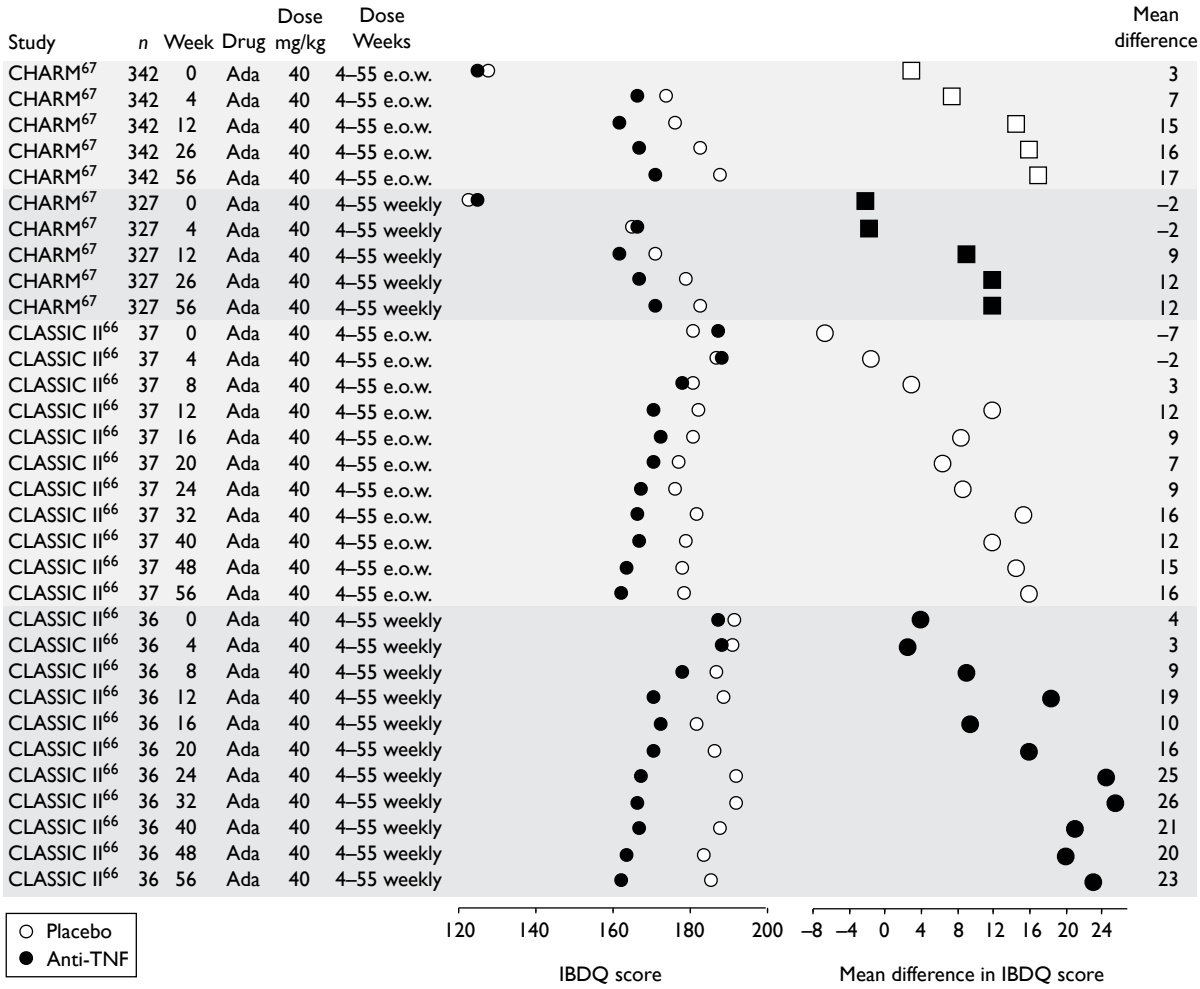


FIGURE 67 Maintenance trials – IBDQ scores for trials reporting mean scores. Ada, adalimumab.

Study	*n*	Week	Drug	Dose mg/kg	Dose Weeks	Difference
Rutgeerts *et al.*[58]	73	2	Inflix	10	0, 8, 16, 24 (?)	7
Rutgeerts *et al.*[58]	73	4	Inflix	10	0, 8, 16, 24 (?)	–4
Rutgeerts *et al.*[58]	73	8	Inflix	10	0, 8, 16, 24 (?)	–4
Rutgeerts *et al.*[58]	73	12	Inflix	10	0, 8, 16, 24 (?)	15
Rutgeerts *et al.*[58]	73	16	Inflix	10	0, 8, 16, 24 (?)	15
Rutgeerts *et al.*[58]	73	20	Inflix	10	0, 8, 16, 24 (?)	22
Rutgeerts *et al.*[58]	73	24	Inflix	10	0, 8, 16, 24 (?)	19
Rutgeerts *et al.*[58]	73	28	Inflix	10	0, 8, 16, 24 (?)	22
Rutgeerts *et al.*[58]	73	32	Inflix	10	0, 8, 16, 24 (?)	26
Rutgeerts *et al.*[58]	73	36	Inflix	10	0, 8, 16, 24 (?)	29
Rutgeerts *et al.*[58]	73	40	Inflix	10	0, 8, 16, 24 (?)	25
Rutgeerts *et al.*[58]	73	44	Inflix	10	0, 8, 16, 24 (?)	20
Rutgeerts *et al.*[58]	73	48	Inflix	10	0, 8, 16, 24 (?)	–10
ACCENT I[2,3]	223	0	Inflix	5	0, 2, 6: every 8	–1
ACCENT I[2,3]	223	2	Inflix	5	0, 2, 6: every 8	–4
ACCENT I[2,3]	223	6	Inflix	5	0, 2, 6: every 8	9
ACCENT I[2,3]	223	10	Inflix	5	0, 2, 6: every 8	10
ACCENT I[2,3]	223	14	Inflix	5	0, 2, 6: every 8	12
ACCENT I[2,3]	223	22	Inflix	5	0, 2, 6: every 8	22
ACCENT I[2,3]	223	30	Inflix	5	0, 2, 6: every 8	18
ACCENT I[2,3]	223	38	Inflix	5	0, 2, 6: every 8	14
ACCENT I[2,3]	223	46	Inflix	5	0, 2, 6: every 8	9
ACCENT I[2,3]	223	54	Inflix	5	0, 2, 6: every 8	14
ACCENT I[2,3]	222	0	Inflix	10	0, 2, 6: every 8	1
ACCENT I[2,3]	222	2	Inflix	10	0, 2, 6: every 8	0
ACCENT I[2,3]	222	6	Inflix	10	0, 2, 6: every 8	–4
ACCENT I[2,3]	222	10	Inflix	10	0, 2, 6: every 8	9
ACCENT I[2,3]	222	14	Inflix	10	0, 2, 6: every 8	17
ACCENT I[2,3]	222	22	Inflix	10	0, 2, 6: every 8	27
ACCENT I[2,3]	222	30	Inflix	10	0, 2, 6: every 8	23
ACCENT I[2,3]	222	38	Inflix	10	0, 2, 6: every 8	33
ACCENT I[2,3]	222	46	Inflix	10	0, 2, 6: every 8	34
ACCENT I[2,3]	222	54	Inflix	10	0, 2, 6: every 8	31

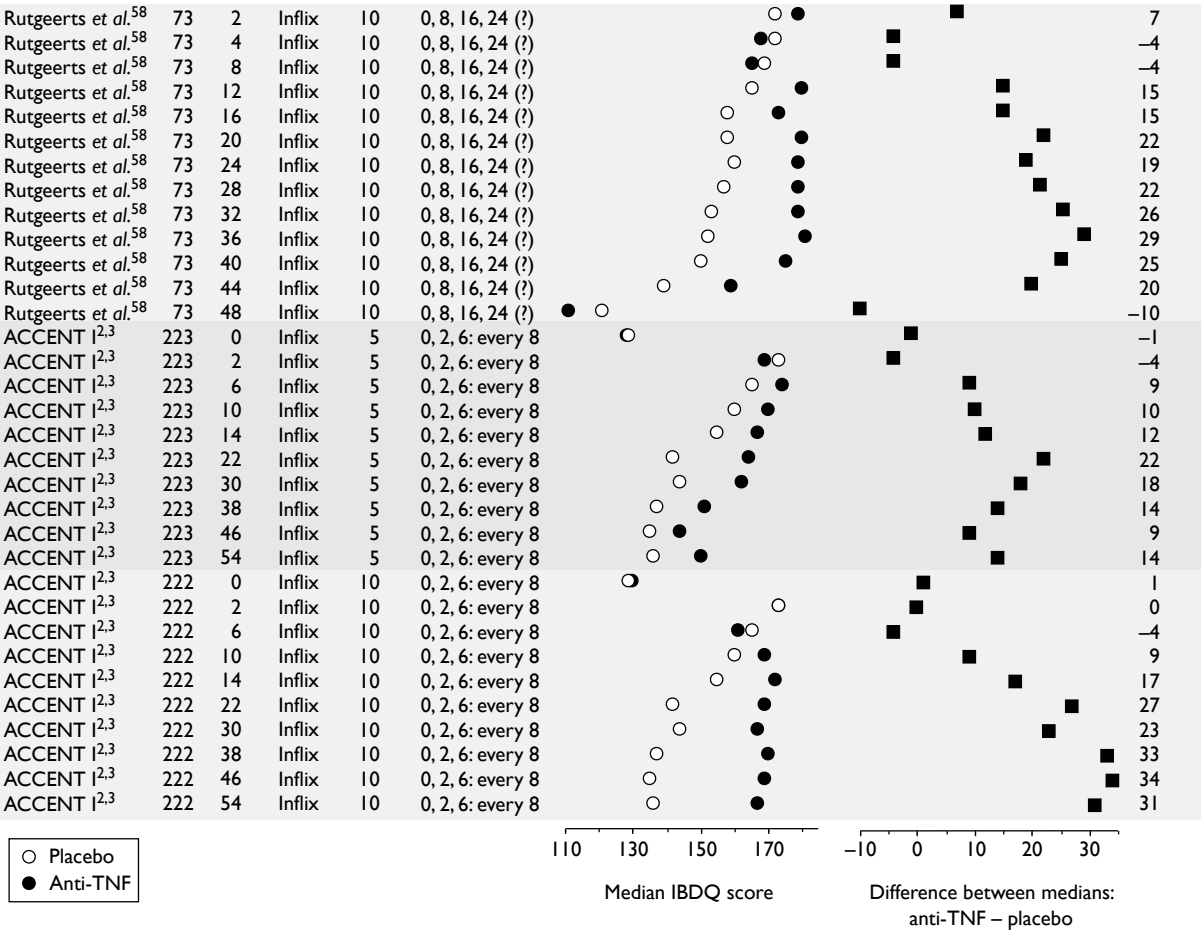


FIGURE 68 Maintenance trials – IBDQ scores for trials reporting median scores. ('Dose weeks' refers to all scheduled doses including those prior to randomisation.) ?, the dosing schedule was not clear from the published papers; Inflix, infliximab.

Study	*n*	Drug	Week	Dose mg/kg	Dose Weeks	Difference (%)
ACCENT I[2,3]	380	Inflix	0	5	0, 2, 6: every 8	0.4
ACCENT I[2,3]	380	Inflix	2	5	0, 2, 6: every 8	–3.3
ACCENT I[2,3]	380	Inflix	6	5	0, 2, 6: every 8	8.2
ACCENT I[2,3]	380	Inflix	10	5	0, 2, 6: every 8	6.6
ACCENT I[2,3]	380	Inflix	14	5	0, 2, 6: every 8	8.2
ACCENT I[2,3]	380	Inflix	22	5	0, 2, 6: every 8	7.7
ACCENT I[2,3]	380	Inflix	30	5	0, 2, 6: every 8	6.1
ACCENT I[2,3]	380	Inflix	38	5	0, 2, 6: every 8	–0.2
ACCENT I[2,3]	380	Inflix	46	5	0, 2, 6: every 8	1.9
ACCENT I[2,3]	380	Inflix	54	5	0, 2, 6: every 8	2.4
ACCENT I[2,3]	381	Inflix	0	10	0, 2, 6: every 8	3.5
ACCENT I[2,3]	381	Inflix	2	10	0, 2, 6: every 8	0.1
ACCENT I[2,3]	381	Inflix	6	10	0, 2, 6: every 8	4.8
ACCENT I[2,3]	381	Inflix	10	10	0, 2, 6: every 8	4.8
ACCENT I[2,3]	381	Inflix	14	10	0, 2, 6: every 8	11.1
ACCENT I[2,3]	381	Inflix	22	10	0, 2, 6: every 8	14.8
ACCENT I[2,3]	381	Inflix	30	10	0, 2, 6: every 8	10.5
ACCENT I[2,3]	381	Inflix	38	10	0, 2,6: every 8	12.6
ACCENT I[2,3]	381	Inflix	46	10	0, 2, 6: every 8	15.2
ACCENT I[2,3]	381	Inflix	54	10	0, 2, 6: every 8	11.0

FIGURE 69 Maintenance trials – IBDQ scores for trials reporting % of patients with IBDQ score >170 (taken as an indicator of remission). The results above refer to all the patients in the ACCENT I[2,3] trial (not just 'responder' patients). Inflix, infliximab.

Appendix 11

Response rates among non-responders in maintenance trials

In this appendix, results for non-responders in the ACCENT I[2,3] trial (infliximab) are presented, followed by results for non-responders and for all patients in the CHARM[67] trial (adalimumab).

ACCENT I trial CDAI scores

Examination of median CDAI scores in the two separate publications[2,3] allowed an approximation of the response to treatment in 'non-responders' at least to week 14, after which crossover to increased infliximab dosage was allowed for relapsing patients. The pertinent results for median CDAI scores are summarised in *Figure 70*.

At randomisation (week 2), the difference in CDAI score of 'responders' minus 'all' was at its maximum, 50 points for infliximab and 40 for placebo, and was determined by patient selection. After randomisation up to week 14, the difference for the infliximab-treated patients (responders – all) remained fairly stable (at approximately 40 points), implying that during this phase of the trial, 'responders' and 'non-responders' fare about equally well with respect to their CDAI score at randomisation. After the introduction of permitted crossover for the 'all-patient' analysis at

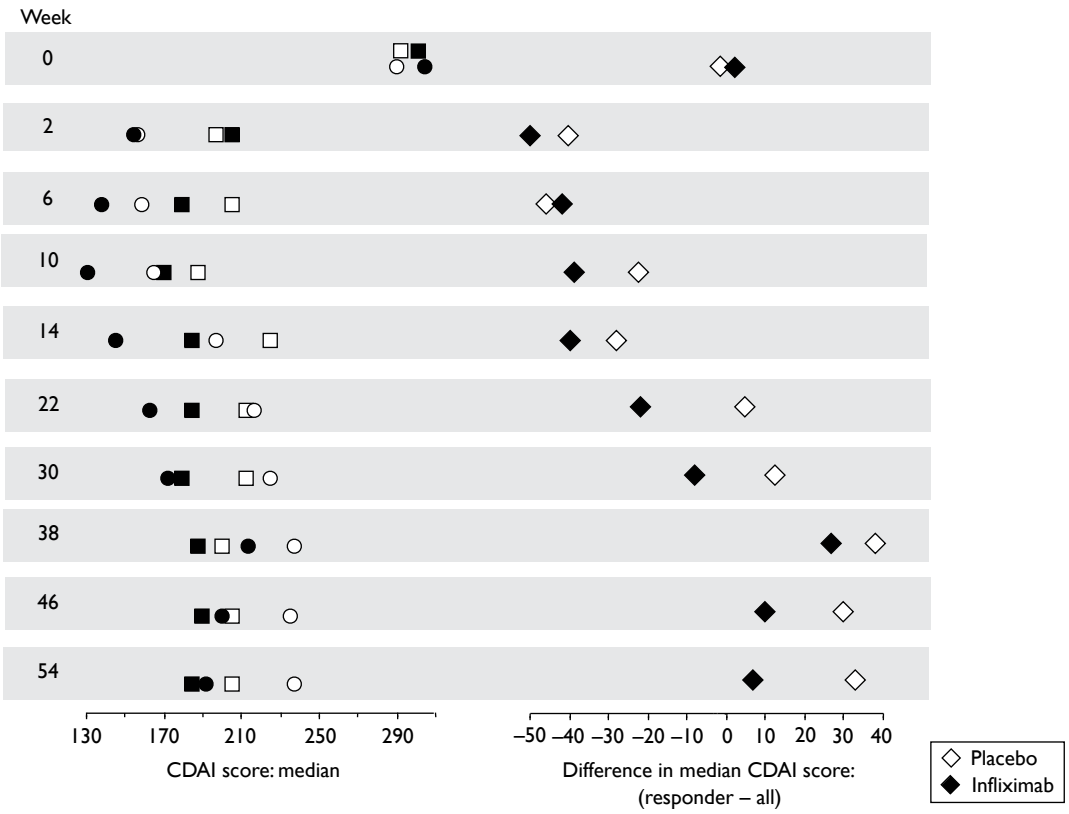


FIGURE 70 Median CDAI scores in ACCENT I[2,3] trial and score difference between placebo and intervention. Placebo scores are hollow symbols, infliximab scores solid; responders are represented by circles, all patients by squares.

week 14 both infliximab- and placebo-treated groups exhibited striking increases in the score difference 'responders' – 'all'. Given that increased CDAI implies a worse disease state, this trend implies non-responders were able to respond to treatment better than responders during this phase of the trial.

ACCENT I remission and responder 70 rates

Figure 71 shows the placebo and intervention response 70 rates for responders and calculated for non-responders. At week 2 a very large difference was evident as would be expected from the act of dichotomising patients into subgroups. Thereafter to week 14, response rates in the intervention and placebo arms gradually approached more closely. For non-responders there was only weak evidence that intervention was better than placebo. At week 14 both placebo groups and the non-responder intervention arm had a response rate of about 50%. The major difference between the responder and non-responder subgroups appeared to be the much larger proportion of placebo responders in the non-responder group; or, conversely among the responder group, there was a greater proportion of patients who required early doses of infliximab to achieve response. Unfortunately, information beyond 14 weeks was not available except for responders.

Similar results were seen for remission (*Figure 72*). At week 14, 20% of non-responders had attained remission irrespective of treatment. At week 14, the responder intervention arm exhibited 20% more patients in remission than the responder placebo group; thereafter this difference diminished. Unfortunately, no information for non-responders was available beyond 14 weeks.

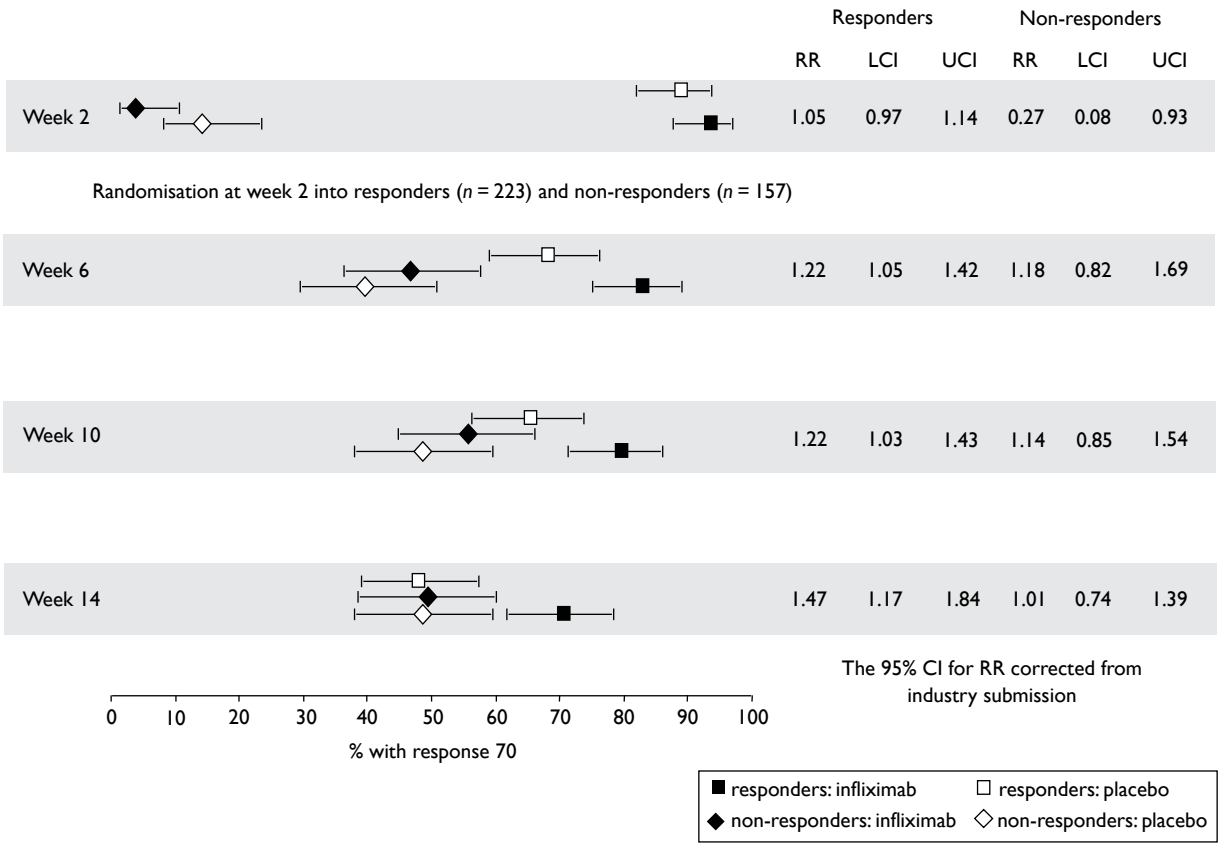


FIGURE 71 Response 70 rates and risk ratios for responders and non-responders in ACCENT I[2,3] trial. LCI, lower confidence interval; UCI, upper confidence interval; RR, risk ratio.

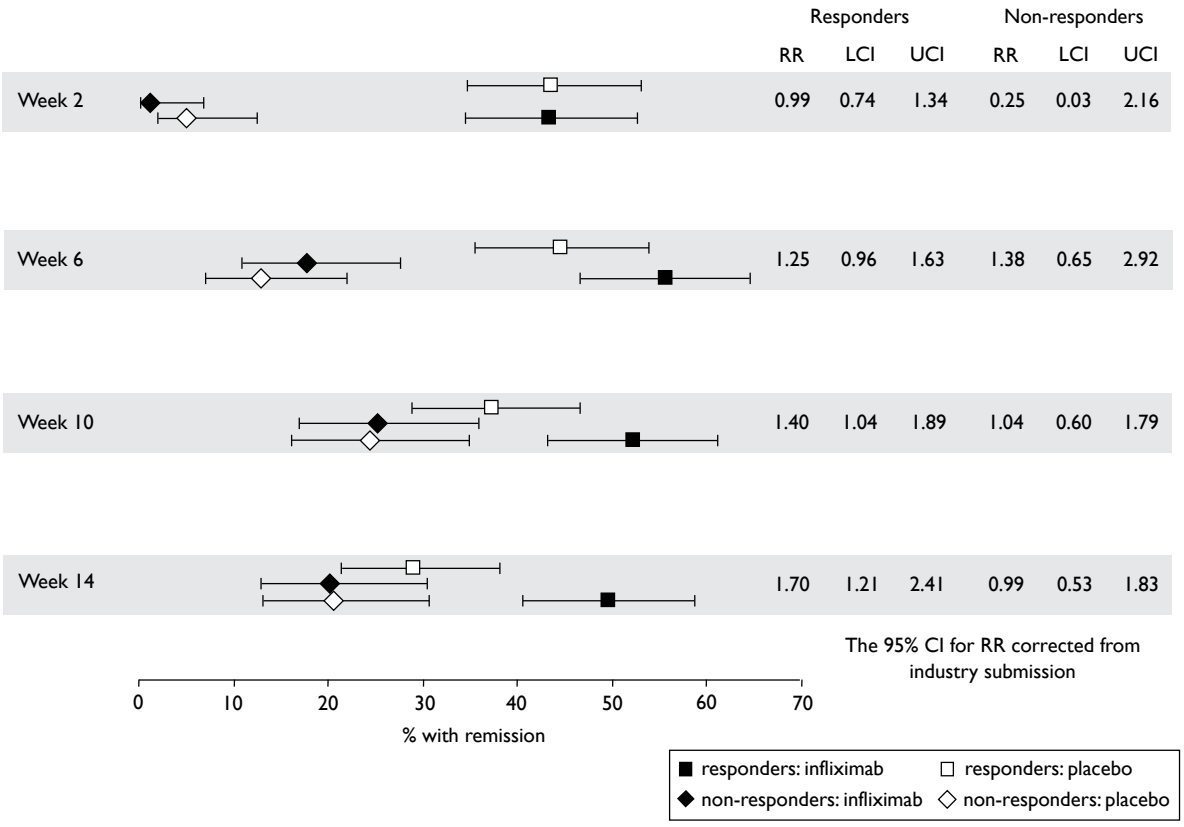


FIGURE 72 Remission rates and risk ratios for responders and non-responders in ACCENT I[2,3] trial. LCI, lower confidence interval; UCI, upper confidence interval; RR, risk ratio.

At week 14 the yield in percentage of patients with response 70 per dose, and in percentage of patients with remission per dose for strategies in which all patients received one dose, all patients received three doses or responders received three doses and non-responders a single dose was 49%, 21% and 25% for response 70 respectively, and 25%, 13% and 17% for remission respectively.

CHARM trial remission and response 70 and 100 rates

(CiC information has been removed.)

FIGURE 73 (CiC information has been removed.)

FIGURE 74 (CiC information has been removed.)

Appendix 12

Quality assessment of trials

Study	Trial design	Blinding	Handling of missing data (binary and continuous); ITT	% of withdrawals and/or crossovers and loss to follow-up Other comments
Induction				
Hanauer *et al.*, 2006[63] CLASSIC I (Adalimumab)	4-week multicentre, randomised, double-blind, placebo-controlled trial; 299 patients randomised to placebo, or 40/20 mg (weeks 0 and 2), 80/40 mg or 160/80 mg adalimumab	■ Placebo identical in appearance to adalimumab ■ Pharmacist preparing injections blinded ■ Patients blinded ■ Study investigators/co-ordinators blinded	All 299 patients included in efficacy analyses. Those with missing data at week 4 classified as remission failures (assume that also counted as response failures but not explicitly stated) Also states that 'all analyses were as observed with the exception of the IBDQ data that assessed the last observation carried forward' (unclear what 'as observed' means)	284/299 (95%) patients completed the trial; remaining patients withdrew. No loss to follow-up. Unclear how many patients contributing to each analysis
Sandborn *et al.*, 2007[64] GAIN (Adalimumab)	4-week multicentre, randomised, double-blind, placebo-controlled trial; 325 patients randomised to placebo or 160/80 mg adalimumab	■ No details on placebo ■ Patients blinded ■ Study investigators and data analysts blinded ■ Study site and Abbott Laboratories personnel blinded	For clinical remission and response measures, all patients included: considered patients with missing data to be non-responders For continuous variables included only those patients with complete data	No loss to follow-up; 14/325 (4%) discontinued intervention or placebo; unclear how many patients were counted as non-responders owing to missing data or how many did not contribute to continuous outcome data
D'Haens *et al.*, 1999[68] (Infliximab)	4-week multicentre, randomised, double-blind, placebo-controlled trial; 30 patients randomised to placebo, 5, 10 or 20 mg/kg infliximab	■ Placebo identical in appearance to infliximab solution ■ Patients blinded ■ Study investigators/ personnel blinded ■ Pathologist assessing biopsy specimens blinded	Unclear if missing data or how missing data were handled; states that second colonoscopy could not be performed in two patients; states that 'only biopsy specimens from patients who underwent two endoscopic procedures and biopsy sampling were used for the final analysis ($n=9$)'. Unclear which analysis this refers to	% of withdrawal/loss to follow-up unclear

Study	Trial design	Blinding	Handling of missing data (binary and continuous); ITT	% of withdrawals and/or crossovers and loss to follow-up Other comments
Targan *et al.*, 1997[57] (Infliximab)	4-week multicentre, randomised, double-blind, placebo-controlled trial; 108 patients randomised to placebo, 5, 10 or 20 mg/kg infliximab Patients without a response at week 4 were enrolled in a parallel, open-label study and were followed for 12 additional weeks	(Refers to first 4 weeks) ■ Placebo identical in appearance to infliximab solution ■ Patients blinded ■ Study investigators/ personnel blinded	Unclear how missing data were handled States that the original study protocol did not specify the use of ITT analysis, but that patients were analysed according to assignment (except two patients who did not receive treatment and were excluded from the analysis). For assessing the response and remission rates in all evaluation periods after the initial blinded infusion, patients who received an open-label infusion or those with a change in concomitantly administered medication were considered non-responders. It is unclear if patients who did not contribute data during the blinded period were also counted as non-responders Not clear how missing continuous data were handled	Based on data in *Figure 1* it appears that at most 7/108 (6%) patients were not evaluated for results (at week 2) 100% of patients completed 4 weeks of double-blind therapy
Maintenance				
Hanauer *et al.*, 2002[3] and Rutgeerts *et al.*, 2004[2] ACCENT I (Infliximab)	54-week, multicentre, randomised, double-blind placebo-controlled trial; all patients initially received 5 mg/kg (week 0), then randomised to placebo ('episodic treatment') or 5 mg/kg (5 mg/kg weeks 2 and 6, then every 8 weeks) or 10 mg/kg infliximab (5 mg/kg weeks 2 and 6, then 10 mg/kg every 8 weeks) All patients included in analysis – responders and non-responders (in Rutgeerts *et al.*[2]) Responders only analysis in Hanauer *et al.*[3] Note: at week 14 or later patients who had responded at any time to infliximab therapy but then worsened were eligible to cross over to 'active episodic' treatment *as needed* with infliximab 5, 10 or 15 mg/kg for patients originally assigned to episodic, 5 mg/kg or 10 mg/kg respectively	■ Placebo identical in appearance to infliximab solution ■ Patients blinded (until crossover if applicable) ■ Study investigators blinded (until patient crossover if applicable)	Rutgeerts *et al.*[2] – responder and non-responder analysis: ■ Data from the patients who participated in the crossover to treatment with a higher dose, upon loss of response, were analysed under the original treatment group assignment ■ Patients who withdrew from the study or did not have a value at an originally scheduled visit because of crossover, and those with missing CDAI or IBDQ scores had their last value carried forward for these analyses Hanauer *et al.*[3] responder analysis: ■ Data obtained after episodic re-treatment were not included in the efficacy analysis ■ Patients who crossed over to episodic infliximab retreatment, who received a protocol-prohibited drug, who had surgery for CD or who discontinued follow-up owing to lack of efficacy or loss of response were judged to have failed treatment, irrespective of the CDAI score ■ Patients who discontinued the study for reasons other than lack of efficacy or loss of response and those with missing CDAI scores were censored in the analysis of time to loss of response up to week 54 ■ These patients were treated as not in clinical response or clinical remission for other analyses	124/573 (22%) patients had withdrawn by week 54; 201/573 (35%) had crossed over to active episodic treatment by week 54 [92/188 (49%) of patients crossed over from placebo to episodic treatment] No loss to follow-up Results include any patients with a response or in remission at different time points, not just patients maintaining a response (also includes non-responders)

Study	Trial design	Blinding	Handling of missing data (binary and continuous); ITT	% of withdrawals and/or crossovers and loss to follow-up Other comments
Rutgeerts *et al.*, 1999[58] (Infliximab)	36-week, multicentre, randomised, double-blind placebo-controlled trial; patients randomised to placebo or 10 mg/kg infliximab; eligible patients had previously shown a response in the RCT by Targan *et al.*[57] (see induction trials) or, if initial non-response, a response in an 8 week open-label extension of Targan *et al.*;[57] unclear if this included any patients who had shown a response to placebo, or if all had received infliximab Responders only randomised	■ Patients blinded No explicit statement regarding blinding of other parties	Treatment was considered a failure in patients who underwent surgery or were treated with medication regimens excluded from the study regardless of CDAI Last measure carried forward for continuous measures (CDAI, IBDQ) in patients who discontinued follow-up, had a CD-related surgical procedure or had non-permitted medication change	Results include any patients with a response at different time points, not just patients maintaining a response; unclear why data do not start with 100% of patients with a response as only responders included 24/73 (33%) patients withdrawn by end of study. No details regarding potential crossovers
Colombel *et al.*, 2007[67] CHARM (Adalimumab)	56-week, multicentre, randomised, double-blind placebo-controlled trial; all patients received adalimumab 80 mg subcutaneously at week 0, followed by 40-mg dose at week 2; randomisation at week 4, stratified by responder status to placebo or 40-mg adalimumab weekly or 40-mg adalimumab e.o.w.; only responders included in efficacy analysis States that secondary efficacy analyses include non-responders also, but present results for responders only in this publication; only fistula results include non-responders Note: those patients who experienced a disease flare or sustained non-response at or after week 12 were switched to open-label treatment (40 mg e.o.w., which could be escalated to 40 mg weekly)	■ No details regarding placebo ■ Patients blinded (until open label if applicable) ■ Study investigators and co-ordinators blinded (until open label if applicable)	Patients who switched to open-label therapy or withdrew from the study were counted as remission failures. Patients without CDAI assessments at weeks 26 or 56 were classified as remission failures (remission = primary end point) Unclear if patients also counted as treatment failures for secondary outcomes (response) No details on how continuous data were handled	Results include any patients in remission at different time points, not just patients maintaining remission 505/778 (65%) of patients completed study (note: paper states 59% unclear); 50% of these remained on double-blind therapy, 50% completed the study on open-label treatment Of 499 patients (responders) included in efficacy analysis, 29% withdrew and 38% were still on double-blind therapy. Assume 33% therefore on open-label treatment, though not clearly stated No details on loss-to follow-up

Study	Trial design	Blinding	Handling of missing data (binary and continuous); ITT	% of withdrawals and/or crossovers and loss to follow-up Other comments
Sandborn *et al.*, 2007[66] CLASSIC II (Adalimumab)	56-week, multicentre, randomised, double-blind placebo-controlled trial; all patients from CLASSIC I[63] trial eligible if they demonstrated remission at weeks 0 and 4 (unclear if this includes patients from placebo group in remission); randomisation to placebo, 40-mg adalimumab weekly or 40-mg adalimumab eow (unclear if placebo weekly or e.o.w.) Randomised patients in remission only Note: randomised patients experiencing a flare or with continued non-response could switch to open-label adalimumab 40 mg e.o.w.; patients on open-label adalimumab e.o.w. could switch to adalimumab 40 mg weekly	■ No details regarding placebo (unless assume same as in CLASSIC I[63]) ■ Patients blinded (until open label if applicable) ■ Study investigators and co-ordinators blinded (until open label if applicable)	Efficacy analysis included all randomised patients; patients who switched to open label or with missing data were classified in a 'no maintenance of remission' category Secondary analyses used 'last observation carried forward'	10/55 (18%) withdrew (of these, one lost to follow-up) 32/55 (58%) patients completed 56 weeks of double-blind therapy (6/18, 33% of patients in placebo group completed 56 weeks of double-blind therapy); remainder completed study on open-label therapy Results include any patients in remission at different time points, not just patients maintaining remission
Fistulising				
Present *et al.*, 1999[62] (Infliximab)	18-week multicentre, randomised, double-blind placebo-controlled trial; patients randomised to placebo, 5 mg/kg infliximab or 10 mg/kg infliximab	■ Placebo identical in appearance to infliximab solution No details on blinding (other than to state that this was a double-blind trial)	Treatment considered to have failed in patients who had changes in medication that were not permitted, who underwent surgery related to CD or who did not return for follow-up visits For continuous variables, measurements from the last evaluation were carried forward	88/94 (94%) completed trial; no loss to follow-up Appear to be no crossovers
Sands *et al.*, 2004[65] ACCENT II (Infliximab)	54-week multicentre, randomised, double-blind placebo-controlled trial; all patients received 5 mg/kg infliximab at weeks 0, 2 and 6; responders at week 14 randomised to placebo or 5 mg/kg infliximab every 8 weeks Responders only included in primary analysis Non-responders also randomised for secondary analysis From week 22, patients could crossover from placebo to 5 mg/kg or from 5 mg/kg to 10 mg/kg infliximab	■ Placebo identical in appearance to infliximab solution ■ Patients blinded ■ Study investigators blinded	All patients included in analysis. Data for patients who crossed over from placebo to infliximab were censored before crossover occurred. Not stated for patients who crossed over from lower to higher infliximab dose For continuous variables (CDAI, IBDQ), measurements from the last evaluation were carried forward	95/282 (34%) crossed over (total randomised population; 2223 from placebo group to treatment) 78/195 (40%) crossed over (responder only) by week 54 (28% from placebo group to treatment) No details on withdrawals or loss to follow-up post randomisation
Paediatric				
Baldassano *et al.*, 2003[46] (Infliximab)	12-week multicentre, randomised (no placebo control); 21 patients randomised to 1 mg/kg, 5 mg/kg or 10 mg/kg infliximab	■ No placebo, all received infliximab ■ Patients blinded to dose ■ Study investigators blinded to dose	No details. Numbers included in different analyses vary at different time points	19/21 (90%) of patients completed trial. No further details

Study	Trial design	Blinding	Handling of missing data (binary and continuous); ITT	% of withdrawals and/or crossovers and loss to follow-up Other comments
Hyams *et al.*, 2007[45] REACH (Infliximab)	54-week multicentre, randomised, open-label (no placebo control); 112 patients received induction therapy (5 mg/kg infliximab) for 10 weeks; only patients with response (n = 103) randomised at week 10 to 5 mg/kg infliximab every 8 weeks or 5 mg/kg infliximab every 12 weeks; patients losing clinical response eligible to cross over one time to receive treatment more frequently or at higher dose (10 mg/kg every 8 weeks)	No blinding: open-label study	All analyses based on ITT principle. Patients who lost response and crossed over were considered non-responders (treatment failures) for the remainder of the study Last non-missing score used for continuous data where patients discontinued study or had insufficient data	59/103 (57%) patients in treatment arms as randomised at study end. 35 patients (34%) crossed over in total and nine (9%) withdrew No loss to follow-up

Appendix 13

Rates of response and remission in placebo arms of induction trials for anti-TNF interventions

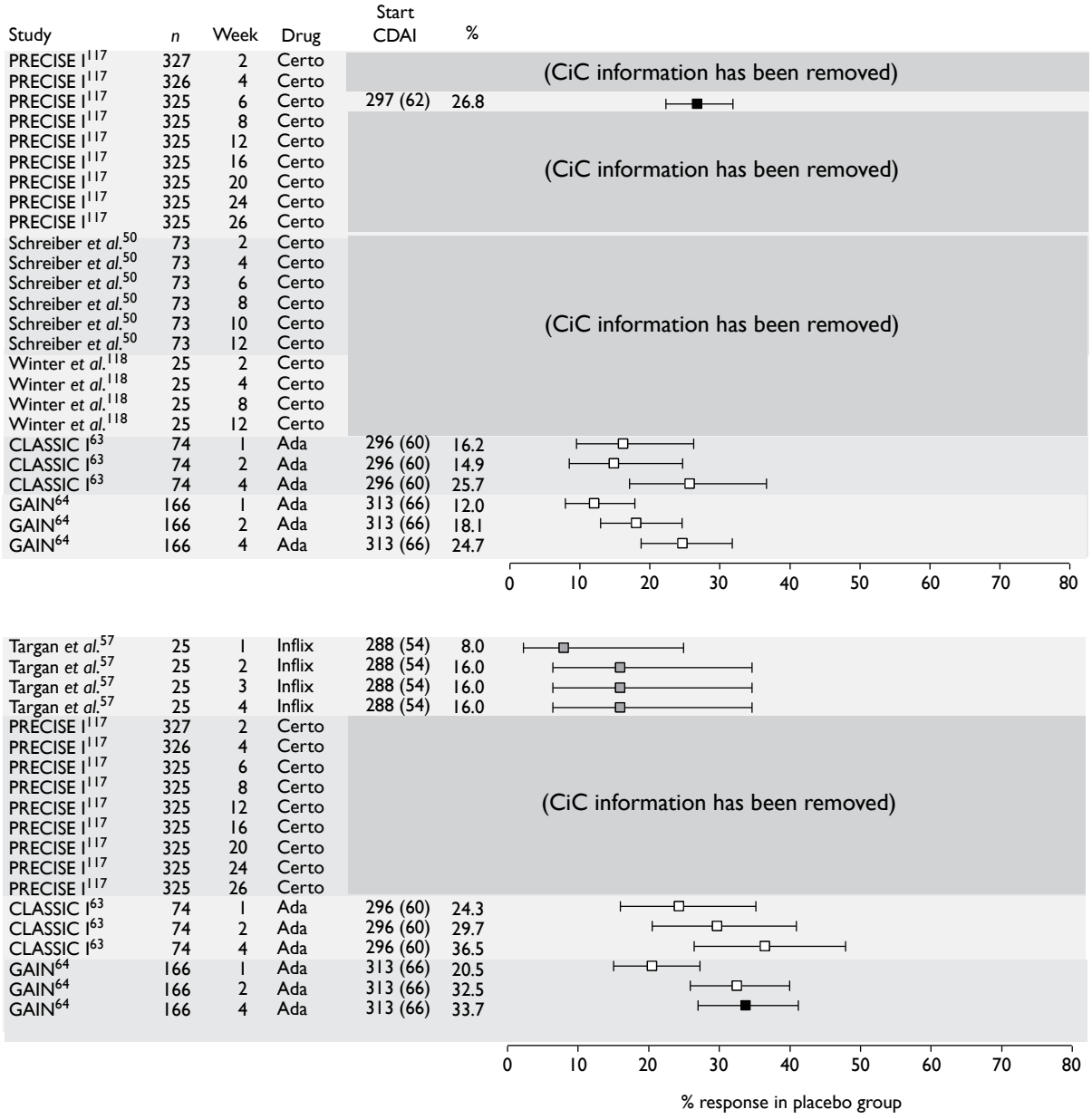


FIGURE 75 Placebo rates for response 100 (upper panel) and response 70 (lower panel) in induction trials. Ada, adalimumab; certo, certolizumab; inflix, infliximab.

Study	*n*	Week	Drug	Start CDAI	%
Targan *et al.*[57]	25	1	Inflix	288 (54)	4.0
Targan *et al.*[57]	25	2	Inflix	288 (54)	4.0
Targan *et al.*[57]	25	3	Inflix	288 (54)	4.0
Targan *et al.*[57]	25	4	Inflix	288 (54)	4.0
PRECISE 1[117]	327	2			
PRECISE 1[117]	327	4			
PRECISE 1[117]	326	6	Certo	297 (62)	17.5
PRECISE 1[117]	326	8			
PRECISE 1[117]	326	12			
PRECISE 1[117]	326	16			
PRECISE 1[117]	326	20			
PRECISE 1[117]	326	24			
PRECISE 1[117]	326	26			
Schreiber *et al.*[50]	73	2			
Schreiber *et al.*[50]	73	4			
Schreiber *et al.*[50]	73	6			
Schreiber *et al.*[50]	73	8			
Schreiber *et al.*[50]	73	10			
Schreiber *et al.*[50]	73	12			
Winter *et al.*[118]	25	2	Certo	315	16.0
Winter *et al.*[118]	25	4	Certo	315	20.0
Winter *et al.*[118]	25	8	Certo	315	32.0
Winter *et al.*[118]	25	12	Certo	315	32.0
CLASSIC I[63]	74	1	Ada	296 (60)	6.8
CLASSIC I[63]	74	2	Ada	296 (60)	13.5
CLASSIC I[63]	74	4	Ada	296 (60)	12.2
GAIN[64]	166	1	Ada	313 (66)	3.6
GAIN[64]	166	2	Ada	313 (66)	6.0
GAIN[64]	166	4	Ada	313 (66)	7.2

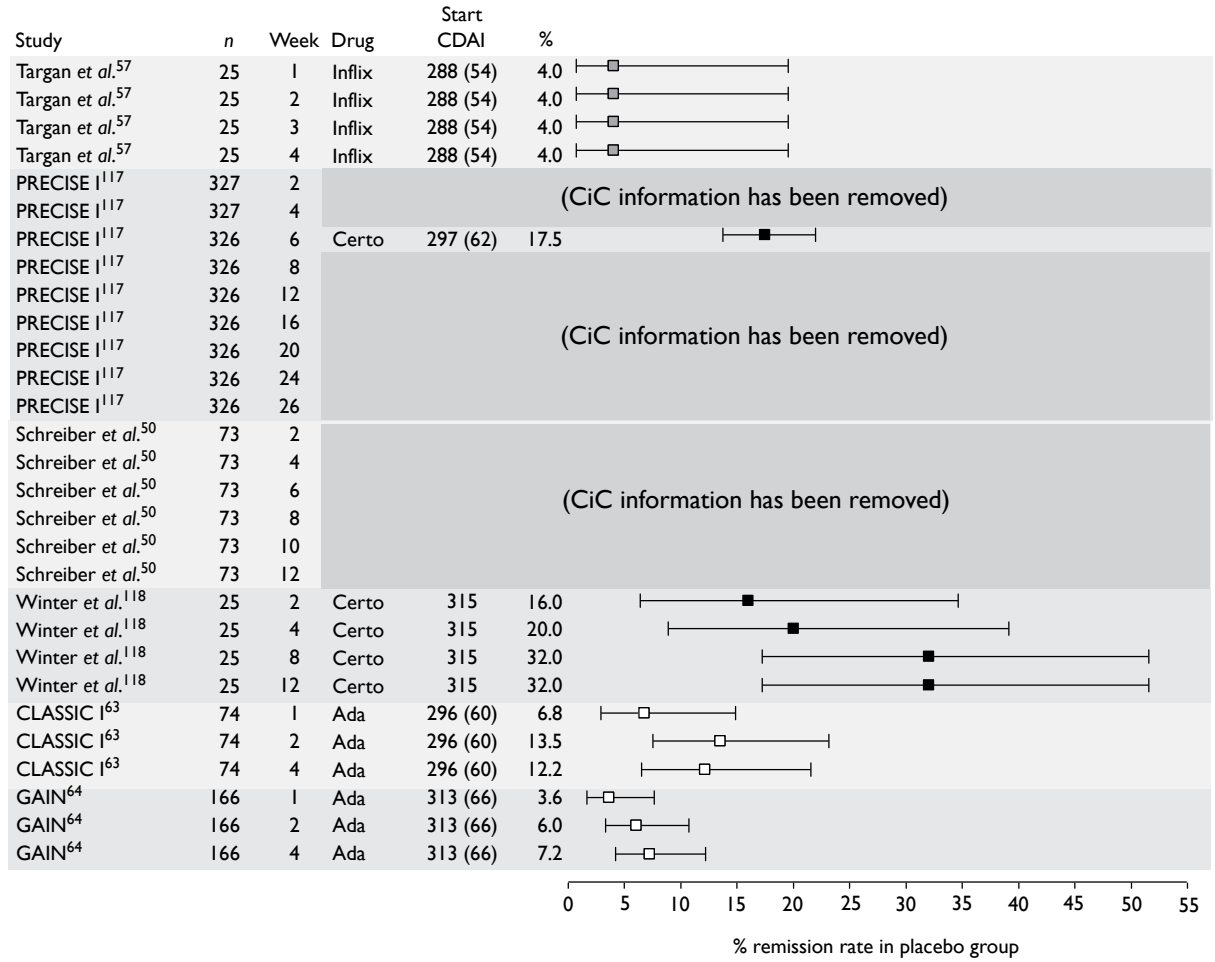


FIGURE 76 Placebo rates for remission in induction trials. Ada, adalimumab; certo, certolizumab; inflix, infliximab.

Appendix 14

Search strategy for economic evaluation

Note: certolizumab pegol and natalizumab were originally part of this appraisal; they were subsequently excluded after searching had been completed

Source – MEDLINE (Ovid), 1950 to week 4 May 2007

1. (adalimumab or humira).mp. (540)
2. (certolizumab or cimzia).mp. (19)
3. (infliximab or remicade).mp. (3096)
4. (natalizumab or tysabri).mp. (208)
5. or/1-4 (3473)
6. Crohn Disease/ (21,624)
7. crohn$.mp. (25,626)
8. or/6-7 (25,626)
9. 5 and 8 (1046)
10. economics/ (24,885)
11. exp "costs and cost analysis"/ (129,414)
12. cost of illness/ (9149)
13. exp health care costs/ (28,541)
14. economic value of life/ (4847)
15. exp economics medical/ (11,355)
16. exp economics hospital/ (14,731)
17. economics pharmaceutical/ (1764)
18. exp "fees and charges"/ (22,970)
19. (econom$or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (244,897)
20. (expenditure$not energy).tw. (10,410)
21. (value adj1 money).tw. (10)
22. budget$.tw. (10,892)
23. or/10-22 (358,461)
24. 9 and 23 (51)
25. limit 24 to yr="2000 - 2007" (48)

Source – MEDLINE (Ovid), 1950 to week 3 June 2007*

1. ca2.mp. (105,908)
2. d2e7.mp. (23)
3. cdp870.mp. (26)
4. pha-738144.mp. (0)
5. pha 738144.mp. (0)
6. (anti adj2 4 integrin).mp. (45)
7. anti alpha4 integrin.mp. (49)
8. anti alpha 4 integrin.mp. (32)
9. or/1-8 (106,047)
10. crohn disease/ (21,699)
11. crohn$.mp. (25,732)

12. or/10-11 (25,732)
13. 9 and 12 (66)
14. economics/ (24,922)
15. exp "costs and cost analysis"/ (130,028)
16. cost of illness/ (9244)
17. exp health care costs/ (28,753)
18. economic value of life/ (4854)
19. exp economics medical/ (11,385)
20. exp economics hospital/ (14,773)
21. economics pharmaceutical/ (1786)
22. exp "fees and charges"/ (23,036)
23. (econom$or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (246,746)
24. (expenditure$not energy).tw. (10,484)
25. (value adj1 money).tw. (10)
26. budget$.tw. (10,945)
27. or/14-26 (360,657)
28. 13 and 27 (1)

*Additional search to account for alternative terminology used for the drugs.

Source – EMBASE (Ovid), 1980 to 2007 week 22

1. (adalimumab or humira).mp. (2036)
2. (certolizumab or cimzia).mp. (230)
3. (infliximab or remicade).mp. (7811)
4. (natalizumab or tysabri).mp. (843)
5. or/1-4 (8685)
6. Crohn Disease/ (20,817)
7. crohn$.mp. (23,756)
8. or/6-7 (23,756)
9. 5 and 8 (2554)
10. cost benefit analysis/ (26,197)
11. cost effectiveness analysis/ (48,867)
12. cost minimization analysis/ (1140)
13. cost utility analysis/ (1927)
14. economic evaluation/ (3621)
15. (cost or costs or costed or costly or costing).tw. (146,502)
16. (economic$or pharmacoeconomic$or price$or pricing).tw. (70,477)
17. (technology adj assessment$).tw. (1366)
18. or/10-17 (223,990)
19. 9 and 18 (151)
20. limit 19 to yr="2000 - 2007" (149)

Source – EMBASE (Ovid), 1980 to 2007 week 25*

1. ca2.mp. (115,879)
2. d2e7.mp. (65)
3. cdp870.mp. (16)
4. pha-738144.mp. (1)
5. pha 738144.mp. (1)
6. (anti adj2 4 integrin).mp. (9)
7. anti alpha4 integrin.mp. (37)
8. anti alpha 4 integrin.mp. (2)

9. or/1-8 (116,001)
10. crohn disease/ (20,928)
11. crohn$.mp. (23,876)
12. or/10-11 (23,876)
13. 9 and 12 (72)
14. cost benefit analysis/ (26,342)
15. cost effectiveness analysis/ (49,154)
16. cost minimization analysis/ (1156)
17. cost utility analysis/ (1947)
18. economic evaluation/ (3637)
19. (cost or costs or costed or costly or costing).tw. (147,257)
20. (economic$or pharmacoeconomic$or price$or pricing).tw. (70,847)
21. (technology adj assessment$).tw. (1367)
22. or/14-21 (225,192)
23. 13 and 22 (3)

*Additional search to account for alternative terminology used for the drugs.

Quality of life

Source – MEDLINE (Ovid), 1950 to week 4 May 2007

1. (adalimumab or humira).mp.
2. (certolizumab or cimzia).mp.
3. (infliximab or remicade).mp.
4. (natalizumab or tysabri).mp.
5. or/1-4 (3473)
6. Crohn Disease/ (21,624)
7. crohn$.mp. (25,626)
8. or/6-7 (25,626)
9. 5 and 8 (1046)
10. quality of life/ (59,486)
11. life style/ (25,902)
12. health status/ (33,125)
13. health status indicators/ (10,984)
14. value of life/ (4847)
15. quality adjusted life.mp. (3912)
16. or/10-15 (124,425)
17. 8 and 16 (427)
18. limit 17 to yr="2000 - 2007" (246)
19. from 18 keep 1-246 (246)

Source – EMBASE (Ovid), 1980 to 2007 week 22

1. (adalimumab or humira).mp. (2036)
2. (certolizumab or cimzia).mp. (230)
3. (infliximab or remicade).mp. (7811)
4. (natalizumab or tysabri).mp. (843)
5. or/1-4 (8685)
6. Crohn Disease/ (20,817)
7. crohn$.mp. (23,756)
8. or/6-7 (23,756)
9. 5 and 8 (2554)
10. quality of life/ (75,452)
11. quality adjusted life year/ (3013)

12. health status/ (31,455)
13. health status indicator$.mp. (129)
14. or/10-13 (104,174)
15. 8 and 14 (624)
16. limit 15 to yr="2000 - 2007" (481)

Source – HEED, June 2007

Search terms: (adalimumab OR humira OR certolizumab OR cimzia OR infliximab OR remicade OR natalizumab OR tysabri OR ca2 OR d2e7 OR cdp870 OR pha-738144 OR pha 738144 OR anti 4 integrin OR anti alpha4 integrin OR anti alpha 4 integrin) AND (crohn OR crohns)

Cohort studies of infliximab and Crohn's disease

Source – MEDLINE (Ovid), 1950 to week 4 May 2007

1. (infliximab or remicade).mp. (3096)
2. crohn$.mp. (25,626)
3. crohn disease/ (21,624)
4. or/2-3 (25,626)
5. 1 and 4 (992)
6. cohort studies/ (73,136)
7. Risk/ (74,606)
8. cohort$.mp. (132,834)
9. risk$.mp. (848,754)
10. or/6-9 (922,221)
11. 5 and 10 (186)

Clinical guidelines

Source – MEDLINE (Ovid), 1950 to week 5 May 2007

1. Crohn Disease/ (21,659)
2. crohn$.mp. (25,672)
3. or/1-2 (25,672)
4. exp "guideline [publication type]"/ (15,854)
5. exp "consensus development conference [publication type]"/ (5531)
6. guideline$.mp. (137,797)
7. recommend$.mp. (215,591)
8. consensus.mp. (63,448)
9. or/4-8 (381,390)
10. 3 and 9 (631)
11. or/4-5 (20,617)
12. 3 and 11 (51)

Appendix 15

Details of studies included in cost-effectiveness review

TABLE 80 Study characteristics of studies in cost-effectiveness review

Study	Type of evaluation and synthesis	Interventions	Study population	Country	Duration of study
Jaisson-Hot *et al.*[7] (2004; non-fistulising)	CUA	(A) Surgery and medical treatment (without infliximab) (B) Infliximab (infusions + episodic reinfusions for relapse) (C) Infliximab (maintenance)	Adult patients with non-responsive, non-fistulising CD, (CDAI between 220 and 440) 38 years old at baseline	France	Lifetime
Clark *et al.*[5] (2003; non-fistulising)	CUA	(A) Placebo (B) Single dose: infliximab (C) Episodic: initial infliximab + (for responders) up to three treatments at subsequently relapses (flare)	Adult patients (70 kg) with non-responsive, non-fistulising CD, 37 years at baseline	UK	Unclear, probably 1 year
Marshall *et al.*[6] (2002; non-fistulising)	CUA	(A) Usual care (B) Single dose: infliximab infusion at week 0, relapses treated with usual care (C) Episodic: infliximab infusion at week 0, relapses treated with single infusion of infliximab (D) Maintenance: infliximab infusion at week 0, with responding patients (CDAI drop of 70) receiving maintenance infusions of infliximab 5 mg/kg every 8 weeks starting at week 12. Non-responding or subsequently relapsing patients receive usual care	Adult patients (70 kg) with CD resistant to conventional medical therapy	Canada	1 year
Clark *et al.*[5] (2003; fistulising)	CUA	(A) Placebo (B) Initial treatment only	Adult patients with fistulising CD	UK	1 year
Arseneau *et al.*[90] (2001; fistulising)	CUA	(A) 6MP/met as first- and second-line treatment (B) Infliximab infusions (infliximab infusions + 6MP/met for treatment failures/relapse) (C) Infliximab (infusions + episodic infliximab reinfusions for treatment failures/relapse) (D) Second-line infliximab (6MP/met + episodic infliximab reinfusions for treatment failures/relapse)	Adult patients (70 kg) with symptomatic perianal fistulas	USA	1 year

CUA, cost–utility analysis.

TABLE 81 Type of model used in studies in cost-effectiveness review

			Model assumptions	
Study	**Type of model**	**Perspective**	**Outcomes**	**Costs and resource use**
Jaisson-Hot *et al.*[7] (2004; non-fistulising)	Markov model, cycle length of 2 months	Third-party payer perspective	Lifetime model but no stated mortality assumptions	Infliximab dose at 5 mg/kg per infusion Maintenance treatment every 8 weeks
Clark *et al.*[5] (2003; non-fistulising)	Modified industry submission Markov model, cycle length of 2 months	Unclear	Benefits related to the numbers in remitted health state (CDAI < 150). Report also gives outcomes under industry assumption (benefit = reduction of 70 CDAI points)	Unclear
Marshall *et al.*[6] (2002; non-fistulising)	Markov model: initial cycle length of 12 weeks, with subsequent cycles at 8 weeks	Third-party (Canadian provision ministry of health) perspective	US data (Olmstead County) used to estimate transition probabilities in usual care No transitions between remission and drug-responsive states (owing to data limitations) Retreatment strategy assumed to have equivalent effectiveness to initial dosage. All infliximab dosages (5 mg/kg, 10 mg/kg, 20 mg/kg) treated as equally effective	20% of patients in drug-refractory state would be admitted to hospital, with the remaining 80% receiving outpatient care Only 5 mg/kg infliximab dosages used Acute infusion reactions are mild, and have no effect on treatment efficacy or cost Methotrexate and ciclosporin not used by the model cohort No medication given in the period following surgery as post-operative prophylaxis
Clark *et al.*[5] (2003; fistulising)	Unclear	Unclear	Time spent with fistulas closure	Infliximab dose (unclear) offset by possible savings in surgery
Arseneau *et al.*[90] (2001; fistulising)	Markov model, cycle length of 1 month	Third-party payer perspective	Episodic remission figures assumed to equal remission from initial infusion Benefits from initial infusion assumed to occur within the first month following infusion The chance of fistula recurrence increases by 3% per month after 4 months Pancreatitis state includes 1 week with acute pancreatitis, and 3 weeks of fistula/improved fistula	Initial infliximab infusions at 5 mg/kg (weeks 0, 2 and 6), according to FDA-approved protocol

TABLE 82 Cost and resource use data sources for studies in cost-effectiveness review

Study	Cost items	Cost data sources	Resource use	Resource data source	Currency and currency year	Discount rate
Jaisson-Hot *et al.*[7] (2004; non-fistulising)	Hospitalisations Outpatient care (physicians' visits, nursing care, laboratory), medications, and patient transportation	Some unit costs based on diagnosis-related group estimates and negotiated prices	Based on expert opinion. No details given	Not given	Not given	5%
Clark *et al.*[5] (2003; non-fistulising)	Drug and administration costs Other items unclear	Not given	Not given	Not given	Not given	Not discounted (probably 1 year)
Marshall *et al.*[6] (2002; non-fistulising)	Infliximab infusion; CD-related outpatient prescriptions; outpatient physician visits; medical hospital admissions for CD; surgical hospital admissions for CD	Unit costs based on: 2001 Drug Benefits Formulary, McMaster University Medical Centre outpatient pharmacy	Appears in appendices to CCOHTA report	Three-member expert panel of gastroenterologists based on text description Surgical costs from patient-level database	Canadian dollars, 2001	Not discounted (1 year)
Clark *et al.*[5] (2003; fistulising)	Drug costs; surgery Other items unclear	Not given	Not given	Not given	Not given	Not discounted (1 year)
Arseneau *et al.*[90] (2001; fistulising)	Diagnostic, physician, medication. Surgical costs in abscess state only	Administrative database of hospital and physician billing data Cost data calculated according to hospital cost–charge ratios	Usage split by state and treatment	Not given	US dollars, 1999	3%

CCOHTA, Canadian Coordinating Office for Health Technology Assessment.

TABLE 83 Efficacy data and health outcomes/utility for studies in cost-effectiveness review

Study	Efficacy data	Efficacy data sources	Health outcomes/utility	Health outcome data sources	Discount rate
Jaisson-Hot *et al.*[7] (2004; non-fistulising)	Derived from published data and expert opinion	Unclear Some figures from Targan *et al.*[57]	QALY QoL figures unclear	Gregor *et al.*[92]	5%
Clark *et al.*[5] (2003; non-fistulising)	Response from treatment continued for 80 days (median) in both initial and subsequent treatment. 100% success of initial responders in retreatment. Large numbers of data removed because of confidentiality Scenario 1: uses company's effectiveness estimates. 19.4% more patients achieve remission (CDAI < 150) over infliximab arms Scenario 2: uses estimates on remission at different dosages to infer the proportion of those achieving mild disease at a 5-mg dosage. 28.7% more patients achieve remission (CDAI < 150) under 5-mg infliximab	Olmstead County data (usual care) Infliximab data from clinical trials but not ACCENT I[2,3]	Interpolation used to SG utilities Mild disease: 0.86 Drug-refractory disease: 0.74	Gregor *et al.*[92] plus Olmstead County data	Not discounted (probably 1 year)
Marshall *et al.*[6] (2002; non-fistulising)	8-week transitions: usual care Drug-refractory from remission: 0.2150 Remission from drug-refractory: 0.0524 Remission from drug-dependent: 0.0540 8-week transitions: infliximab Probability of remaining in clinical response (remission or drug-responsive) over 8 weeks = 0.796 (single dose) 0.937 (maintenance) Remission at CDAI < 150	Olmstead County data (usual care) Targan *et al.*[57] trial (infliximab, initial values 46) Rutgeerts *et al.*[58] trial (infliximab, after 12 weeks)	Mild (0.82) used for remission states and mild disease Moderate (0.73) used for drug-responsive/dependent states Severe (0.54) used for drug-refractory and surgery states	Gregor *et al.*[92] provides standard gamble utility values for three states (mild, moderate and severe)	Not discounted (1 year)
Clark *et al.*[5] (2003; fistulising)	Based on Present *et al.*[62] study into time spent with close fistulas in first 12 months after treatment	Present *et al.*[62] study	Based on CDAI and PDAI scores using an unpublished algorithm provided in industry submission	Unpublished data	Not discounted (1 year)
Arseneau *et al.*[90] (2001; fistulising)	Fistula recurrence based on clinical data in first 4 months (18% per month), then 3% in subsequent months Monthly transitions: ■ Fistula improves (complete closure or symptomatic improvement) after infliximab: 0.70 ■ Recurrent fistula after infliximab (≤ 4 months): 0.18 ■ Recurrent fistula after infliximab (> 4 months): 0.03 ■ Abscess after infliximab: 0.06 ■ Abscess recurs after incision and drainage: 0.03 ■ Fistula improves after 6MP/met: 0.48 ■ Recurrent fistula after 6MP/met is stopped: 0.14 ■ Recurrent fistula while taking 6MP/met: 0.01 ■ Pancreatitis: 0.03 ■ Paresthesias: 0.10	Various studies (named)	QALY *QoL figures from patients:* Infliximab: ■ Fistula: 0.73 ■ Improved fistula: 0.85 ■ Perianal abscess: 0.62 6MP/met: ■ Fistula: 0.69 ■ Improved fistula: 0.81 ■ Pancreatitis + fistula: 0.61 ■ Pancreatitis alone: 0.70 ■ Paresthesias + fistula: 0.66 ■ Paresthesias: 0.75	Standard gamble utilities from 32 CD patients (17 fistulising, 15 non-fistulising) Descriptions of valued states not given	3%

TABLE 84 Cost-effectiveness ratios for studies in cost-effectiveness review

Study	Cost of anti-TNF-α therapy	Total costs	Total incremental costs	Total outcome	Total incremental outcomes	Cost-effectiveness ratios
Jaisson-Hot *et al.*[7] (2004; non-fistulising)	Not given	(A) Surgery + medical management €71,296.44 (B) Infliximab (episodic) €119,801.60 (C) Infliximab (maintenance) €687,086.96	B vs A: €48,505.16 C vs A: infliximab (maintenance) €615,790.52	Not given	Not given	B vs A: infliximab (episodic) €63,700.82/QALY C vs A: infliximab (maintenance) vs usual care €784,057.49/QALY
Clark *et al.*[5] (2003; non-fistulising)	£1457 per dose	Not given	vs placebo Single treatment £1457 per patient Episodic treatment (vs placebo) £3861	Not given	QALY vs placebo *Single treatment* Scenario 1: 0.006 Scenario 2: 0.009 *Episodic treatment* Scenario 1: 0.043 Scenario 2: 0.067	vs placebo *Single treatment* Scenario 1: £244,756 per QALY Scenario 2: £165,445 per QALY *Episodic treatment* Scenario 1: £72,261 per QALY Scenario 2: £62,016 per QALY
Marshall *et al.*[6] (2002; non-fistulising)	Single dose cost C$5064.11	(A) C$9940 (B) C$12,702 (C) C$13,739 (D) C$21,597	B vs A: C$2762 C vs B: C$1037 D vs C: C$7858	0.6281 0.6433 0.6455 0.6568	B vs A: 0.0152 C vs B: 0.0022 D vs C: 0.00132762	B vs A: C$181,201/QALY C vs B: C$480,111/QALY D vs C: C$696,078/QALY
Clark *et al.*[5] (2003; fistulising)	Unclear	Not given	Not given	Not given	Not given	Initial treatment vs placebo is £102,000–123,000 per QALY depending on cost offsets
Arseneau *et al.*[90] (2001; fistulising)	Single dose cost $2030 for 5 mg/kg dose, 70-kg person	(A) $2894 (B) $10,003 (C) $10,112 (D) $6664	All vs comparator: B vs A: $7109 C vs A: $7218 D vs A: $3770	0.76 0.78 0.78 0.77	Not given	All vs comparator: B vs A: $355,450 C vs A: $360,900 D vs A: $377,000

TABLE 85 Sensitivity analyses for studies in cost-effectiveness review

Study	Sensitivity analysis methods	Sensitivity analysis results
Jaisson-Hot *et al.*[7] (2004; non-fistulising)	'Influential' variables considered, but choice of variables not justified. Tornado diagram used to identify utility weights for 'post-surgery remission' and 'remission not following surgery' as important	Surgery and non-infliximab treatment become dominant where post-surgery remission receives utility value 0.92. No dominance found when varying the value for non-surgical remission utility
	Only one-way sensitivity analyses reported	
Clark *et al.*[5] (2003; non-fistulising)	One-way sensitivity analyses for utility (to 0.20 from 0.12), duration of response (120 days from 80 days), averted surgery (50% averted surgeries)	None of the one-way sensitivity analyses reduced the ICERs below £40,000 per QALY
Marshall *et al.*[6] (2002; non-fistulising)	Probabilistic sensitivity analysis conducted in addition to one-way sensitivity analysis: use of medical/surgical treatment in drug-refractory state (varying 0%–100% from 20% baseline). Surgical admissions varied (0%–100%, 13% baseline). Infliximab cost (0%–100% of baseline cost)	Rate of surgical admission for drug-refractory CD found to have little effect on ICER
		Proportion of patients with drug-refractory disease treated medically fell to C$39,000/QALY at 60% for B vs A
		At 75% of baseline cost, ICERs are: (B vs A) C$98,186; (C vs B) C$329,204; (D vs C) C$522,511/QALY. Usual care dominated by Strategy B (one single dose) where prices reduced to 25% of baseline cost.
		Usual care favoured for maximum willingness to pay per QALY (λ) $<$ C$180,000
		One single dose of infliximab (B) favoured for C$180,000 $<\lambda<$ C$430,000
Clark *et al.*[5] (2003; fistulising)	Success rate for retreatment and reclosure of fistulas varied, alongside the level of costs offset due to averted surgery	Even at the most favourable assumptions, the ICER remains above £80,000 per QALY
Arseneau *et al.*[90] (2001; fistulising)	One-way sensitivity analyses for all cost, probability and utility estimates in the model	All ICERs remain above $100,000 per QALY, except where comparator treatment dominates (equal or more effective, lower cost)
	Cost estimates varied by 25%, probability and utility estimates over 95% CI	ICER above $100,000 per QALY even with 100% chance of improvement following either first-line, second-line, or reinfused infliximab
	One-way sensitivity analyses as assumptions varying fistula recurrence $>$ 4 months after infliximab usage (0% or 18% recurrence)	Assuming 18% recurrence rate of fistulas after infliximab following month 4 increases ICERs to: $736,400, $409,500 and $412,700 per QALY (Interventions I, II and III vs comparator respectively)
	One-way sensitivity analysis on the effectiveness of infliximab as first- and second- line therapy (0%–100%)	Assuming 0% recurrence rates of fistulas after infliximab following month 4 decreases ICERs to: $339,450, $218,133 and $361,200 per QALY (Interventions I, II and III vs comparator respectively)
	Tornado diagram used to identify influential variables (not given)	Intervention II) Infliximab (infusions + episodic infliximab reinfusions for treatment failures/relapse) falls beneath $100,000 per QALY where infliximab dose is reduced in price by 75% (to $508/dose)
	Threshold analysis on the cost of a single dose of infliximab	
	Utility estimates from healthy volunteers	

TABLE 86 Author conclusions for studies in cost-effectiveness review

Study	Author conclusions	Industry author affiliation
Jaisson-Hot *et al.*[7] (2004; non-fistulising)	Infliximab treatment (episodic) could be cost-effective but infliximab treatment (maintenance) may not justify increased cost	None declared
Clark *et al.*[5] (2003; non-fistulising)	Re-estimation of the cost-effectiveness using company estimates for the proportion of patients gave a cost/QALY for episodic treatment of £72,000 when using efficacy data from all infliximab arms, and £62,000 when using 5 mg/kg dosing. These findings were relatively insensitive to major changes in key assumptions. The key issue appears to be the duration of benefit from treatment	None declared. Study funded by UK HTA
Marshall *et al.*[6] (2002; non-fistulising)	For cost-effectiveness thresholds < C$180,000, usual care was more likely to maximise net benefit than infliximab treatment strategies	None declared. Study funded by CCOHTA
Clark *et al.*[5] (2003; fistulising)	The cost per QALY estimates from the industry model were high, at £82,000 even in the most favourable re-treatment assumptions on closure rates	None declared. Study funded by UK HTA
Arseneau *et al.*[90] (2001; fistulising)	The ICER for infliximab is > $350,000 per QALY, driven by both the high cost of infliximab and the similar effectiveness of infliximab and 6MP/met treatment strategies	None declared

CCOHTA, Canadian Coordinating Office for Health Technology Assessment.

TABLE 87 Quality assessment for studies in cost-effectiveness review

	Jaisson-Hot *et al.* (2004)[7]	Marshall *et al.* (2002)[6]	Arseneau *et al.* (2001)[90]
(1) The research question is stated	Yes	Yes	Yes
(2) The economic importance of the research question is stated	Yes	Yes	Yes
(3) The viewpoint(s) of the analysis are clearly stated and justified	Yes	Yes	Yes
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Yes	Yes	Unclear
(5) The alternatives being compared are clearly described	Yes	Yes	Yes
(6) The form of economic evaluation used is stated	Yes	Yes	Yes
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Yes	Yes	Yes
(8) The source(s) of effectiveness estimates used are stated	Unclear	Yes	Yes
(9) Details of the design and results of effectiveness study are given (if based on a single study)	No	NA	NA
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies	NA	Yes	Yes
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Yes	Unclear
(12) Methods to value health states and other benefits are stated	Yes	Yes	Yes
(13) Details of the subjects from whom valuations were obtained are given	Yes	Yes	Yes
(14) Productivity changes (if included) are reported separately	NA	NA	NA
(15) The relevance of productivity changes to the study question is discussed	Yes	Yes	Yes
(16) Quantities of resources are reported separately from their unit costs	No	Yes	Yes
(17) Methods for the estimation of quantities and unit costs are described	No	Yes	Yes
(18) Currency and price data are recorded	No	Yes	Yes
(19) Details of currency of price adjustments for inflation or currency conversion are given	No	Yes	NA
(20) Details of any model used are given	Unclear	Yes	Yes
(21) The choice of model used and the key parameters on which it is based are justified	No	Yes	Yes
(22) Time horizon of costs and benefits is stated	Yes	Yes	Yes
(23) The discount rate(s) are stated	Yes	1 year	Yes
(24) The choice of rate(s) are justified	No	1 year	No
(25) An explanation is given if costs or benefits are not discounted	NA	1 year	NA
(26) Details of statistical tests and confidence intervals are given for stochastic data	No	Yes	Partial
(27) The approach to sensitivity analysis is given	Yes	Yes	Yes
(28) The choice of variables for sensitivity analysis is justified	Yes	Yes	Yes
(29) The ranges over which the variables are varied are stated	No	Yes	Yes
(30) Relevant alternatives are compared	Yes	Yes	Yes
(31) Incremental analysis is reported	No	Yes	No
(32) Major outcomes are presented in a disaggregated as well as aggregated form	No	Yes	No
(33) The answer to the study question is given	Yes	Yes	Yes
(34) Conclusions follow from the data reported	Yes	Yes	Yes
(35) Conclusions are accompanied by the appropriate caveats	Yes	Yes	Yes
	18/35	34/35	26/35

NA, not applicable.

TABLE 88 Included and excluded studies cost-effectiveness review

Paper	Included/Excluded	Reason
Arseneau *et al.* (2001)[90]	Included	
Clark *et al.* (2003)[5]	Included	
Jaisson-Hot *et al.* (2004)[7]	Included	
Marshall *et al.* (2002)[6]	Included	
Marshall *et al.* (2002)[91]	Excluded	See Marshall *et al.* (2002)[6]
Dubinsky *et al.* (2005)	Excluded	Comparators not relevant
Williams *et al.* (2000)	Excluded	Comparators not relevant
Condino *et al.* (2005)	Excluded	Comparators not relevant
Harrison and Rubensteini (2003)	Excluded	Abstract only
Wong (1999)	Excluded	Abstract only
Andersson *et al.* (2003)	Excluded	Not ee
Arnott *et al.* (2001)	Excluded	Not ee
Balfour Sartor (2004)	Excluded	Not ee
Barkun (2002)	Excluded	Not ee
Bassi *et al.* (2004)	Excluded	Not ee
Bernklev *et al.* (2005)	Excluded	Not ee
Bernklev *et al.* (2006)	Excluded	Not ee
Bodger (2002)	Excluded	Not ee
Bodger (2005)	Excluded	Not ee
Broering *et al.* (2001a)	Excluded	Not ee
Broering *et al.* (2001b)	Excluded	Not ee
Buller (2001)	Excluded	Not ee
Cadahia *et al.* (2004)	Excluded	Not ee
Caprilli *et al.* (2006)	Excluded	Not ee
Casellas (2000)	Excluded	Not ee
Casellas *et al.* (2003)	Excluded	Not ee
Casellas *et al.* (2005a)	Excluded	Not ee
Casellas *et al.* (2005b)	Excluded	Not ee
Cohen (2002a)	Excluded	Not ee
Cohen (2002b)	Excluded	Not ee
Cohen (2003)	Excluded	Not ee
Cohen (2006)	Excluded	Not ee
Cohen *et al.* (2002)	Excluded	Not ee
Colombel *et al.* (2007)	Excluded	Not ee
D'Haens (2002)	Excluded	Not ee
Etienney *et al.* (2004)	Excluded	Not ee
Feagan (2001)	Excluded	Not ee
Feagan *et al.* (2003)	Excluded	Not ee
Feagan *et al.* (2005)	Excluded	Not ee
Fleurence and Spackman (2006)	Excluded	Not ee
Garnett and Yunker (2001)	Excluded	Not ee
Ghosh (2003)	Excluded	Not ee
Goldfarb *et al.* (2004)	Excluded	Not ee
Gregor *et al.* (1997)	Excluded	Not ee
Hanauer (2005)	Excluded	Not ee
Hanauer (2007)	Excluded	Not ee
Hilsden (2002)	Excluded	Not ee

continued

TABLE 88 Included and excluded studies cost-effectiveness review *(continued)*

Paper	Included/Excluded	Reason
Hyams (2003)	Excluded	Not ee
Inadomi and Terdiman (2006)	Excluded	Not ee
Jewel *et al.* (2005)	Excluded	Not ee
Kam (2000)	Excluded	Not ee
Kay (2003)	Excluded	Not ee
Kennedy *et al.* (2000)	Excluded	Not ee
Kennedy *et al.* (2004)	Excluded	Not ee
Koelewijn *et al.* (2006)	Excluded	Not ee
Leshno (2001)	Excluded	Not ee
Lichtenstein (2004)	Excluded	Not ee
Lichtenstein (2005)	Excluded	Not ee
Lichtenstein *et al.* (2004)	Excluded	Not ee
Lichtenstein *et al.* (2006)	Excluded	Not ee
Luces and Bodger (2006)	Excluded	Not ee
Marshall (2002a)	Excluded	Not ee
Mealy and Bayes (2005)	Excluded	Not ee
Mitton (2002)	Excluded	Not ee
Nahar *et al.* (2003)	Excluded	Not ee
Nash and Florin (2005)	Excluded	Not ee
Odes *et al.* (2006)	Excluded	Not ee
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Sartor (2004)	Excluded	Not ee
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Silverstein *et al.* (1999)	Excluded	Not ee
Strong (2001)	Excluded	Not ee
Thaler *et al.* (2005)	Excluded	Not ee
van Balkom *et al.* (2002)	Excluded	Not ee
Wicks (2002)	Excluded	Not ee
Williams and Meyers (2002)	Excluded	Not ee

ee, economic evaluation.

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Consultant in Old Age Psychiatry, Coventry and Warwickshire Partnership Trust

Dr Lesley Stockton,
Lecturer, School of Health Sciences, University of Liverpool

Dr Simon Wright,
GP Partner, Walkden Medical Centre, Manchester

Observers

Dr Kay Pattison,
Senior NIHR Programme Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health Services and Public Health Services Board, Medical Research Council

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

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We look forward to hearing from you.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

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