NICE National Institute for Health and Care Excellence

NICE guidance

# Infliximab and adalimumab for the treatment of Crohn's disease

Technology appraisal guidance
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# Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guidance replaces TA40.

# 1 Guidance

This guidance replaces 'NICE technology appraisal guidance 40' issued in April 2002. For details, see 'About this guidance'.

1.1 Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease (see 1.6) whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see 1.4) to determine whether ongoing treatment is still clinically appropriate.

1.2 Treatment as described in 1.1 should normally be started with the less expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.

1.3 Infliximab, within its licensed indication, is recommended as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab should be given as a planned course of treatment until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see 1.4) to determine whether ongoing treatment is still clinically appropriate.

1.4 Treatment with infliximab or adalimumab (see 1.1 and 1.3) should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.

1.5 Infliximab, within its licensed indication, is recommended for the treatment of people aged 6–17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months.

1.6 For the purposes of this guidance, severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more, or a Harvey-Bradshaw score of 8 to 9 or above.

1.7 When using the CDAI and Harvey-Bradshaw Index, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the scores and make any adjustments they consider appropriate.

1.8 Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNF inhibitors and of managing Crohn's disease.

# 2 Clinical need and practice

2.1 Crohn's disease is a chronic inflammatory condition affecting the gastrointestinal tract (gut). It can affect any part of the gut from the mouth to the anus. The lining of the affected area becomes inflamed and may be ulcerated, and the wall of the intestine thickens. The clinical features of Crohn's disease vary and are determined partly by the site of the disease. Symptoms include diarrhoea, abdominal pain, weight loss, malaise, lethargy, anorexia, nausea, vomiting and fever.

2.2 Crohn's disease can be complicated by the development of strictures (narrowing of the intestine), obstructions, fistulae and perianal disease. Fistulae – abnormal connections between areas of the intestine or adjacent organs – develop in 17–43% of people with Crohn's disease. Perianal disease includes fissures, fistulae and abscesses. Other complications of Crohn's disease include acute dilation, perforation and massive haemorrhage of the gut, and carcinoma of the small bowel or colon.

2.3 People with Crohn's disease have acute 'flares' of the disease in between periods of remission or less active disease. These flares can affect any part of the gut. They may be defined by location (terminal ileal, colonic, ileocolonic, upper gastrointestinal), or by the pattern of the disease (inflammatory, fistulising or stricturing).

2.4 The prevalence of Crohn's disease in the UK is estimated to be about 50–100 per 100,000 people. It affects approximately 60,000 people in the UK. The incidence of Crohn's disease is greatest in people aged between 15 and 30 years. However, it may affect people of any age: 15% of people with the disease are older than 60 years at diagnosis and 20–30% are younger than 20 years. Mortality among people with Crohn's disease is only slightly higher than in the general population.

2.5 Crohn's disease is not medically or surgically curable. Treatment aims to control manifestations of Crohn's disease to reduce symptoms, and to maintain or improve quality of life while minimising short- and long-term adverse effects.

2.6 Clinical management depends on disease activity, site, behaviour of disease (inflammatory, fistulising or stricturing), response to previous medications, side-effect profiles of medications and extra-intestinal manifestations. Because Crohn's disease is unpredictable, successful treatment focuses on inducing and maintaining clinical remission.

2.7 Current treatment includes aminosalicylates, corticosteroids, immunosuppressants, TNF inhibitors, antibiotics, nutritional supplementation and dietary measures. Crohn's disease is typically treated in the short term (4–8 weeks) with corticosteroids. In severe active disease, hospital admission and intravenous administration of corticosteroids may be required. There is evidence that Crohn's disease in some people, despite a good initial response, becomes resistant to corticosteroids. Other people may become dependent on corticosteroid treatment, relapsing once the dose is reduced or treatment is stopped. Azathioprine and 6-mercaptopurine are widely used in the management of active Crohn's disease.

2.8 Between 50 and 80% of people with Crohn's disease will require surgery at some stage. The main reasons for surgery are strictures causing obstructive symptoms, lack of response to medical therapy, and complications such as fistulae and perianal disease.

2.9 The CDAI is frequently used to assess disease severity. It is a composite of overall activity of Crohn's disease as assessed by clinicians, and has eight variables weighted according to their ability to predict disease activity. It gives a score ranging from 0 to over 600, based on a diary of symptoms kept by the patient for 1–7 days, and other measurements such as the patient's weight and haematocrit. A CDAI score of less than 150 is considered to be remission, a score greater than 220 is considered to define moderate to severe disease, and a score greater than 300 is considered to be severe disease. The paediatric CDAI (PCDAI) is an instrument similar to the CDAI but with less emphasis on subjectively reported symptoms and more emphasis on laboratory parameters of intestinal inflammation.

2.10 The Harvey-Bradshaw Index is another commonly used tool, which correlates well with CDAI. It is based on assessments of general

wellbeing, abdominal pain, number of diarrhoeal stools per day, and the presence of abdominal mass and associated complications. Patients with a score of 8 to 9 or higher are considered to have severe disease.

# 3 The technologies

## Infliximab

3.1 Infliximab (Schering-Plough Ltd) is a chimeric human–murine monoclonal antibody that binds with high affinity to TNF-α and inhibits its functional activity. Infliximab has a UK marketing authorisation for the treatment of:

- severe, active Crohn's disease in people whose disease has 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
- fistulising, active Crohn's disease in people whose disease has not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy)
- severe, active Crohn's disease in people aged 6–17 years whose disease has 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.

3.2 The most common adverse events reported during infliximab therapy include acute infusion-related reactions, infections and delayed hypersensitivity reactions. Infliximab is contraindicated in people with moderate or severe heart failure and active infections. Before treatment is started, people must be screened for active and inactive tuberculosis. The summary of product characteristics (SPC) specifies a number of uncommon but serious adverse events related to the immunomodulatory activity. For full details of side effects and contraindications, see the SPC.

3.3 For severe, active Crohn's disease, infliximab is given as a 5-mg/kg intravenous infusion over a 2-hour period followed by another 5-mg/kg infusion 2 weeks after the first. If a person's disease does not respond after two doses, no additional treatment with infliximab should be given. In people whose disease responds, infliximab regimens include

maintenance treatment (another 5-mg/kg infusion at 6 weeks after the initial dose, followed by infusions every 8 weeks) or re-administration, otherwise known as episodic treatment (an infusion of 5-mg/kg if signs and symptoms of the disease recur) in line with the marketing authorisation. In adults, dose escalation is an option for people whose disease has stopped responding. According to the SPC, continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

3.4 For fistulising, active Crohn's disease, infliximab is given as a 5-mg/kg infusion over a 2-hour period followed by additional 5-mg/kg infusions at 2 and 6 weeks after the first. If a person's disease does not respond after three doses, no further treatment with infliximab should be given. In people whose disease responds, infliximab can be given as maintenance treatment (5-mg/kg infusions every 8 weeks) or as re-administration treatment (5-mg/kg when signs and symptoms recur, followed by infusions of 5-mg/kg every 8 weeks). In adults, dose escalation is an option for people whose disease has stopped responding.

3.5 For people aged 6–17 years, infliximab is given as a 5-mg/kg intravenous infusion followed by additional 5-mg/kg doses at 2 and 6 weeks after the first dose, then every 8 weeks thereafter.

3.6 A 100-mg vial of infliximab costs £419.62 (excluding VAT; 'British national formulary' [BNF], 58th edition). The drug cost differs between individuals because the dose is adjusted to each person's body weight. For example, if it is assumed that vials are not shared between patients, for a person weighing 73 kg the cost per infusion would be £1678, corresponding to four 100-mg vials needed for a dose of 365 mg. For a course of two infusions, with an assumed drug administration cost for each infusion of £258, the total cost is approximately £3872. The total cost of continuing therapy at a standard dosage for 12 months is approximately £12,584. Costs may also vary in different settings because of negotiated procurement discounts.

# Adalimumab

3.7 Adalimumab (Abbott Laboratories) is a recombinant human monoclonal

antibody that binds specifically to TNF-α, blocking interaction with its cell-surface receptors and thereby limiting the promotion of inflammatory pathways. Adalimumab is indicated for the treatment of severe, active Crohn's disease in people whose disease has not responded despite full and adequate treatment with an immunosuppressant and/or corticosteroid, or who are intolerant to or have contraindications to such therapies. For induction therapy adalimumab should be given in combination with corticosteroids. Adalimumab can be given as monotherapy if a person is intolerant to corticosteroids or when continued treatment with corticosteroids is inappropriate.

3.8 Common adverse events associated with adalimumab include injection site reactions and infections. Before therapy is started, all patients must be screened for active and inactive tuberculosis. Adalimumab is contraindicated in patients with moderate to severe heart failure, active tuberculosis and other severe infections. For full details of side effects and contraindications, see the SPC.

3.9 The adalimumab induction treatment dose regimen for adults with severe Crohn's disease is 80 mg via subcutaneous injection, followed by 40 mg 2 weeks later. If there is a need for a more rapid response to therapy, a dose of 160 mg followed by 80 mg 2 weeks later can be used, though the risk of adverse events with this higher dose is greater during induction. After induction treatment the recommended dose is 40 mg every other week. This can be increased to 40 mg every week in people whose disease shows a decrease in response to treatment. According to the SPC, continued therapy should be carefully reconsidered in patients whose disease does not respond within 12 weeks of initiating treatment.

3.10 Adalimumab costs £357.50 per 40-mg prefilled syringe (excluding VAT; BNF, 58th edition). Normal induction treatment costs approximately £1073 and the cost to continue treatment at a standard dosage for 1 year is £9295. Costs may vary in different settings because of negotiated procurement discounts.

# 4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

## 4.1 Clinical effectiveness

4.1.1 Eleven randomised controlled trials (RCTs) that included licensed doses of infliximab and adalimumab met the criteria for inclusion in the assessment report (seven for infliximab and four for adalimumab). These trials covered short treatment regimens that aimed to induce remission in people with active Crohn's disease (induction regimens) and longer-term regular dosing regimens that aimed to prevent relapse in people who had already responded to an induction regimen (maintenance regimens). The RCTs included people with moderate to severe Crohn's disease. Seven studies wholly or predominantly included adults with non-fistulising disease, two trials included adults with fistulae and two studies were in children and young people.

4.1.2 The outcomes reported in the clinical trials were mainly based on the CDAI. The PCDAI was reported in the paediatric studies. The inflammatory bowel disease questionnaire (IBDQ), a health-related quality-of-life measure, was also reported in some studies.

4.1.3 Two placebo-controlled trials of induction regimens were identified for each of infliximab and adalimumab. Another study investigated infliximab induction treatment in children and young people with Crohn's disease, but there was no placebo arm in this study. One infliximab trial mainly included people with non-fistulising disease (n = 108), and the other included people with fistulising disease only (n = 94). One of the studies of adalimumab induction treatment (CLASSIC I, n = 299) included people with moderate to severe Crohn's disease (11% had fistulae at baseline) who had not previously received treatment with a TNF inhibitor. The second (GAIN, n = 325) included people who had previously been treated with infliximab, but had either not responded to the treatment or had not tolerated it. The Assessment Group was unable to carry out an

indirect comparison or meta-analysis because of heterogeneity between the trials.

4.1.4 The trial of infliximab that mainly included people with non-fistulising disease studied a single-dose regimen. Participants were randomised to infliximab 5 mg/kg, 10 mg/kg, 20 mg/kg or placebo. Results were reported at 4 weeks. Infliximab at the licensed dose of 5 mg/kg achieved significant improvements in remission rate versus placebo. The rate ratio (RR) for remission (the rate of remission in the 5 mg/kg group divided by the rate of remission in the placebo group; remission defined as CDAI score below 150) was 12.04 (95% confidence interval [CI] 1.70 to 85.44). There were also significantly greater rates of 70-point reductions in CDAI (referred to below as response 70) in the infliximab 5 mg/kg group.

4.1.5 The study of infliximab induction treatment in fistulising disease compared infliximab at a dose of 5 mg/kg or 10 mg/kg with placebo. Follow-up extended to at least week 18. The primary outcome was a 50% reduction in the number of draining fistulae; the rate difference between the infliximab 5 mg/kg and placebo groups was 0.42 (95% CI 0.19 to 0.64). The secondary outcome was complete absence of fistulae; the rate difference between the infliximab 5 mg/kg and placebo groups was 0.42 (95% CI 0.21 to 0.63). Infliximab groups had statistically significant improvements in CDAI and PCDAI scores at week 2.

4.1.6 The studies of adalimumab as induction treatment used a regimen of an initial dose followed by a second, lower dose 2 weeks later. In CLASSIC I, the participants were randomised to one of three dosing schedules (40 mg/20 mg, 80 mg/40 mg or 160 mg/80 mg) or placebo. Only the 80 mg/40 mg and 160 mg/80 mg doses were in line with the SPC. In the other study (GAIN) participants were randomised to 160 mg followed by 80 mg adalimumab or placebo. For the 160 mg/80 mg regimen versus placebo, both studies reported statistically significant improvements in the end points of remission (RR 2.92 and 2.96 for CLASSIC I and GAIN respectively), response 70 (RR 1.62 and 1.53 for CLASSIC I and GAIN respectively) and response 100 (RR 1.95 and 1.55 for CLASSIC I and GAIN respectively). The results for the 80 mg/40 mg regimen did not achieve statistical significance against placebo for the endpoints of remission (RR 1.97, 95% CI 0.95 to 4.11) or response 100 (RR 1.56, 95% CI 0.97 to

2.51).

4.1.7 Four studies of maintenance treatment in adults that mainly included people with non-fistulising disease were identified for inclusion by the Assessment Group. For infliximab, two trials were identified. In one of these (ACCENT I, n = 573) all patients received a single infusion of 5 mg/kg infliximab and were then randomised to receive placebo, or infliximab at a dose of 5 mg/kg at weeks 2 and 6 and then every 8 weeks to week 54 (known as the 5 mg/kg group), or infliximab 5 mg/kg at weeks 2 and 6 and then 10 mg/kg every 8 weeks to week 54 (known as the 10 mg/kg group). However, those whose disease initially responded but then worsened were allowed to cross over to treatment with a higher dose of infliximab at week 14. Those who crossed over from the placebo group were considered to have had episodic treatment, and those who crossed over from an active treatment arm were considered to have disease that did not respond for most analyses. The other infliximab trial (n = 73) recruited patients from one of the infliximab induction trials. Only those who responded to infliximab in the induction trial were eligible to enter this study. Participants were randomised to placebo or infliximab 10 mg/kg at 8-week intervals (note that the dose recommended in the SPC is 5 mg/kg every 8 weeks). Follow-up was for 48 weeks.

4.1.8 Results for ACCENT I demonstrated that infliximab improved the point prevalence of remission at weeks 30 and 54. At week 54 the point prevalence of remission RR for the infliximab 5 mg/kg group was 2.08 (95% CI 1.19 to 3.61), and the response 70 RR was 2.46 (95% CI 1.50 to 4.04).

4.1.9 Two studies (CHARM, n = 778 and CLASSIC II, n = 55) examined adalimumab maintenance at a dose of 40 mg either every other week or every week in people whose disease had already responded to an induction regimen. They mainly included people with non-fistulising disease. In both studies, patients were followed up for 56 weeks, and the primary outcome was the proportion of patients in remission (at week 26 and 56 in CHARM and at week 56 in CLASSIC II). Patients were allowed to switch to open-label treatment if there was sustained non-response or a disease flare. In the CHARM trial, adalimumab every other week and weekly dosing schedules led to statistically significant improvements in

the rate of remission at week 56 (RR versus placebo 3.06 [95% CI 1.94 to 4.84] for the every other week schedule, and 3.52 [95% CI 2.24 to 5.53] for the weekly schedule). In the CLASSIC II trial, the point estimate for remission RR versus placebo at week 56 was 1.78 (95% CI 1.01 to 3.13) for the every other week schedule and 1.88 (95% CI 1.08 to 3.27) for the weekly schedule.

4.1.10 The Assessment Group identified an additional study that investigated maintenance treatment with infliximab in fistulising disease (n = 282). All participants received an induction course of three doses of infliximab 5 mg/kg and then responders and non-responders were randomised at week 14 to infliximab 5 mg/kg or placebo every 8 weeks for five doses. Patients were followed up for 54 weeks. After week 22 patients whose disease lost response could cross over to infliximab 5 mg/kg or 10 mg/kg. The primary outcome was time to loss of response (defined as a reappearance of a draining fistula, a change in therapy, a need for surgery, drop-out because of lack of efficacy, or worsening symptoms). Median time to loss of response after randomisation was 14 weeks for the placebo group and more than 40 weeks for the infliximab group.

4.1.11 The Assessment Group identified two trials that analysed infliximab in children and young people: one 12-week trial of induction treatment (n = 21) and one 54-week trial of maintenance treatment (n = 103). Both trials included an arm that examined the licensed dose and neither trial included a placebo arm. The results presented suggested that both CDAI and PCDAI decreased and response improved with infliximab treatment. In the induction trial, infliximab 5 mg/kg was associated with a 13% median improvement in PCDAI from baseline at 12 weeks. For the groups receiving infliximab 1 mg/kg and 10 mg/kg the median improvements were 27% and 40% respectively. For the infliximab maintenance regimen a 27-point improvement in PCDAI was reported at week 54 for the treatment arms combined.

4.1.12 In addition to the data from clinical trials, new research evidence was submitted by consultees. The National Association for Colitis and Crohn's Disease (NACC) circulated a questionnaire to 320 of its members who had been offered or refused treatment with biological therapies. It received responses from 183 members who had Crohn's disease. The

questionnaire included sections on characteristics, experiences of the treatment and condition and an EQ-5D questionnaire to assess quality of life before and after treatment. The main findings from the questionnaire were that the participants' experiences of biological treatment were generally positive and this was demonstrated in an overall improvement in the EQ-5D scores. This trend was repeated in people with fistulae and in seven people aged between 11 and 18 years.

4.1.13 Further data about the effect of discontinuing treatment with infliximab and adalimumab at 12 months was submitted in response to the appraisal consultation document (ACD) published in November 2009. An abstract by Louis et al. (2009), which reported the STORI study ('Stop infliximab in patients with Crohn's disease') by the GETAID research group, described outcomes when continuous treatment with infliximab was stopped after a period of at least 12 months. Overall 45 out of 115 (39%) people with Crohn's disease relapsed following treatment discontinuation after a median follow-up of 12 months. It was noted that patients in the study had been in steroid-free remission for at least 6 months before infliximab was stopped. Data from a retrospective study by Armuzzi et al. (2009) was also submitted. This stated that 44% of people relapsed during a median follow-up of 13 months, after infliximab treatment was stopped following sustained clinical benefit. In addition, a survival analysis in this study identified mucosal healing as a predictor of sustained clinical benefit after stopping treatment with infliximab.

4.1.14 In response to the Committee's concerns about a lack of long-term data to support continued treatment, the manufacturer of adalimumab highlighted data from the ADHERE study (an open-label extension of the pivotal CHARM study) for patients on adalimumab treatment for 3 years. Remission rates were between 64% and 83% at week 108 depending on the analysis method used (clinical specialists predicted that the true value would be between these two figures). The clinical specialists confirmed that the evidence base would grow as a result of audits, registries and the development of alternative treatments but did not specify particular long-term studies.

4.1.15 In response to the ACD published in November 2009, both manufacturers submitted further data on dose escalation for infliximab and adalimumab.

The Committee noted that the number of patients who require dose escalation with both agents was different in each study. Another consultee confirmed dose escalation with both drugs was widespread in clinical practice but that precise numbers were difficult to obtain. It was noted that in both the clinical trial setting and in clinical practice, many patients who receive adalimumab may have already been treated with infliximab. Clinical specialists also described an increasing tendency for higher induction doses of 160/80 mg of adalimumab being used in the UK as in the USA.

## 4.2 Cost effectiveness

4.2.1 The Assessment Group reviewed the cost-effectiveness data submitted by the manufacturers of infliximab and adalimumab. It also conducted a literature search for any published cost-effectiveness studies.

4.2.2 The Assessment Group identified four published economic analyses that examined infliximab in fistulising and non-fistulising Crohn's disease (no published economic studies were found for adalimumab). The studies used an epidemiological model constructed by Silverstein et al. (1999) that reported a 2-monthly transition matrix estimated from 20 years of follow-up of a cohort of 174 people with Crohn's disease. The published analyses also used health-related quality-of-life values from Canadian people with Crohn's disease. The analyses produced incremental cost-effectiveness ratios (ICERs) above £50,000 per QALY gained for non-fistulising disease and above £100,000 per QALY gained for fistulising disease.

4.2.3 Schering-Plough carried out three analyses comparing infliximab with standard care in adults with severe active Crohn's disease, in fistulising disease and in children and young people. The analyses used a Markov model with states representing progression over a 5-year period. For fistulising disease the same basic model was expanded to include health states relating to fistulae. The model considered two infliximab dosing schedules: maintenance treatment and infliximab clinical discretion (ICD). ICD approximates episodic treatment: an induction dose of 5 mg/kg at week 0, and 5 mg/kg thereafter according to clinical discretion. The Assessment Group noted that the definition didn't guarantee episodic

treatment or rule out maintenance treatment. Maintenance was modelled as 5 mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter. The base-case ICER for severe active Crohn's disease for maintenance treatment compared with standard care was £25,903 per QALY gained. For ICD treatment, infliximab dominated standard care (that is, infliximab was more effective and less expensive than standard care). When maintenance treatment was compared with ICD the ICER was £457,386 per QALY gained. In fistulising disease the ICER was £30,005 per QALY gained, and for paediatric patients the ICER was £13,891 per QALY gained, both for maintenance treatment compared with standard care. Sensitivity analysis suggested that the results were most sensitive to changes in the average weight used for patients. When this was increased from 60 kg to 70 kg, it caused the ICERs to increase to over £30,000 per QALY gained in all adult analyses.

4.2.4 Abbott produced two economic models, one comparing the cost effectiveness of adalimumab as a maintenance treatment against standard care, and the other comparing infliximab and adalimumab as maintenance treatments. The model comparing adalimumab with standard care had a lifetime horizon with a baseline age of 37 and a life expectancy of 66 years. The model was structured around states based on severity of disease and defined by CDAI score. Clinical data for adalimumab were derived from the CHARM trial, and data for the standard care arm were derived from the CLASSIC I trial. For the model comparing adalimumab with infliximab, data came from the published articles of ACCENT I.

4.2.5 In Abbott's model, the base-case ICER for adalimumab compared with standard care for moderate and severe Crohn's disease was £30,319 per QALY gained. For severe disease only, the ICER was £11,998 per QALY gained. In this model it was assumed that people stay on treatment for life. To explore the effect of this, the Assessment Group modelled a scenario in which people were assumed to stop treatment at the same rate as was seen in the 40 mg every other week arm of the CHARM trial. At 56 weeks these ICERs changed to £56,621 and £30,964 for moderate and severe, and severe-only Crohn's disease respectively. When the time horizon was increased from 56 weeks to 4 years this reduced the ICER for the moderate-and-severe group from £56,621 to £52,713 per QALY

gained. If this was increased to a lifetime horizon, the ICER fell to £24,385 per QALY gained.

4.2.6 Abbott argued that it could not access enough data on infliximab to carry out a full comparative economic analysis. Therefore it simplified the analysis to one that examined the proportions of remission and non-remission and the associated costs. The results of this analysis were that adalimumab was more efficacious in achieving remission and was associated with lower costs. The manufacturer concluded that adalimumab dominated infliximab.

4.2.7 The Assessment Group carried out analyses for courses of induction treatment given when required and scheduled maintenance treatment for moderate and severe Crohn's disease. In induction treatment patients received active treatment only when relapsing. The Assessment Group stated that this is comparable to episodic use. The Assessment Group constructed a four-stage Markov model based on the model by Silverstein et al., but included only four health states (out of an original seven): remission, relapse, surgery and post-surgery remission. The transition probabilities to model natural history were derived from the Silverstein data set. The treatments were then assumed to have an equivalent effect on the probability of remaining in remission or relapse for both moderate and severe Crohn's disease. A 1-year time horizon was used and the effect of increasing the time horizon was examined in the sensitivity analysis.

4.2.8 In response to comments on the assessment report the Assessment Group made alterations to its cost-effectiveness analysis. The Assessment Group used the ACCENT I and CHARM 6-week trial data for all the effectiveness estimates for infliximab and adalimumab. It also added a transitional state to allow transitions to standard care. The Assessment Group presented sensitivity analyses to explore the effect of increasing the relapse rate on the cost-effectiveness estimates. The results reported in sections 4.2.9 to 4.2.14 are based on the updated analysis.

4.2.9 The Assessment Group only presented ICERs for infliximab and adalimumab compared with standard care. Only the results for severe

disease were presented because the drugs are not licensed for the treatment of moderate Crohn's disease. For induction treatment, both infliximab and adalimumab dominated standard care. For maintenance treatment in severe disease, the ICER for adalimumab relative to standard care was £7478 per QALY gained. However, because standard care is dominated by induction treatment, it is appropriate to compare maintenance treatment with induction treatment rather than with standard care. For this comparison the ICER was £4,980,000 per QALY gained. For infliximab maintenance treatment the ICER relative to standard care was £67,619 per QALY gained and the ICER relative to induction treatment was £5,030,000 per QALY gained.

4.2.10 Following comments from consultees on the assumptions about relapse rates based on the model by Silverstein et al., the Assessment Group performed sensitivity analyses using various probabilities of relapsing from the remission state. This indicated that as the relapse rate increased, induction treatment became less cost effective, and maintenance treatment became more cost effective. When the probability of relapse was increased to 0.3 (a 51 times increase) the ICER for infliximab induction treatment in severe disease compared with standard care was £153,136 per QALY gained. For infliximab maintenance treatment compared with standard care the ICER was £43,744 per QALY gained. Using the same assumptions, maintenance treatment with adalimumab dominated standard care, and the ICER for adalimumab maintenance treatment compared with induction treatment was £37,007 per QALY gained.

4.2.11 The Assessment Group presented a threshold analysis for the use of infliximab in children and young people. The Assessment Group extrapolated the utilities, effectiveness and non-drug costs from the adult analyses to children. Only the drug costs associated with infliximab that were because of the lower body weight were changed. The Assessment Group carried out analyses at body weights of 20–40kg and 40–60kg. If it was assumed that infliximab improved a child's health to 'full' (a full QALY) the ICER for maintenance treatment in severe disease was £193,328 per QALY gained. For induction treatment, infliximab dominated standard care in children with severe Crohn's disease for all body weights.

4.2.12 In response to uncertainties raised by consultees and the Committee about the validity of the cost-effectiveness evidence, the Decision Support Unit (DSU) was commissioned to reconcile the economic models produced by the Assessment Group and the manufacturers. The DSU noted that the models were substantially different in terms of their structures and input parameters. However, one of the key causes for the differences in the cost-effectiveness estimates among the models was the relapse rate used. Given the importance of this parameter, the DSU carried out a systematic review to identify literature that specified the relapse rate of people having standard care with moderate to severe Crohn's disease who were already in remission. Four studies were identified that suggested that 4-week probabilities of relapse ranging from 7% to 14% in this population may be typical. This rate was noted to differ substantially from the relapse rate of 0.59% used in the Assessment Group model for initially severe disease, and from other relapse rates proposed by the manufacturers from their clinical trials.

4.2.13 The DSU sought to reconcile the differences between the Schering Plough and Assessment Group models by populating the Assessment Group model with input parameters from Schering Plough's analysis. The DSU noted that these changes did align the models to an extent, but there were still substantial differences in the results produced by each model because it was not possible to reconcile every element of the Markov process. The revised Assessment Group model was also run with parameters from the Abbott model. The DSU noted that the outcomes from the revised Assessment Group model were not to be considered as representative of the most plausible ICERs for each treatment scenario; rather the intention was to demonstrate the impact each parameter had on the ICERs, to highlight the areas of uncertainty and the caution that the Committee should exercise when considering the economic evidence.

4.2.14 Comments on the DSU report from consultees highlighted that the course of episodic treatment with infliximab used in the original Assessment Group model was not consistent with the marketing authorisation, and therefore the assumed cost of episodic treatment was incorrect. The DSU conducted additional analyses with the reconciled model using revised costs for episodic treatment with infliximab, and

noted that this lowered the ICER.

4.2.15 Consultees also highlighted that a publication by Bodger et al. (2009) compared the cost effectiveness of maintenance treatment with infliximab or adalimumab with standard care over a lifetime horizon in patients with moderate to severely active Crohn's disease. The publication suggested that after 1 year of maintenance treatment with infliximab in initial responders, the ICER was £19,050 per QALY gained, and £7190 per QALY gained for 1 year of maintenance treatment with adalimumab, both compared with standard care. After 2 years of maintenance treatment, the ICERs increased to £21,300 per QALY gained and £10,310 per QALY gained for infliximab and adalimumab respectively, compared with standard care. The authors noted that outcomes were sensitive to the time horizon chosen for the analysis, and that neither infliximab nor adalimumab maintenance treatment was cost effective compared with standard care when the time horizon was shortened to match the base-case treatment duration.

4.2.16 In response to consultation on the ACD published in November 2009, consultees submitted further data on the annual treatment costs of infliximab and adalimumab. The data highlighted the variation in costs and the uncertainty about the true cost of infliximab and adalimumab. Further cost estimates were submitted by consultees incorporating varying levels of dose escalation, patient weight, administration cost, vial-sharing practice and local discounting arrangements.

## 4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of infliximab and adalimumab, having considered evidence on the nature of Crohn's disease and the value placed on the benefits of infliximab and adalimumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources and comments made during consultation on the previous appraisal consultation documents.

4.3.2 The Committee heard from clinical specialists and patient experts about the effects of severe active Crohn's disease. The clinical specialists

stated that the majority of people with Crohn's disease were diagnosed under the age of 30, emphasising the chronic long-term nature of the condition. The Committee heard that Crohn's disease and its treatment (in particular corticosteroids) could severely impair growth in children and young people, especially during puberty. The Committee heard from the patient experts about the difficulties of living with Crohn's disease, the substantial disruptive effects that relapses have on everyday activities and the major impact on quality of life in general. Effective treatment and avoidance of relapses were considered of paramount importance by people with Crohn's disease.

4.3.3 The Committee considered the definition of severe Crohn's disease. It heard from clinical specialists and patient experts about the limitations of the CDAI in assessing the severity of a patient's condition. In particular, that the instrument takes into account the patient's prior treatment and may not be the most suitable means of defining severity in those who have had surgery. The Committee heard from the clinical specialists that the definition of severe as specified in 'Guidance on the use of infliximab for Crohn's disease' (NICE technology appraisal guidance 40) was appropriate; that is, normally corresponding to a CDAI score of 300 or more. However, the clinical specialists emphasised that the phrase 'normally corresponds to a CDAI score of 300 or more' should not be misinterpreted as a strict threshold for treatment because some people with severe disease may not meet this criterion as a result of their current or previous treatment. The Committee concluded that the definition of severe Crohn's disease should remain as specified in technology appraisal guidance 40, but emphasised that although this normally corresponds to a CDAI score of more than 300, this was not exclusively so and should be interpreted in the light of the specific clinical situation. They also acknowledged that the Harvey-Bradshaw Index is another useful measure of disease severity and that patients with a score of 8 to 9 or above are considered to have severe disease. The Committee therefore decided that either CDAI score or the Harvey-Bradshaw Index should be used to assess disease severity for the purpose of this technology appraisal guidance.

4.3.4 The Committee noted that both infliximab and adalimumab were licensed for the treatment of severe active Crohn's disease, but the trials included

people with moderate to severe Crohn's disease. The Committee noted that the results of the trials suggested that response to treatment did not differ between moderate and severe disease. The Committee was mindful of the limitations of the trial data, but considered that the analyses presented provided the most reasonable estimates of treatment effectiveness. In line with clinical experience, the clinical specialists considered infliximab and adalimumab to be equally effective treatments for Crohn's disease. Furthermore, in the absence of any direct comparative studies, the Committee was persuaded that infliximab and adalimumab could not be differentiated in terms of clinical effectiveness.

4.3.5 The Committee discussed the different modes of treatment with infliximab and adalimumab in severe Crohn's disease, namely induction, episodic and maintenance treatment. The Committee heard from the clinical specialists that for people with severe Crohn's disease the use of episodic treatment was not clinically appropriate for the following reasons:

- The high potential for relapse meant that patients may be exposed to a rapid increase in their symptoms after each episode of treatment, and in reality the length of time between episodes would be very short.
- Episodic treatment was not favoured by clinicians and would be unlikely to be used in routine clinical practice because of concerns about the higher risk of developing antibodies to the drug and the potential for loss of effect. It was accepted that this was more of an issue with infliximab than adalimumab.
- Although early clinical trials of infliximab and adalimumab in moderate to severe Crohn's disease had used episodic therapy, the evidence from clinical practice now strongly favoured a longer-term approach to treatment with infliximab and adalimumab.

  The Committee discussed the definition of episodic treatment and maintenance treatment and concluded that these were not clearly defined. It was agreed that a 'planned course of treatment' was a clearer way of defining a longer-term approach to treatment for a specified period of time.

4.3.6 The Committee discussed the cost-effectiveness analyses presented by the manufacturers and the Assessment Group, and the limitations of

each evaluation, as noted in the DSU report. It considered the differences between the models in terms of their structure and inputs, even after reconciliation efforts by the DSU, and the effect these differences had on the resulting economic outcomes. It noted that the source of data used to estimate the distribution of patients between various health states was a key difference between the models. Furthermore, assumptions of constant utilities in the health states and of instantaneous transitions did not accurately reflect the course of the condition, especially the variation in health-related quality of life. The Committee was persuaded that it was not possible for the DSU to completely reconcile the models given the substantial differences between them. However, despite this limitation, the Committee decided that the collective body of evidence was sufficient to inform their decision on the cost-effectiveness of infliximab and adalimumab.

4.3.7 The Committee agreed that, despite the limitations of the available evidence, the transition probabilities from remission to relapse with standard care (relapse rate) could be considerably higher in those people for whom infliximab and adalimumab is indicated than the transition probabilities used in the Assessment Group's model. The Committee considered the DSU's sensitivity analyses on the impact on the cost effectiveness of each treatment strategy when the relapse rates in the Assessment Group model were increased in line with published evidence, and those provided by the manufacturers. The Committee noted that the cost effectiveness of each treatment strategy was more favourable using the higher relapse rates. Because these rates may reflect more accurately the clinical situation for people with severe disease, it concluded that its decision should be informed by outcomes generated using higher relapse rates than those used in the Assessment Group model.

4.3.8 The Committee noted that for episodic treatment of severe Crohn's disease (broadly defined as people having the opportunity to have another course of treatment if their disease initially responded to a short course of treatment but then relapsed) both infliximab and adalimumab were more effective and less costly than standard care in the analyses presented. However, in light of testimony from the clinical specialists (see section 4.3.5), the Committee considered that repeated induction or

episodic treatment with infliximab or adalimumab should not be the preferred option for treating severe Crohn's disease. Therefore its recommendations should be based on the clinical and cost effectiveness of a planned course of treatment relative to standard care alone.

4.3.9 The Committee noted that both infliximab and adalimumab appeared to be clinically and cost effective when used continuously for defined periods in people who responded to induction treatment. However, it noted the limitations in the evidence base relating to the duration of the clinical trials and the time horizons used in the economic models. The Committee concluded that there was considerable uncertainty about the clinical and cost effectiveness of both drugs over periods longer than 1 year.

4.3.10 The Committee heard from the clinical specialists that they were concerned about the longer-term effectiveness and safety of infliximab and adalimumab. They also stated that there was evidence suggesting that it may be reasonable to try withdrawing treatment in people whose disease demonstrated a complete response. The Committee acknowledged the limitations of this evidence and noted that there may still be a significant risk of relapse after treatment is stopped, but that relapse would also occur in some patients who continued on treatment. The clinical specialists also noted that Crohn's disease usually fluctuated between periods of high and low activity.

4.3.11 The Committee noted that for planned courses of treatment, the ICERs for adalimumab were lower than those for infliximab, when both were compared with standard care. Given the lack of head-to-head trials, the Committee was unable to comment reliably on which drug was superior in terms of clinical effectiveness, and therefore concluded that they could only be differentiated by their cost. The Committee also discussed evidence provided by the manufacturers and the DSU on administration and drug costs for infliximab and adalimumab, and noted that there was uncertainty over the true costs for each agent. The estimated annual cost of infliximab varied according to the assumption of average number of vials used, which was dictated by patient body weight and whether vials could be shared to avoid wastage. It was also noted that the induction dose for adalimumab could be either 80 mg followed by 40 mg

at week 2 or 160 mg followed by 80 mg at week 2. The Committee also reviewed different sources of data on average patient body weight and considered the feasibility of vial sharing. The Committee concluded that infliximab and adalimumab should be recommended for a planned course of treatment for 12 months after induction for non-fistulising disease and that choice of treatment should be based on cost, taking into account any local discounting agreements and vial-sharing arrangements.

4.3.12 The Committee considered the evidence on the use of infliximab in patients with fistulae. It heard from the clinical specialists that people with fistulae would not all be classified as having severe Crohn's disease. The clinical specialists also stated that in their experience, TNF inhibitors have the greatest benefit in patients with complex fistulae (for example, recto-vaginal fistulae), which are associated with significant impairment of quality of life. The Committee accepted that such complications may not be fully captured by the CDAI, but could contribute to clinical judgement of the definition of severe disease. The Committee therefore considered that infliximab was potentially cost effective in this situation.

4.3.13 The Committee noted that the Assessment Group had not modelled the cost effectiveness of infliximab for fistulising disease separately because of the lack of a long-term standard care cohort study. The Committee considered the estimate of cost effectiveness provided by the manufacturer. It noted that the manufacturer had only provided a comparison of maintenance treatment with standard care, giving an ICER of £30,300 per QALY gained. Although this ICER was considered to be relatively high, the Committee considered the severity of the disease and noted that there were few treatment options available to these patients. The Committee therefore concluded that a planned course of treatment with infliximab for people with fistulising disease could be cost effective if the definition of severe disease was met.

4.3.14 The Committee discussed the use of infliximab for the treatment of children and young people aged 6–17 years. The Committee noted that the trials were not placebo controlled. However, it acknowledged the difficulties of conducting clinical trials in children and young people and considered that it was plausible to generalise results from studies in adults to the paediatric population. It considered the cost-effectiveness

estimates presented for children and young people and noted the Assessment Group's concerns over the data and analysis. It considered the lower weight of children and young people and the consequent lower infliximab drug costs. In addition, the Committee noted children and young people could potentially benefit more from treatment than adults, especially with regard to the potential lifelong effects on quality of life and avoiding potential toxicity from alternative therapies. Given these factors the Committee concluded that infliximab would be cost effective for the treatment of children and young people with severe Crohn's disease.

4.3.15 The Appraisal Committee discussed the additional data submitted in response to the ACD published in November 2009 about stopping treatment with infliximab and adalimumab at 12 months. The Committee noted that patients in the study by Louis et al. (2009) had been in steroid-free remission for at least 6 months before treatment was stopped. It heard from clinical specialists that this was a highly selected subgroup of people with Crohn's disease, and that it was difficult to apply data from this study to all patients on treatment. The Committee heard from two patient experts about their fear of their treatment being stopped at 12 months regardless of need. The patient experts informed the Committee that they preferred to avoid taking drug treatments when it was not necessary but feared deterioration in their condition if they stopped treatment when their disease was still active. The Committee then heard from clinical specialists that people with active disease would be more likely to relapse even if they were no longer symptomatic and that because of the diverse nature of Crohn's disease it was difficult to define which patients should stop treatment and when. The Committee noted that the evidence supporting continued treatment after 1 year was limited despite some data from open-label extension studies for adalimumab, and accepted that the available evidence supported a trial withdrawal of treatment in people who have been in steroid-free remission for at least 6 months. However, the Committee was uncertain of particular subgroups that would be at risk of relapse after stopping treatment or who would benefit from continued treatment. They discussed available evidence of mucosal healing as a predictor of sustained clinical benefit after stopping treatment with infliximab, but were aware of issues accessing colonoscopy in clinical practice to

confirm this. The clinical specialists considered it reasonable to review the need for biological treatment in patients who were in stable remission. The Committee therefore agreed that people who continue treatment with infliximab or adalimumab beyond 1 year should have their disease reassessed at least every 12 months to determine whether they still have active disease and if ongoing treatment is clinically appropriate. In addition, they agreed that people whose disease relapses after treatment is stopped should have the option to start treatment again.

4.3.16 The Committee was concerned that there was little incentive to produce additional data on treatment discontinuation or long-term efficacy in future, and emphasised that a register of individuals who receive TNF inhibitors for the treatment of Crohn's disease may help to provide valuable information on long-term outcomes.

4.3.17 Despite additional data on dose escalation for both infliximab and adalimumab from clinical trials and observational studies, the Committee remained uncertain about true treatment costs for infliximab and adalimumab and accepted that local arrangements would have an impact on relative costs.

# 5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has Crohn's disease and the doctor responsible for their care thinks that infliximab or adalimumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools to help organisations put this guidance into practice (listed below).

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Audit support for monitoring local practice.

# 6 Recommendations for further research

6.1 Randomised controlled trials should be carried out that directly compare infliximab and adalimumab.

6.2 Trials should be carried out of continuous treatment with infliximab and adalimumab that are designed to allow a true, unbiased comparison with standard care.

6.3 Trials of continuous treatment with adalimumab should be carried out exploring less-frequent dosing regimens.

6.4 Data should be collected on the effect of TNF inhibitors on the natural history of Crohn's disease, particularly the effect on relapse rates.

6.5 Health-related quality-of-life information about people with Crohn's disease should be collected.

6.6 Clinically meaningful instruments should be developed to help identify patients for whom treatment with infliximab and adalimumab would be suitable.

6.7 A register should be set up to monitor people who receive TNF inhibitors for the treatment of Crohn's disease in order to obtain data on long-term outcomes and relapse rates after withdrawal.

# 7 Related NICE guidance

- Guidance on the use of infliximab for Crohn's disease. NICE technology appraisal guidance 40 (2002).

# 8 Review of guidance

The guidance on this technology will be considered for review by the Guidance Executive in September 2011. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
May 2010

# Appendix A: Appraisal Committee members and NICE project team

## A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

**Dr Jane Adam (Chair – from September 2009)**
Department of Diagnostic Radiology, St George's Hospital

**Professor A E Ades**
Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

**Dr Amanda Adler**
Consultant Physician, Cambridge University Hospitals Trust

**Dr Tom Aslan**
General Practitioner, The Hampstead Group Practice, London

**Professor David Barnett (Chair – until September 2009)**
Professor of Clinical Pharmacology, Leicester Royal Infirmary

**Dr Matt Bradley**
Value Demonstration Director, AstraZeneca

**Mrs Elizabeth Brain**
Lay Member

**Dr Robin Carlisle**
Deputy Director of Public Health, Rotherham PCT

**Dr Karl Claxton**
Professor of Health Economics, Department of Economics & Related Research, the University of York

**Dr Fiona Duncan**
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

**Dr Simon Dixon**
Reader in Health Economics, University of Sheffield

**Mr Christopher Earl**
Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

**Dr Paul Ewings**
Statistician, Taunton & Somerset NHS Trust, Taunton

**Professor John Geddes**
Professor of Epidemiological Psychiatry, University of Oxford

**Mr John Goulston**
Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

**Professor Jonathan Grigg**
Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

**Dr Richard Harling**
Director of Public Health, Worcestershire PCT and Worcestershire County Council

**Dr Peter Heywood**
Consultant Neurologist, Dept. of Neurology, Frenchay Hospital,

**Professor Philip Home (Vice Chair)**
Professor of Diabetes Medicine, Newcastle University

**Dr Terry John**
General Practitioner, The Firs, London

**Dr Ian Lewin**
Consultant Endocrinologist, North Devon District Hospital

**Dr Simon Maxwell**
Senior Lecturer in Clinical Pharmacology and Honorary Consultant Physician, Queens Medical Research Institute, University of Edinburgh

**Dr Alec Miners**
Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

**Dr James Moon**
Consultant Cardiologist and Senior Lecturer, University College London Hospital (UCLH) and UCL

**Dr Nick Murray**
Senior Lecturer and Consultant in Medical Oncology, University of Southampton

**Dr David Newsham**
Lecturer (Orthoptics), University of Liverpool

**Dr Ann Richardson**
Lay Member

**Mrs Angela Schofield**
Chairman, Bournemouth and Poole Teaching PCT

**Mr Mike Spencer**
General Manager, Facilities and Clinical Support Services, Cardiff and Vale NHS Trust

**Professor Iain Squire**
Consultant Physician, University Hospitals of Leicester

**Dr Simon Thomas**
Consultant Physician and Reader in Therapeutics, Newcastle Hospitals NHS Foundation Trust and Newcastle University

**Mr David Thomson**
Lay Member

**Dr William Turner**
Consultant Urologist, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust

**Dr Norman Vetter**
Reader, Department of Primary Care and Public Health, School of Medicine, University of Cardiff

**Dr Paul Watson**
Director of Commissioning, East of England Strategic Health Authority

**Dr John Watkins**
Clinical Senior Lecturer and Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

**Dr Anthony S Wierzbicki**
Consultant in Metabolic Medicine and Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

**Dr Olivia Wu**
Reader in Health Economics, University of Glasgow

# B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Prashanth Kandaswamy**

Technical Lead (until May 2009)

**Fiona Rinaldi**
Technical Lead (from June 2009)

**Jennifer Priaulx**
Technical Lead (from October 2009)

**Janet Robertson**
Technical Adviser (until August 2009)

**Bhash Naidoo**
Technical Adviser (from August 2009)

**Fiona Rinaldi**
Technical Advisor (from November 2009)

**Eloise Saile**
Project Manager (until September 2008)

**Bijal Joshi**
Project Manager (from September 2008)

# Appendix B: Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by the West Midlands Health Technology Assessment Collaboration:

- Dretzke J et al. Use of tumour necrosis factor alpha (TNF α) inhibitors (adalimumab and infliximab [review]) for Crohn's disease: a systematic review and economic evaluation, July 2008.

B. The Decision Support Unit (DSU) reports for this appraisal were prepared by The School of Health and Related Research, University of Sheffield:

- Wailoo, A et al. Use of tumour necrosis factor alpha (TNF α) inhibitors (adalimumab and infliximab) for Crohn's disease: Report by the Decision Support Unit, January 2009.
- Wailoo, A et al. Use of tumour necrosis factor alpha (TNF α) inhibitors (adalimumab and infliximab) for Crohn's disease: Report by the Decision Support Unit, June 2009.

C. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I) Manufacturers/sponsors:

- Abbott Laboratories Ltd (adalimumab)
- Schering Plough (infliximab)

II) Professional/specialist and patient/carer groups:

- National Association for Colitis and Crohn's Disease (NACC)
- Association of Coloproctology of Great Britain and Ireland
- British Society of Gastroenterology

- Royal College of Nursing
- Royal College of Physicians

III) Other consultees:

- Hammersmith and Fulham PCT
- Department of Health
- Welsh Assembly Government

IV) Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Dr Falk Pharma UK Ltd (mesalazine, budesonide)
- Ferring Pharmaceuticals Ltd (mesalazine) (Not participating)
- Forest Laboratories UK Ltd (prednisolone) (Not participating)
- Teva UK Ltd (mesalazine) (Not participating)
- HalcyGen Pharmaceuticals Ltd (methotrexate) (Not participating)
- Novartis Pharmaceuticals Ltd (ciclosporin)
- Pfizer Ltd (sulfasalazine)
- Procter and Gamble Pharmaceuticals (UK) Ltd (mesalazine)
- Sandoz Ltd (mesalazine, metronidazole) (Not participating)
- Sanofi-Aventis Ltd (sodium cromoglicate, metronidazole)
- UCB Pharma Ltd (olsalazine sodium, prednisolone)
- Winthrop Pharmaceuticals UK Ltd (metronidazole)

- National Coordinating Centre for Health Technology Assessment
- West Midlands Health Technology Assessment Collaboration

D. The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on infliximab and adalimumab for the treatment of Crohn's disease by attending the initial Committee discussions and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Mr Charlie Croft, nominated by the National Association for Colitis and Crohn's Disease – patient expert
- Ms Elaine Steven, nominated by the National Association for Colitis and Crohn's Disease – patient expert
- Professor Subrata Ghosh, Consultant in General Medicine, Imperial College School of Medicine, nominated by the British Society of Gastroenterology – clinical specialist
- Professor Sally Mitton, Consultant Paediatric Gastroenterologist, British Society for Paediatric Gastroenterology, Hepatology and Nutrition, nominated by the National Association for Colitis and Crohn's Disease – clinical specialist
- Professor Chris Hawkey, President of BSG, nominated by British Society of Gastroenterology – clinical specialist (from August 2009)
- Professor Jon Rhodes, Professor of Medicine and Honorary Consultant Gastroenterologist, nominated by the Royal College of Physicians – clinical specialist (from August 2009)
- Dr Tim Orchard, Consultant Gastroenterologist, nominated by British Society of Gastroenterology – clinical specialist (from January 2010)

E. Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Abbott Laboratories Ltd (adalimumab)
- Schering Plough (infliximab)

# Changes after publication

**February 2014:** implementation section updated to clarify that infliximab and adalimumab are recommended as options for treating Crohn's disease. Additional minor maintenance update also carried out.

**March 2012:** minor maintenance

# About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE multiple technology appraisal process.

It replaces NICE technology appraisal guidance 40 issued in April 2002.

The review and re-appraisal of infliximab for the treatment of severe active or active fistulising Crohn's disease has resulted in a change in the guidance. Specifically, infliximab should now be given as a planned course of treatment until treatment failure (including the need for surgery) or for 12 months, whichever is shorter. Treatment should then only be continued if there is clear evidence of ongoing active disease. Adalimumab is now also recommended as another treatment option for people with severe active Crohn's disease.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

**Your responsibility**

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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# Accreditation