

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy

Technology appraisal guidance

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This guidance replaces TA140, TA262 and ESNM6.

1 Recommendations

- 1.1 Infliximab, adalimumab and golimumab are recommended, within their marketing authorisations, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.

Golimumab is recommended only if the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme.

- 1.2 The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).

- 1.3 Infliximab is recommended, within its marketing authorisation, as an option for treating severely active ulcerative colitis in children and young people aged 6 to 17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.

- 1.4 Infliximab, adalimumab or golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the patient, and their parent or carer if appropriate:

- They should continue treatment only if there is clear evidence of response as

determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. People who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.

- They should consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again.

2 Clinical need and practice

- 2.1 Ulcerative colitis is a chronic condition in which inflammation develops in the large intestine. Its exact cause is unknown although hereditary, infectious and immunological factors have been proposed as possible causes. Symptoms vary according to the extent and severity of the disease and may include bloody diarrhoea, abdominal pain, weight loss, fatigue, anaemia and an urgent need to defaecate. Some patients may also have extra-intestinal manifestations involving joints, eyes, skin and liver. Symptoms can flare up then disappear for months or even years, but approximately 50% of patients with ulcerative colitis will relapse at least once a year. Ulcerative colitis can cause complications such as primary sclerosing cholangitis (inflamed and damaged bile ducts), bowel cancer, osteoporosis and toxic megacolon (swelling of the colon caused by trapped gases, which can be life-threatening).
- 2.2 Ulcerative colitis can develop at any age but the peak incidence is between 15 and 25 years of age with a second, smaller peak between 55 and 65 years. It is estimated that approximately 128,400 people in England have ulcerative colitis. Around 80% of the people affected have mild or moderate disease and 20% have severe disease.
- 2.3 The modified Truelove and Witts severity index is widely used to classify the severity of ulcerative colitis. It defines mild ulcerative colitis as fewer than 4 bowel movements daily; moderate ulcerative colitis as more than 4 daily bowel movements but the patient is not systemically ill; and severe ulcerative colitis as more than 6 bowel movements daily and the patient is also systemically ill (as shown by tachycardia, fever, anaemia or a raised erythrocyte sedimentation rate). Severe ulcerative colitis, as defined by the Truelove and Witts severity index, is potentially life threatening and normally requires hospitalisation and emergency care. This is aligned with the UK definition of 'acute severe ulcerative colitis'. [NICE's guideline on ulcerative colitis](#) equates 'subacute ulcerative colitis' to moderately to severely active ulcerative colitis, which would normally be managed in an outpatient setting and does not require hospitalisation or the consideration of urgent surgical intervention. This appraisal includes moderately to severely active ulcerative colitis but not acute severe ulcerative colitis (that is, severe ulcerative colitis according to the Truelove and Witts severity index).

Recommendations for treating acute severe ulcerative colitis can be found in NICE's guideline on ulcerative colitis and [NICE's technology appraisal guidance on infliximab for acute exacerbations of ulcerative colitis](#).

- 2.4 Treatment for ulcerative colitis aims to relieve symptoms during a flare-up and then to maintain remission. The management of moderately to severely active ulcerative colitis involves treatment with oral or topical aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), or with corticosteroids if aminosalicylates are contraindicated or not tolerated. Oral corticosteroids or drugs that affect the immune response can also be added if the disease does not respond to aminosalicylates. Colectomy is a treatment option if symptoms are inadequately controlled or if the patient has a poor quality of life on conventional therapy.

3 The technologies

- 3.1 Adalimumab (Humira, AbbVie), golimumab (Simponi, Merck Sharp & Dohme) and infliximab (Remicade, Merck Sharp & Dohme; Inflectra, Hospira; Remsima, Celltrion) are monoclonal antibodies that inhibit the pro-inflammatory cytokine, TNF-alpha. All 3 have the same marketing authorisation in the UK for the 'treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies'. Infliximab is also indicated for the 'treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies'.

Adalimumab

- 3.2 Adalimumab is administered by subcutaneous injection. The recommended induction dose regimen is 160 mg at week 0 and 80 mg at week 2. After induction treatment, the recommended dose is 40 mg every other week. The summary of product characteristics recommends that therapy should be stopped in patients whose disease failed to respond to adalimumab within 2 to 8 weeks after starting treatment.
- 3.3 The summary of product characteristics includes the following adverse reactions for adalimumab: infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (including erythema, itching, haemorrhage, pain or swelling), headache, musculoskeletal pain, hepatitis B reactivation, various malignancies and serious haematological, neurological and autoimmune reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.4 The price of adalimumab is £352.14 for a pre-filled 40 mg pen or syringe, or a 40 mg/0.8 ml vial (excluding VAT; BNF edition 67). Assuming the recommended

dosage for adalimumab is followed (see section 3.2), the cost of adalimumab induction therapy is £2,113; the cost of 4 weeks of adalimumab maintenance therapy is £704. Costs may vary in different settings because of negotiated procurement discounts.

Golimumab

- 3.5 Golimumab is administered by subcutaneous injection. The dose regimen of golimumab depends on the patient's body weight. For patients with a body weight of less than 80 kg, golimumab is licensed at an initial dose of 200 mg, followed by 100 mg at week 2, and then 50 mg every 4 weeks. For patients with a body weight of 80 kg or more, it is licensed at an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks. The summary of product characteristics recommends that continued golimumab therapy should be reconsidered in patients who do not benefit within 12 to 14 weeks after starting treatment (that is, after 4 doses).
- 3.6 The summary of product characteristics includes the following adverse reactions for golimumab: upper respiratory tract infection and other serious infections (including sepsis, pneumonia, tuberculosis, and invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, hepatitis B reactivation, congestive heart failure, autoimmune processes (lupus-like syndrome) and haematologic reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.7 The price of golimumab is £762.97 for a pre-filled 50 mg pen or syringe and £1,525.94 for a 100 mg pre-filled pen (excluding VAT; BNF edition 67). Merck Sharp & Dohme has agreed a patient access scheme with the Department of Health. This will make the 100 mg dose of golimumab available to the NHS at the same cost as the 50 mg dose. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. Including the patient access scheme and assuming that the recommended dosage for golimumab is followed (see section 3.5), the cost of golimumab induction therapy is £2,289; the cost of 4 weeks of golimumab maintenance therapy is £763.

Infliximab

- 3.8 Infliximab is administered by intravenous infusion. For both the adult and paediatric populations, the recommended dose of infliximab is 5 mg/kg at weeks 0, 2 and 6, then at every 8 weeks. The summary of product characteristics recommends that continued infliximab therapy should be carefully reconsidered in adults who do not benefit within the first 14 weeks of treatment. It also states that available data do not support further infliximab therapy in children and young people aged 6 to 17 years whose disease does not respond within the first 8 weeks of treatment.
- 3.9 The summary of product characteristics includes the following adverse reactions for infliximab: upper respiratory tract infection, hepatitis B reactivation, congestive heart failure, serious infections (including sepsis, opportunistic infections and tuberculosis), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, hepatosplenic T-cell lymphoma, and serious infusion reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.10 The price of infliximab is £419.62 for a 100 mg vial containing powder for reconstitution (excluding VAT; BNF edition 67). Assuming the patient weighs 77 kg and the recommended dose for infliximab is followed (see section 3.8), the cost of infliximab induction therapy is £5,035; the cost of 4 weeks of infliximab maintenance therapy is £839. Costs may vary in different settings because of negotiated procurement discounts.
- 3.11 Biosimilar versions of infliximab (Inflectra, Hospira; Remsima, Celltrion) have a marketing authorisation in the UK for the same indications. The therapeutic indications, dosage and method of administration for Remsima and Inflectra are identical to those for the reference product (Remicade). Adverse reactions are also similar. Neither Inflectra nor Remsima had an approved list price in the UK at the time of the appraisal.

4 Evidence and interpretation

The [Appraisal Committee](#) considered [evidence from a number of sources](#).

Clinical effectiveness

Adult population

- 4.1 The Assessment Group's systematic review identified 9 relevant randomised controlled trials (RCTs) in adults: ULTRA1, ULTRA2 and Suzuki et al. for adalimumab; PURSUIT-SC and PURSUIT-Maintenance for golimumab; and ACT1, ACT2, Probert et al. and UC-SUCCESS for infliximab. All the RCTs were multicentre, double-blind trials that were conducted worldwide (except the study by Suzuki et al., which was conducted in Japan and the study by Probert et al., which was conducted in the UK and Germany). Apart from UC-SUCCESS, which compared infliximab with azathioprine or with infliximab plus azathioprine, all the trials compared adalimumab, golimumab or infliximab with placebo. Most trials included licensed and unlicensed dosages of the treatment; only the results for the licensed dosages are presented here. Of the 9 trials identified by the Assessment Group, 4 followed up patients in open-label extension studies (ULTRA1, ULTRA2, ACT1 and ACT2). Because no head-to-head evidence was available from RCTs for adalimumab, golimumab or infliximab, the Assessment Group performed a network meta-analysis using the placebo-controlled RCTs for each treatment (that is, an analysis combining direct and indirect evidence for particular pairwise comparisons).
- 4.2 All the RCTs except the study by Probert et al. used the Mayo score to assess the eligibility of patients. The Mayo score assesses 4 outcomes (stool frequency, rectal bleeding, endoscopic findings and physician's global assessment) on a scale of 0 to 12, with the score increasing with disease severity. In all these trials patients were eligible if they had a Mayo score of 6 to 12 with disease identified by endoscopic examination, which represents moderate to severe disease. Probert et al. used instead the ulcerative colitis symptom score, but the Assessment Group considered this to be equivalent to the Mayo score. Patients had to have taken conventional therapies before. These therapies varied across

the trials but generally included corticosteroids, aminosalicylates and/or a drug that affects the immune response. Only in ULTRA2 were patients allowed to have had a TNF-alpha inhibitor before (40% of patients had been treated with one). Patients were excluded from the trials if they had any of the following: ulcerative proctitis (ulcerative colitis that is limited to the rectum), a history of or a risk of having bowel surgery, diseases of the central nervous system, previous serious infection or a deficient immune system, previous cancer, or dysplasia (signs of abnormal growth of cells).

- 4.3 The average age of patients in the included RCTs ranged from 37 to 42.5 years; 41 to 73% were male and the average duration of disease was 4.9 to 8.5 years. Mayo scores at baseline were consistent across the trials and ranged from 8.1 to 8.9. The Assessment Group noted that, even though TNF-alpha inhibitors are licensed for patients whose disease has had an inadequate response to, or who are intolerant to or have medical contraindications for, such therapies, UC-SUCCESS included patients if they had never had azathioprine or not had it within the 3 months preceding randomisation. As a result, 90% of the patients enrolled in the trial had not had azathioprine before. In addition, Suzuki et al. included Japanese patients aged 15 years or older. However, the Assessment Group considered it appropriate to use this trial because the average age of patients was over 40 years.
- 4.4 The primary end point in all the RCTs was clinical response or remission. Of the 9 trials in adults, 8 trials assessed how well the treatment induced clinical response or remission, and 6 trials assessed how well the treatment maintained it (5 trials assessed both). To assess clinical response or remission, all trials except the study by Probert et al. used the Mayo score, which the Assessment Group considered to be applied consistently in the individual trials. Probert et al. used the ulcerative colitis symptom score. In the trials that used the Mayo score, clinical response was generally defined as:
- a decrease in Mayo score from baseline of at least 3 points and at least 30%, and
 - a decrease in the rectal bleeding sub-score from baseline of at least 1 point, or having an absolute rectal bleeding sub-score of 0 or 1.

Similarly, the definition of remission was broadly the same across the RCTs:

Mayo score of 2 or less, with no individual sub-score greater than 1.

Adalimumab

- 4.5 In ULTRA1, 18.5% of patients who were treated with adalimumab 160 mg at week 0 and 80 mg at week 2 (the licensed dose) were in remission at week 8 compared with 9.2% of those who had placebo; a result that was statistically significant ($p=0.031$). A higher proportion of patients in the adalimumab group had a clinical response (54.6% compared with 44.6%) but the difference was not statistically significant. In ULTRA2, the rate of remission was higher in patients treated with adalimumab than in those treated with placebo both at week 8 (16.5% compared with 9.3%; $p=0.019$) and at week 52 (17.3% compared with 8.5%; $p=0.004$). The difference at both time points was statistically significant. Of patients who were in remission at week 8, 8.5% of those having adalimumab and 4.1% of those having placebo remained in remission at week 52 ($p=0.047$). The open-label extension study ULTRA3 showed that patients generally continued to benefit from adalimumab therapy up to week 60, although 23% did not benefit and stopped treatment.
- 4.6 The incidence of adverse events was similar with adalimumab or placebo in ULTRA1 (50.2% compared with 48.4%, respectively) and ULTRA2 (82.9% compared with 83.8%). The most frequently reported adverse event in both RCTs was worsening or flare-up of ulcerative colitis (ULTRA1 adalimumab 3.6%, placebo 4.0%; ULTRA2 adalimumab 22.6%, placebo 29.2%). The difference in the incidence of adverse events between the adalimumab and the placebo groups was statistically significant only for iron deficiency anaemia, gastroenteritis, and nasopharyngitis, although the incidence was higher with adalimumab for all adverse events. Most adverse events were mild or moderate in severity. In ULTRA2, more patients randomised to placebo stopped treatment because of an adverse event (13.1%) than did patients randomised to adalimumab (8.9%).
- 4.7 ULTRA1 and ULTRA2 reported health-related quality of life data for adalimumab measured using the Inflammatory Bowel Disease Questionnaire (IBDQ) or Short Form-36 (SF-36) – IBDQ scores range from 32 (poor health) to 224 (perfect health). In ULTRA1, changes from baseline scores on IBDQ and SF-36 at week 8 were similar in the adalimumab (160 mg at week 0 and 80 mg at week 2) and

placebo groups. In ULTRA2, however, changes in IBDQ scores at week 52 were higher with adalimumab than with placebo (27 compared with 19; $p < 0.05$).

- 4.8 In the study by Suzuki et al., patients were randomised to adalimumab 160 mg at week 0 and 80 mg at week 2 then 40 mg every other week (licensed dose), or adalimumab 80 mg at week 0 then 40 mg every other week (unlicensed dose), or placebo. Results were reported at 8 weeks and 52 weeks, but the 2 adalimumab groups were combined for the analysis at 52 weeks. At week 8, remission rates were similar among treatment groups, but more patients treated with adalimumab 160 mg at week 0 and 80 mg at week 2 (the licensed dose) had a clinical response than did patients treated with placebo (50% compared with 35%; $p = 0.044$). At week 52, more patients having adalimumab maintenance therapy had a clinical response (18% compared with 31%; $p = 0.021$) and remission (7% compared with 23%; $p = 0.001$) than did patients having placebo.
- 4.9 In response to the appraisal consultation document, the company presented an interim analysis of the INSPIRADA study. This was a multicentre observational study evaluating the impact of adalimumab on the quality of life of patients with ulcerative colitis and on the utilisation of healthcare resources in clinical practice. The primary endpoints were the change in the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) score at week 26 from baseline, and the change in medical care costs related to ulcerative colitis (apart from the cost of adalimumab). The SIBDQ uses 10 questions to measure the impact of the disease on social, emotional and physical wellbeing. Total scores range from 10 (worst health) to 70 (best health). The company reported that adalimumab was associated with a statistically significant improvement in SIBDQ scores in the interim analysis (18.36, 95% confidence interval [CI] 14.89 to 21.84; $p < 0.001$). Adalimumab also reduced the costs related to ulcerative colitis in the 6 months after starting treatment compared with the 6 months before starting treatment (-£1,296, 95% CI -£1,729 to -£863; $p < 0.001$), a difference that was statistically significant. This analysis was not critiqued by the Assessment Group.

Golimumab

- 4.10 PURSUIT-SC was an integrated trial that included a double-blind dose-finding study and a dose confirmation study. In the dose confirmation study, rates of

clinical response at week 6 were 51.0% among patients who had golimumab 200 mg followed by golimumab 100 mg (the licensed dose), and 30.3% among those who had placebo, a difference that was statistically significant ($p < 0.0001$). Golimumab treatment was also associated with a statistically significantly higher rate of remission than placebo (17.8% compared with 6.4%; $p < 0.0001$). Patients who had golimumab (200 mg then 100 mg) reported a greater change in IBDQ scores from baseline to week 6 than did patients having placebo (27.0 compared with 14.8, $p < 0.0001$).

- 4.11 In PURSUIT-Maintenance patients whose disease had responded to golimumab induction therapy in 2 previous golimumab trials (including PURSUIT-SC) were randomised to golimumab 50 mg, golimumab 100 mg or to placebo. Clinical response was maintained throughout PURSUIT-Maintenance to week 54 in 47.0% of patients who had 50 mg golimumab, 49.7% of patients who had 100 mg golimumab and 31.2% of patients who had placebo ($p = 0.010$ and $p < 0.001$ respectively). The proportion of patients who were in remission at both weeks 30 and 54 was higher in the golimumab 100 mg group (27.8%) and the golimumab 50 mg group (23.2%) than in the placebo group (15.6%; $p = 0.004$ and $p = 0.122$ respectively), although the difference between golimumab 50 mg and placebo was not statistically significant. Because PURSUIT-Maintenance included patients whose disease had responded to golimumab induction therapy in 2 earlier trials, the Assessment Group indicated that the results of PURSUIT-Maintenance may be biased.
- 4.12 In PURSUIT-Maintenance, the number of adverse events was similar in the golimumab 50 mg and 100 mg groups. However, among patients having golimumab 50 mg, 8.4% had a serious adverse event and 5.2% stopped treatment because of an adverse event, compared with 14.3% and 9.1% respectively for patients having golimumab 100 mg (most patients who stopped treatment did so because their disease got worse).

Infliximab

- 4.13 In both the ACT1 and ACT2 trials, clinical response at week 8 occurred in a higher proportion of patients who were treated with infliximab 5 mg/kg (the licensed dose) than in patients treated with placebo (ACT1 69% compared with 37%,

$p < 0.001$; ACT2 65% compared with 29%, $p < 0.001$). Patients who had infliximab were also more likely to have a clinical response at week 30 than patients who had placebo ($p \leq 0.002$ in both studies). In ACT1, clinical response at week 54 was reported for 46% of patients who had infliximab 5 mg/kg compared with 20% of those who had placebo ($p < 0.001$). A statistically significant improvement in quality of life was observed in the infliximab group compared with the placebo group.

- 4.14 In ACT1 and ACT2, similar proportions of patients in the infliximab and placebo groups had an adverse event. However, more adverse events occurred among patients having infliximab in ACT1 than among those having it in ACT2 (87.6% compared with 81.8%). The most common adverse event in ACT1 was worsening of ulcerative colitis (infliximab 19.0%, placebo 33.1%), whereas in ACT2 it was headache (infliximab 15.7%, placebo 14.6%). There were more serious adverse events reported by patients having placebo in both RCTs (ACT1 infliximab 21.5%, placebo 25.6%; ACT2 infliximab 10.7%, placebo 19.5%). Stopping treatment because of an adverse event was more common in the placebo group than in the infliximab group in both studies.
- 4.15 Probert et al. reported remission rates (ulcerative colitis symptom score less than 2) of 39% in the infliximab group and 30% in the placebo group at week 6, a difference of 9% that was not statistically significant (95% CI -19% to 34%; $p = 0.76$). At that time, health-related quality of life measured using IBDQ and EQ-5D improved more with infliximab than with placebo (p -value not reported). In UC-SUCCESS, a greater proportion of patients who had infliximab plus azathioprine were in corticosteroid-free remission at week 16 (39.7%) than patients who had infliximab alone (22.1%; $p = 0.017$) or azathioprine alone (23.7%; $p = 0.813$). The greatest changes in IBDQ and SF-36 scores from baseline were for infliximab plus azathioprine (for both IBDQ and SF 36 score changes, $p < 0.05$ compared with azathioprine alone or with infliximab alone).
- 4.16 Inflectra and Remsima are biosimilar products to infliximab that were developed as a single product, CT-P13. CT-P13 was compared with Remicade (the reference proprietary product) in 2 RCTs:
- PLANET-AS: a trial comparing the pharmacokinetics, efficacy and safety of CT-P13 and Remicade in patients with ankylosing spondylitis ($n = 250$).

- PLANET-RA: a trial comparing the efficacy and safety of CT-P13 and Remicade in patients with rheumatoid arthritis whose disease had an inadequate response to methotrexate (n=606).

The objective of these trials was to demonstrate that CT-P13 was similar to the reference product. The European Public Assessment Reports for Inflectra and Remsima acknowledged that the pharmacokinetics, efficacy, safety, and immunogenicity profiles of CT-P13 were similar to those of Remicade in PLANET-AS and PLANET-RA. Although neither of the trials was for ulcerative colitis, the European Public Assessment Reports state that the overall data comparing CT-P13 with Remicade allow for the extrapolation of the evidence generated by PLANET-AS and PLANET-RA to all other indications of Remicade.

Network meta-analysis

- 4.17 Because no RCTs compared adalimumab, golimumab or infliximab directly with each other, the Assessment Group performed a network meta-analysis using the placebo-controlled RCTs for each intervention. RCTs were eligible for inclusion if they reported data on both clinical response and remission at either an induction (6 to 8 weeks) or maintenance (30 or 52 weeks) time point. The Assessment Group did not include the study by Probert et al. and UC-SUCCESS because the definition of remission in Probert et al. differed from the other trials and most patients in UC-SUCCESS had not had azathioprine before. ULTRA2 was the only trial to include patients who had been treated before with a TNF-alpha inhibitor as well as those who had not. For its base case, the Assessment Group used the data relating only to patients who had not had TNF-alpha inhibitors before. It also excluded the study by Suzuki et al. from the base case because this study was conducted in Japanese patients only. However, the Assessment Group did 3 sensitivity analyses: firstly using data for the overall population in ULTRA2 (patients who had been treated with a TNF-alpha inhibitor before and also those who had not); secondly, including Suzuki et al.; and thirdly, combining these 2 analyses together.
- 4.18 For the base case and each of the sensitivity analyses, the Assessment Group compared the effects of adalimumab, golimumab, and infliximab with respect to

each of the following:

- induction of clinical response or remission at week 8
- maintenance of clinical response or remission at **week 32** for patients starting with a **clinical response** at **week 8**
- maintenance of clinical response or remission at **week 32** for patients starting in **remission** at **week 8**
- maintenance of clinical response or remission at **week 52** for patients starting with a **clinical response** at **week 32**
- maintenance of clinical response or remission at **week 52** for patients starting in **remission** at **week 32**.

The Assessment Group used between 3 and 5 RCTs to perform the network meta-analysis for each of the listed outcomes, noting mild to moderate heterogeneity between individual study results in all the analyses. For each outcome, the Assessment Group reported:

- the effect of each treatment compared with placebo and with the other treatments on the probit scale (where negative values indicate that the intervention is more effective than the comparator) together with credible intervals (CrI)
- the probability of each treatment being ranked the best, second-best, third-best and so on
- the probability of the disease being active, responding and remitting at the end of therapy (week 8 for induction and week 32 or 52 for maintenance) with each treatment.

4.19 In the Assessment Group's base case, all treatments had a statistically significant favourable effect compared with placebo when assessed for induction therapy. The greatest effect on inducing clinical response or remission was associated with infliximab (effect relative to placebo -0.92, 95% CrI -1.27 to -0.56), which had a 93% probability of being the best treatment for that outcome. The probability of the disease remaining active, responding or remitting after 8 weeks of infliximab therapy was 29%, 35% and 36% respectively.

4.20 For maintenance therapy, the Assessment Group reported the following results:

- Maintenance of clinical response or remission at **week 32** for patients starting with a **clinical response** at **week 8**: golimumab 100 mg had the greatest effect compared with placebo, but the effect was not statistically significant (-0.42, 95% CrI -1.06 to 0.21). The probability of golimumab 100 mg being the best treatment for that outcome was 47%. At the end of the maintenance therapy with golimumab 100 mg, the probability of the disease remaining active, responding or remitting was 37%, 29% and 35% respectively.
- Maintenance of clinical response or remission at **week 32** for patients starting in **remission** at **week 8**: golimumab 50 mg had the greatest effect compared with placebo, but the effect was not statistically significant (-0.63, 95% CrI -1.36 to 0.11). The probability of golimumab 50 mg being the best treatment for that outcome was 47%. At the end of the maintenance therapy with golimumab 50 mg, the probability of the disease remaining active, responding or remitting was 18%, 14% and 69% respectively.
- Maintenance of clinical response or remission at **week 52** for patients starting with a **clinical response** at **week 32**: infliximab had the greatest effect compared with placebo, but the effect was not statistically significant (-0.36, 95% CrI -1.33 to 0.62). The probability of infliximab being the best treatment for that outcome was 56%. At the end of the maintenance therapy with infliximab, the probability of the disease remaining active, responding or remitting was 25%, 34% and 41% respectively.
- Maintenance of clinical response or remission at **week 52** for patients starting in **remission** at **week 32**: adalimumab had the greatest effect compared with placebo, which was statistically significant (-1.04, 95% CrI -1.93 to -0.12). The probability of adalimumab being the best treatment for that outcome was 84%. At the end of the maintenance therapy with adalimumab, the probability of the disease remaining active, responding or remitting was 8%, 8% and 83% respectively.

4.21 In all 3 sensitivity analyses, infliximab had the greatest effect on inducing clinical response or remission, as in the base case. The best treatment for each maintenance outcome was also the same as in the base case in all sensitivity analyses.

Children and young people

- 4.22 The Assessment Group identified 1 open-label RCT in children and young people, by Hyams et al., which evaluated infliximab as maintenance therapy. Patients initially had 5 mg/kg infliximab induction therapy at weeks 0, 2 and 6. Patients whose disease responded were then randomised to 1 of 2 infliximab maintenance groups: infliximab 5 mg/kg every 8 weeks (n=22) or infliximab 5 mg/kg every 12 weeks (n=23). Eligible patients were 6 to 17 years old, had moderately to severely active ulcerative colitis defined as a Mayo score of 6 to 12 (with disease identified endoscopically), and had been treated before with at least 1 conventional treatment (aminosalicylates, a drug that affects the immune response or corticosteroids). The primary end point was clinical response assessed at week 8 for induction therapy (before randomisation) and week 54 for maintenance therapy. Remission, a secondary end point, was defined as a Paediatric Ulcerative Colitis Activity Index (PUCAI) score of less than 10 (a PUCAI score of 65 or more reflects severe disease). Infliximab is licensed in children and young people for treating severely active ulcerative colitis only, but Hyams et al. included patients with moderately to severely active disease. Because the Assessment Group did not identify any RCTs comparing infliximab with placebo or with other active treatments in children and young people, it included Hyams et al., despite it being for moderately to severely active disease.
- 4.23 At week 8, 73.3% (44 out of 60) of patients had a clinical response to infliximab and 40.0% (24 out of 60) were in remission. Of those who had a response, a greater proportion of patients who then had infliximab 5 mg/kg every 8 weeks were in PUCAI remission at week 54 than patients who had infliximab 5 mg/kg every 12 weeks (38.1% compared with 18.2%; $p=0.146$). In addition, 38.5% and 0.0% of patients who had infliximab every 8 weeks or every 12 weeks, respectively, were in PUCAI remission without the use of corticosteroids at week 54. No health-related quality of life data were available from Hyams et al.
- 4.24 All patients in the study by Hyams et al. reported having at least 1 adverse event. By week 54, more patients having infliximab every 12 weeks had stopped treatment because of an adverse event than those having infliximab every 8 weeks (6 out of 23 [26.1%] compared with 3 out of 22 [13.6%]). The number of patients who had 1 or more serious adverse event, infections, or reactions at the site of administration was similar in both infliximab groups.

Comments from other consultees

- 4.25 Patient experts indicated that the symptoms of ulcerative colitis (for example, irregular sleeping patterns, pain and fatigue) and the unpredictable pattern of disease flare-ups cause education, employment, personal relationships, and social and family life to be affected. In addition, the frequent and urgent need to go to the toilet affects self-esteem and social functioning, and can cause anxiety about loss of bowel control if left untreated. Patient experts also noted that ulcerative colitis presents at an early age when people are beginning their career and long-term relationships. They indicated that 30% of patients continue to experience flare-ups or chronic symptoms despite conventional therapy, so TNF-alpha inhibitors offer hope to these patients and can help them resume their normal lives. However, it was noted that access to TNF-alpha inhibitors is currently limited to patients who are able to secure exceptional funding through their clinical commissioning group. This sometimes leaves the patient without adequate treatment until their disease becomes so severe that they may require emergency surgery.
- 4.26 Comments from professional groups indicated that ulcerative colitis is a challenging condition to treat, particularly in patients with disease that does not respond to conventional therapy who, as a result, have a reduced quality of life and often no treatment options but colectomy and the formation of an ileostomy (that is, the diversion of the small intestine through an opening in the abdomen). Comments indicated that often this surgery is needed for young people, in whom a stoma (the artificial opening made into the abdomen) may have an impact on psychological wellbeing and lifestyle. In addition, young patients, who may not have started a family, often delay or dismiss ileo-anal pouch anastomosis (by which an internal reservoir for stool is surgically created) because this is a surgery in the pelvis that can affect fertility. For these patients, TNF-alpha-inhibitor therapy is a valuable option because it can avoid surgery when the patient is in education, has not formed permanent relationships or a family, or risks losing employment because of their illness. Comments noted, however, that it is difficult to extrapolate from clinical trials, with rigid inclusion criteria, to assess the impact of TNF-alpha inhibitors on patients' quality of life compared with surgery.
- 4.27 Professional groups highlighted that the ACT1 and ACT2 trials showed that

infliximab resulted in a statistically significant reduction in the rate of colectomy at week 54 compared with placebo (10% and 17% of patients in the infliximab and placebo groups, respectively, had colectomy). It was also noted that long-term follow-up data from ACT1 and ACT2 demonstrated a persistent response to infliximab and low rates of colectomy at up to 4 years after starting treatment. Patient experts indicated that the risk of colon cancer increases after 8 to 10 years of active disease and that TNF-alpha inhibitors may decrease it. Statements from patients with ulcerative colitis suggested that infliximab is an effective treatment that prevented symptoms from recurring and helped patients maintain a good health state for long periods, although it caused reactions in some patients when first taken. Comments from professional groups stated that, while the clinical evidence base is smaller for adalimumab and golimumab than for infliximab, there are high-quality data with broadly similar results to infliximab for both treatments. Patient experts stated that although TNF-alpha inhibitors are relatively expensive, they reduce the costs of other services, which may offset the high drug costs in the long term.

- 4.28 Comments from professional groups noted that NICE guidance on TNF-alpha-inhibitor therapy differs for Crohn's disease and ulcerative colitis, resulting in TNF-alpha inhibitors being widely available for Crohn's disease but not for ulcerative colitis. The comments indicated that ulcerative colitis shares common genetic factors with Crohn's disease, with the 2 conditions overlapping in some aspects, which sometimes makes them clinically indistinguishable. In addition, both diseases can be associated with chronic active symptoms that do not respond to conventional therapy. The comments summarised that the benefit of TNF-alpha inhibitors for ulcerative colitis is likely to be similar to that for Crohn's disease, and so guidance for these 2 conditions should also be similar.
- 4.29 Clinical experts stated that outcomes should include rates of corticosteroid-free remission. They also advised that treatment goals beyond symptom control and improved quality of life are important, such as complete mucosal healing and reduced complication rates. Long-term corticosteroid use is associated with increased risk of health problems such as hypertension, diabetes and osteoporosis, so reducing the dose of corticosteroids is a desirable goal in the management of ulcerative colitis. Patients who had infliximab explained that some of the side effects of corticosteroids, notably rounded face and severe acne, can lower self-esteem. Patients stated that TNF-alpha inhibitors can help

overcome these problems because they allow the patient to reduce the dose of corticosteroids.

Cost effectiveness

- 4.30 The Assessment Group's systematic review of the cost-effectiveness evidence identified 3 published economic evaluations of TNF-alpha inhibitors for ulcerative colitis. However, the Assessment Group did not consider any of these evaluations to provide sufficient evidence on the cost effectiveness of TNF-alpha inhibitors from a UK perspective. This was mainly because the models did not accurately reflect the natural history of the disease, made questionable assumptions about the relative effectiveness of TNF-alpha inhibitors and used short time horizons.

Company's model: adalimumab

- 4.31 The company's analysis compared the cost effectiveness of adalimumab plus conventional therapy with conventional therapy alone for moderately to severely active ulcerative colitis that had responded inadequately to conventional therapy. The population in the base case comprised both patients who had been treated before with a TNF-alpha inhibitor other than adalimumab and also those who had not. The company also presented a sensitivity analysis in which it modelled only patients who had not previously had a TNF-alpha inhibitor. The analysis estimated the direct healthcare costs to the NHS and quality-adjusted life years (QALYs) over a 10 year time horizon using a cycle length of 2 weeks.
- 4.32 The company used a Markov model simulating 8 states: 3 states before surgery ('remission', 'mild', and 'moderate-to-severe'), 1 'surgery' state, and 4 states after surgery ('post-surgery without complication', 'transient complication', 'chronic complication', and 'surgery-related death'). The company derived the probabilities of patients moving between states before surgery primarily from ULTRA2 and the extension study ULTRA3. It derived the transition probabilities for the surgery and post-surgery states based on published literature.
- 4.33 The company assigned a utility value to each state in the model. ULTRA2 collected health-related quality of life data using the Short Form-36 (SF-36)

survey but the company did not transform these data to SF-6D, arguing that this may overestimate the utility value for patients who had severe disease in ULTRA2. Instead, it obtained the utility values for the states before surgery from a study by Swinburn et al. and those for the states after surgery mainly from a study by Tsai et al. The model included costs associated with: the drug, disease state, hospitalisation, surgery, complications after surgery, and surgery-related death. All costs were derived from published literature.

- 4.34 The base-case ICER for adalimumab plus conventional therapy compared with conventional therapy alone was £34,417 per QALY gained. When the company varied the key parameters in the model 1 at a time, ICERs ranged from £29,437 to £38,073 per QALY gained. The probability of adalimumab plus conventional therapy being cost-effective compared with conventional therapy alone, at a maximum acceptable ICER of £30,000 per QALY gained, was 30%. In the sensitivity analysis relating to patients who had not been treated before with a TNF-alpha inhibitor, the ICER for adalimumab plus conventional therapy was close to the base-case ICER at £35,970 per QALY gained.
- 4.35 The Assessment Group critiqued the company's decision problem and stated that the company – having excluded other TNF-alpha inhibitors (golimumab and infliximab) and surgery as comparators – deviated from the final scope. In addition, it stated that the company used a shorter cycle length than the time point for assessing induction in ULTRA2 (6 weeks); did not transform the data collected in ULTRA2 using SF-36 to SF-6D utility values; assumed that surgery improves the utility score by only 0.06 compared with active disease; and modelled the rate at which patients had surgery based on a questionable study. In response to the Assessment Group's critique, the company revised its model by using a lifetime time horizon, including a general population mortality which is the same as that used by the Assessment Group, deriving the efficacy of adalimumab from the TNF-alpha-inhibitor-naïve subgroup in ULTRA2 and ULTRA3, using a rate of surgery that reflects the average rates in 4 studies, and applying the same stopping rule for adalimumab after year 2 as the Assessment Group. The ICER for adalimumab plus conventional therapy compared with conventional therapy alone from the revised model was £23,027 per QALY gained. This analysis, however, was not critiqued by the Assessment Group.

Company's model: golimumab and infliximab

- 4.36 The company's model compared adalimumab, golimumab and infliximab with each other and with colectomy for moderate to severe ulcerative colitis that had failed previous treatment. Conventional therapy was not a comparator in the analysis. The company chose a cycle length of 2 months and a 10 year time horizon. The perspective on costs was that of the NHS. Costs and health effects were discounted at an annual rate of 3.5%.
- 4.37 The company's model was hybrid in that it used a 'decision tree' to model the probabilities of TNF-alpha inhibitors inducing a clinical response or remission, and the probabilities of surviving and of having surgery-related complications after colectomy; then a Markov model (simulating 11 states) to estimate the long-term outcomes of maintenance therapy and colectomy. If patients had responding or remitting disease at the end of induction therapy, they had maintenance therapy. Patients whose disease did not respond to induction therapy, and those in whom previous response was lost during maintenance therapy, had intravenous corticosteroids. They could then continue on corticosteroids or have colectomy. The probabilities of patients moving between states in the induction and maintenance phases were based on network meta-analyses conducted by the manufacturer.
- 4.38 Costs and utility values were attached to each state. The model incorporated the patient access scheme for golimumab. Utility values were based on PURSUIT-SC in the golimumab model and on ACT1 in the infliximab model. Golimumab and infliximab were assumed to be administered at the licensed dose. For adalimumab, the company used the licensed induction dose regimen of 160 mg at week 0 and 80 mg at week 2, but after induction it assumed that 50% of patients have the licensed initial maintenance dose of 40 mg every other week while the other 50% have 40 mg every week. The company stated that this was because 22.9% of patients in the ULTRA2 trial had 40 mg every week instead of every other week. However, it also stated that, based on clinical advice, up to 80% of patients would have weekly doses in clinical practice. The company assumed that in each treatment group some patients also have background conventional therapy.
- 4.39 The company presented the cost-effectiveness results as pairwise ICERs (that is,

ICERs comparing technologies head-to-head rather than incrementally from the least costly to the most costly). It reported ICERs of £27,994 per QALY gained for golimumab compared with colectomy, and £80,318 saved per QALY lost for golimumab compared with infliximab; compared with adalimumab, golimumab was more effective and less expensive. For infliximab, the ICERs were £38,307 per QALY gained compared with colectomy, £54,564 per QALY gained compared with adalimumab, and £75,998 per QALY gained compared with golimumab.

- 4.40 The Assessment Group critiqued the models for golimumab and infliximab together because they were submitted by the same company and were identical. It stated that the company's analysis was generally in line with the NICE reference case, but deviated from the final scope in that conventional therapy was not included as a comparator. Furthermore, it stated that the company – having assumed that patients can only have corticosteroids or colectomy after TNF-alpha-inhibitor therapy fails – modelled a treatment pathway associated with severe disease, not moderate to severe disease for which further medical treatment would still be considered. The Assessment Group also indicated that the company did not describe its network meta-analyses in sufficient detail, did not explain how it estimated the probabilities of moving between states, and did not justify the selection of the data sources for certain parameters. The 2 company models used different sources for the utility values and made different assumptions about resource use, which the Assessment Group did not consider appropriate given that the 2 models addressed identical decision problems. The Assessment Group indicated that in an incremental analysis, infliximab should be compared with golimumab, which results in ICERs of approximately £76,000 to £80,000 per QALY gained.

Assessment Group's model

- 4.41 The Assessment Group developed a de novo economic model to assess the cost effectiveness of adalimumab, golimumab and infliximab (at their licensed doses) compared with each other and with conventional therapy or surgery for moderate to severe ulcerative colitis that had failed at least 1 previous therapy, in line with the RCTs for these agents. Conventional therapy comprised corticosteroids, aminosalicylates and drugs that affect the immune response. The Assessment Group used a lifetime time horizon that it divided into 2 phases; induction and

maintenance. The cycle length for the induction phase was 8 weeks and for the maintenance phase it was 26 weeks. The perspective of the analysis was that of the NHS and personal social services, and costs and health effects were discounted at an annual rate of 3.5%. The model was fully probabilistic (that is, produced results by varying the input parameters simultaneously with values from a probability distribution).

4.42 The Assessment Group's model was a state-transition Markov cohort model simulating 8 states:

- on biological therapy (adalimumab, golimumab or infliximab) – active disease (that is, no response or remission)
- on biological therapy – response
- on biological therapy – remission
- on conventional therapy – active disease
- on conventional therapy – response
- on conventional therapy – remission
- post-surgery (with or without complications)
- death.

Surgery was incorporated as an event rather than a state (that is, patients had colectomy then moved to the post-surgery state if they survived or to the death state if not). The probability of patients moving between states was based on the Assessment Group's network meta-analysis. The model used the same definitions of response and remission as the RCTs identified from the systematic review (see section 4.4).

4.43 The Assessment Group assumed that patients enter the model at the age of 40 years and have an average body weight of 77 kg, in line with the patient characteristics in the RCTs. In the model, all patients started in the induction phase and had biological or conventional therapy, or had surgery (early colectomy). Patients who had TNF-alpha-inhibitor therapy were assumed to also have conventional background therapy. If the TNF-alpha inhibitor led to a clinical

response or remission, the patient continued on the same treatment in the maintenance phase; if not, they stopped that treatment and had conventional therapy. Patients who continued TNF-alpha-inhibitor therapy in the maintenance phase had it for as long as response or remission was maintained; if response was lost, they moved to conventional therapy. Patients who started on conventional therapy and those who started on a TNF-alpha inhibitor but then moved to conventional therapy continued conventional therapy in the maintenance phase whether or not their disease responded or remitted, but they could have colectomy if their disease remained active. Therefore, colectomy was included in the analysis both as a comparator (early colectomy) and as an intervention further down the treatment pathway after biological or conventional therapy. All patients who had colectomy remained in the post-surgery state until they died.

4.44 To derive the rate at which patients have colectomy, the Assessment Group used a study by Solberg et al. estimating that every year 1.02% of patients have colectomy. Based on another study by Arai et al., it assumed that 47.3% and 5% of those patients will develop transient or chronic complications respectively. In patients who survived surgery, all transient complications were assumed to occur and resolve during the first cycle after surgery, whereas chronic complications continued until the patient died.

4.45 In the model, the patient's health-related quality of life depended on the outcome of drug therapy (whether the disease remained active, responded or remitted), whether the patient had colectomy, and if so, whether they developed complications afterwards. It did not depend on whether the patient had biological or conventional therapy. The Assessment Group stated that the studies by Woehl et al. and Swinburn et al. were the most useful to source utility values in the model because they were UK-based, included reasonably large number of patients (n=180 and n=230 respectively) and reported EQ-5D utility values for most states in the model:

- Woehl et al.: patients in the study may or may not have had surgery. Among patients who did not have surgery, utility values were reported to be 0.87 (standard deviation [SD] 0.15) for remitting disease, 0.76 (SD 0.18) for mild disease, and 0.41 (SD 0.34) for moderate to severe disease. These categories of disease severity were based on the Simple Colitis Activity Index. The Assessment Group assumed that the utility value for moderate to

severe disease that responded to treatment was equal to the value for mildly active disease in Woehl et al. (0.76). In patients who had surgery, the utility value was 0.71, which the Assessment Group adjusted to account for the effect of chronic complications after colectomy on the patient's quality of life, estimating a utility value of 0.70 in the post-surgery state.

- Swinburn et al.: of the 230 patients included in the study, 30 had previously had surgery. EQ-5D utility values were collected through an online survey across different categories of disease severity measured using the IBDQ. The utility value for patients who had surgery was 0.59 (95% CI 0.55 to 0.63). For patients who did not have surgery, utility values were 0.91 (95% CI 0.87 to 0.95) for remitting disease (n=78); 0.80 (95% CI 0.70 to 0.85) for mild disease (n=47); 0.68 (95% CI 0.58 to 0.78) for moderate disease (n=31); and 0.45 (95% CI 0.35 to 0.55) for severe disease (n=44). Because the model included patients who had 'moderate to severe disease' (rather than moderate or severe disease), the Assessment Group averaged the utility values for 'moderate' and 'severe' disease in Swinburn et al. to derive a value for moderately to severely active disease that did not respond to treatment. It also assumed that the utility value for moderate to severe disease that responded to treatment was equal to the value for mildly active disease in Swinburn et al. (0.80). The Assessment Group noted that Swinburn et al. reported that utility values were, on average, lower in patients who had surgery than in those who did not (p=0.016).

The Assessment Group chose to use values from Woehl et al. in its base case and from Swinburn et al. in a sensitivity analysis (see section 4.50). This was because the utility value after surgery in Woehl et al. (0.71) was more consistent with those reported in other studies than that from Swinburn et al. (0.59).

- 4.46 The Assessment Group modelled the cost of adalimumab, golimumab and infliximab assuming that each treatment would be administered at its licensed dosage. However, it assumed that a fixed proportion of patients (27%) have adalimumab 40 mg as maintenance therapy every week instead of every 2 weeks (the standard regimen) based on data reported in the company's submission for adalimumab. The summary of product characteristics for golimumab recommends that therapy should be reconsidered in patients who do not benefit

within 12 to 14 weeks after starting treatment (that is, after 4 doses). However, only the first 2 doses of golimumab were costed in the induction phase. This was because PURSUIT-SC, from which the data for golimumab were obtained, evaluated golimumab after 2 doses (at week 6). Only infliximab incurred administration costs in the model (adalimumab and golimumab are administered subcutaneously and so are not associated with administration costs if the patient self-administers). The model incorporated the patient access scheme for golimumab. For conventional therapy, the Assessment Group assumed that in both the induction and maintenance phases, 100% of patients have corticosteroids and aminosalicylates, 80% have mercaptopurine, and 20% have azathioprine. Costs associated with consultant visits, endoscopy, hospitalisation, blood tests and surgery (including surgery-related complications) were also modelled.

- 4.47 The Assessment Group presented results for patients in whom colectomy is a potential option, and separately for those in whom it is not. In addition, it performed one-way sensitivity analyses, varying parameters in the model 1 at a time. The parameters varied included the dataset used to estimate clinical effectiveness, the time horizon, utility values, health state costs, and assumptions around hospitalisations, surgery and chronic complications after surgery.

For adults in whom colectomy is an option

- 4.48 The Assessment Group's probabilistic base-case results estimated that colectomy provides 14.72 QALYs at a cost of £41,921. Adalimumab, golimumab, infliximab and conventional therapy were dominated by colectomy; that is, they provided fewer QALYs at a higher cost than colectomy.
- 4.49 The probability of colectomy being the most cost-effective treatment at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained was 97% and 96% respectively. Adalimumab, golimumab and infliximab had a 0% probability of being cost-effective compared with colectomy at these maximum acceptable ICERs.
- 4.50 In all one-way sensitivity analyses but 1, adalimumab, golimumab and infliximab were dominated by colectomy. This result changed only when the Assessment

Group incorporated utility values (except post-surgical complications) from Swinburn et al. In this analysis, colectomy became the least effective option. In the incremental analysis, golimumab and conventional therapy were dominated and excluded from the analysis. Among the remaining alternatives, colectomy was the cheapest, followed by adalimumab then infliximab. The ICER for adalimumab compared with colectomy was £80,315 per QALY gained and that for infliximab compared with adalimumab was £179,374 per QALY gained.

For adults in whom colectomy is not an option

- 4.51 When medical options only were compared with each other, infliximab was dominated by adalimumab (although the difference in QALYs was small), and golimumab was extendedly dominated by adalimumab and conventional therapy (that is, a QALY was attained at a higher cost with golimumab than with adalimumab because the ICER for golimumab compared with conventional therapy [£97,149 per QALY gained] was higher than that for adalimumab compared with conventional therapy). The incremental ICER for adalimumab compared with conventional therapy was £50,624 per QALY gained.
- 4.52 At a maximum acceptable ICER of £20,000 per QALY gained, adalimumab had a 0% probability of being cost-effective compared with conventional therapy. Its probability of being cost-effective compared with conventional therapy at a maximum acceptable ICER of £30,000 per QALY gained was approximately 5%.
- 4.53 Because the difference in effectiveness between adalimumab and infliximab was small (0.01 QALY), the results were sensitive to the dataset used to estimate clinical effectiveness for TNF-alpha inhibitors. In all the sensitivity analyses in which alternative datasets were used, golimumab was extendedly dominated and excluded from the analyses. When the Assessment Group used data from ULTRA2 for the overall population or included data from Suzuki et al., infliximab provided more QALYs than adalimumab but the ICER for infliximab compared with adalimumab was greater than £250,000 per QALY gained in both analyses. For adalimumab compared with conventional therapy, the ICER was £54,309 per QALY gained in the first analysis and £56,656 per QALY gained in the second (compared with a base-case ICER of £50,624 per QALY gained). When the Assessment Group included data from ULTRA2 for the overall population and data

from Suzuki et al. in the same analysis, infliximab was dominated by adalimumab; the ICER for adalimumab compared with conventional therapy was £56,014 per QALY gained. The Assessment Group also presented pairwise analyses comparing adalimumab, golimumab and infliximab head-to-head with conventional therapy using direct evidence from the respective RCTs. Compared with conventional therapy, the ICER for adalimumab was £70,075 per QALY gained, for golimumab it was £90,720 per QALY gained, and for infliximab it was £96,682 per QALY gained.

For children and young people

- 4.54 The Assessment Group presented a scenario analysis comparing infliximab with conventional therapy or colectomy in children and young people (golimumab and adalimumab are not licensed for this population). However, it advised that this analysis should be treated as exploratory because there were no RCTs comparing infliximab with placebo or with other active treatments in children and young people, so the data on the efficacy of infliximab were those provided by trials conducted in adults. This analysis differed from the base case in adults only in that the starting age of patients in the model was set to 15 years (the median age in the study by Hyams et al.).
- 4.55 In children and young people in whom colectomy is a potential option, colectomy provided 17.55 QALYs at a cost of £47,871. Infliximab provided fewer QALYs (13.01) at a higher cost (£106,759), and so was dominated by colectomy. There was a 0% probability of infliximab being cost-effective compared with colectomy or conventional therapy at a maximum acceptable ICER of £20,000 per QALY gained.
- 4.56 When colectomy was not a potential option, infliximab provided an additional 0.34 QALYs at an additional cost of £23,268 to conventional therapy, resulting in an ICER of £68,364 per QALY gained for infliximab compared with conventional therapy. There was a 0% probability of infliximab being cost effective compared with conventional therapy at a maximum acceptable ICER of £20,000 per QALY gained.

Limitations in the Assessment Group's model

4.57 The Assessment Group listed the following as the main limitations in its model:

- There was considerable uncertainty associated with the extrapolation of short-term trial data (maximum 54 weeks) to a lifetime time horizon.
- The model assumed that conventional therapy would not be given sequentially but that in any cycle, fixed proportions of patients would have corticosteroids, 5-aminosalicylates and drugs that affect the immune response.
- Evidence on the complications of colectomy was not identified through a systematic review.

Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of infliximab, adalimumab and golimumab, having considered evidence on the nature of ulcerative colitis and the value placed on the benefits of infliximab, adalimumab and golimumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.58 The Committee discussed with patient experts the nature of the condition and their experience with treatment. It heard that symptoms of ulcerative colitis include bloody diarrhoea, abdominal pain, weight loss, fatigue, irregular sleeping patterns, anaemia, and urgent need to defaecate, and that these can profoundly affect the patient's quality of life and disrupt their education, employment and family and social life. The Committee heard from patient experts that besides the symptoms of their disease which had a negative impact on their quality of life, some conventional therapies have toxic side effects that also affected their physical and psychological wellbeing. The Committee appreciated that, because the peak age of onset of ulcerative colitis is 15 to 30 years, the side effects of using corticosteroids for prolonged periods, as well as having ulcerative colitis, can severely damage the patient's confidence and self-esteem at a critical point in life when there may be other stressful events happening such as exams, university, forming relationships and beginning a family. The Committee heard

from 1 of the patient experts that they struggled to stop treatment with corticosteroids because when the dose was decreased, the symptoms of ulcerative colitis returned. The Committee also heard from the patient expert that they had tried azathioprine but this affected their white blood cell count so they had to stop using that too. Patient experts stated that with TNF-alpha inhibitors, the symptoms of ulcerative colitis had stopped, they felt 'normal' again, were able to work and lead a normal life, and their quality of life improved. The Committee noted from consultation comments that the use of TNF-alpha inhibitors in this patient population has become standard practice in Europe. The Committee concluded that patients and clinicians considered TNF-alpha inhibitors to be a valuable option that could offer long-term remission to some patients with ulcerative colitis.

- 4.59 The Committee discussed the treatment pathway for active ulcerative colitis (but not acute disease). It heard from the clinical expert that standard practice in the UK is to start on conventional therapy. This may include corticosteroids or 5-aminosalicylates (for example, mesalazine), with the possibility of then adding on azathioprine. The clinical expert indicated that approximately 8% to 10% of patients cannot tolerate azathioprine. At this point in the pathway, treatment becomes individualised and may include long-term corticosteroids or ciclosporin. Alternatively, a patient with ulcerative proctitis (where the inflammation is limited to the rectum) may use topical enemas. The Committee understood that conventional therapy is generally regarded as an ongoing option throughout the treatment pathway for ulcerative colitis so, if response to a conventional therapy was inadequate, patients may have further conventional therapy. Other available options at this stage include TNF-alpha inhibitors and surgery. The Committee heard that clinicians consider how unwell the patient is when deciding whether or not surgery is appropriate, and that patients who ultimately choose to have surgery may prefer 2 to 3 years of good quality of life on a TNF-alpha inhibitor to get them through stressful periods in their life and psychologically prepare for surgery. The Committee concluded that the choice of treatment depends on the specific clinical circumstances of each patient and that no single pathway of care could be defined for adults with moderately to severely active ulcerative colitis or children and young people with severely active ulcerative colitis.
- 4.60 The Committee discussed whether surgery was an appropriate comparator for TNF-alpha inhibitors. It heard that in clinical practice, surgery is avoided if

possible because, although potentially curative, it does not fully restore the patient's quality of life. This is because, for example, patients in whom pouches are created will still need to wake up at night to go to the toilet and be on life-long anti-diarrhoea medication. They may also experience complications such as faecal incontinence and chronic pouchitis, and there is a risk that this surgery may affect fertility in both men and women. As a result, some patients would only have a sub-total colectomy with a stoma in the first instance to prevent having surgery in the pelvis. However, stomas have a profound psychological and lifestyle impact (for example, on body image and self-esteem) and need care for the duration of their existence. The Committee heard that, although some of these patients will keep their stoma for life, others may need further surgery to create a pouch and many patients delay this for many years (in some areas of the UK only 30% to 60% of patients end up having a pouch). The Committee noted from consultation comments that many patients do not wish to have surgery because it is an irreversible step, with potential complications and long-term consequences on their physical and psychological wellbeing. It heard that, for patients in whom surgery is not an acceptable option, if a TNF-alpha inhibitor cannot be offered, engagement with the patient may be lost and the patient becomes at risk of further complications including bowel cancer. The Committee concluded that patients and clinicians would rather avoid or delay surgery (unless the patient has acute disease, which is not covered by this appraisal), and that surgery was not an appropriate comparator for TNF-alpha inhibitors for most patients in whom TNF-alpha inhibitors would be considered in clinical practice.

4.61 The Committee considered the role of surgery in the management of severely active ulcerative colitis in children and young people. It heard that children and young people are usually more reluctant to have surgery than adults because the younger the patient, the more likely surgery will impact on their life in terms of education and ability to form relationships and start a family. The Committee understood that the rate of surgery is higher among children and young people than adults because young people tend to present with more extensive and severe disease, which is more likely to need surgery. The Committee concluded that the decision to have surgery may be different for children and young people compared with adults and that TNF-alpha inhibitors are important treatment options that could allow patients to avoid surgery.

4.62 The Committee discussed whether conventional therapy was an appropriate

comparator for TNF-alpha inhibitors. Comments received in response to consultation indicated that TNF-alpha inhibitors are licensed for use after conventional therapy and that it is at this point in the pathway where TNF-alpha inhibitors are likely to be used in clinical practice. Because of this, the comments considered that it would be inappropriate to compare TNF-alpha inhibitors with a treatment that the disease had responded inadequately to, or one that patients cannot tolerate or have medical contraindications for. The Committee heard from patient experts that patients are unlikely to continue on a therapy that did not adequately relieve their symptoms. It was aware that after conventional therapy, if TNF-alpha inhibitors cannot be offered, treatment options are limited and usually include further conventional therapy or surgery. The Committee understood that, if patients choose not to have further conventional therapy, corticosteroids may be the only remaining option because surgery is generally viewed as the last option when the burden of disease can no longer be coped with. It heard that in 30% to 40% of patients who have corticosteroids, the disease will not respond to standard doses and the dose will need to be increased, which may consequently increase the potentially irreversible side effects associated with corticosteroids such as osteoporosis, diabetes, hypertension, increased susceptibility to serious infection, adrenal insufficiency and hepatic and ophthalmologic effects. In addition, the long-term use of corticosteroids in children is of particular concern because of the possible effect on growth. The Committee acknowledged that some patients would rather not have corticosteroids because of the potential long-term consequences on their health. It considered its earlier discussion about conventional therapy and that this is generally regarded as an ongoing option throughout the treatment pathway for ulcerative colitis (see section 4.59). It appreciated that for some patients in whom conventional therapy had failed, continuing the same type of therapy may be suboptimal. However, there was no evidence on the effectiveness of conventional therapy in these circumstances. The Committee concluded that conventional therapy is an option at the same stage at which TNF-alpha inhibitors would be considered.

- 4.63 The Committee heard from the clinical expert that ulcerative colitis shares common genetic factors with Crohn's disease, with the 2 conditions overlapping in some aspects, which sometimes makes them clinically indistinguishable. The Committee heard that, as a result, 10% to 15% of patients have unclassified (indeterminate) disease. The clinical expert noted that for Crohn's disease, there

is positive NICE technology appraisal guidance for using TNF-alpha inhibitors (NICE's technology appraisal guidance on infliximab and adalimumab for the treatment of Crohn's disease), and these provide symptom control in a significant proportion of patients, particularly in those with Crohn's colitis (where the inflammation is limited to the colon). For ulcerative colitis, however, the expert indicated that TNF-alpha inhibitors are available only for patients with severe disease, and in whom ciclosporin is contraindicated or ineffective. The Committee noted that, in the clinical expert's opinion, the benefit of TNF-alpha inhibitors for ulcerative colitis will be similar to that for Crohn's colitis. The Committee concluded that the clinical experience with TNF-alpha inhibitors for Crohn's disease may provide insight into the potential value of these agents for ulcerative colitis.

- 4.64 The Committee discussed with the clinical expert the criteria for stopping treatment that are applied with TNF-alpha inhibitors. It heard that patients normally have induction therapy for 8 to 14 weeks before response is assessed. If no response is achieved at the end of the induction therapy, treatment will be reconsidered and is likely to be stopped. However, if only a partial response was achieved, clinicians may or may not choose to stop treatment because there are no rigid criteria for stopping treatment in these circumstances. The Committee also heard that the difference between response and remission is clinically important because remission is typically associated with better long-term outcomes than response. The Committee noted consultation comments suggesting that assessing the disease 1 year after starting TNF-alpha-inhibitor therapy and stopping treatment in patients whose disease has gone into remission is likely to be a clinically and cost-effective treatment strategy, with further treatment only in those whose disease subsequently relapses. The Committee noted the observational evidence cited in the consultation comments to support this strategy, and heard that this evidence suggested that of patients whose disease remitted on an TNF-alpha inhibitor, two-thirds to three-quarters remained in remission when treatment stopped 1 year or later after starting it. Furthermore, in most patients whose disease subsequently relapsed, retreatment with a TNF-alpha inhibitor was successful. The Committee heard from the clinical expert that there were no RCTs that show what happens to patients with ulcerative colitis when TNF-alpha-inhibitor therapy is stopped, but the expert considered the observational evidence to be encouraging and to suggest that continuing therapy is unnecessary when complete remission has been achieved.

The Committee understood that for patients who are in deep remission (defined as absence of clinical symptoms and evidence of mucosal healing by colonoscopy or a surrogate marker such as faecal calprotectin, see [NICE's diagnostics guidance on faecal calprotectin diagnostic tests for inflammatory diseases of the bowel](#)), the longer the duration of remission the more likely the patient will stay in remission after TNF-alpha-inhibitor therapy is stopped. The Committee heard from patient experts that they would not be concerned about stopping treatment when remission can be maintained and they no longer need to be on therapy. The clinical expert stated that for patients whose disease relapses after stopping TNF-alpha-inhibitor therapy, measuring drug and drug-specific antibody levels in the blood can help determine whether or not to re-treat the patient with a TNF-alpha inhibitor, although these tests are not yet in routine use in the NHS. The Committee appreciated that it would be difficult to adhere to rigid criteria for stopping treatment in clinical practice. However, having heard the clinical and patient experts' views on this matter, it concluded that stopping TNF-alpha-inhibitor therapy after 1 year for patients whose disease goes into remission would be an acceptable treatment strategy for patients and clinicians.

- 4.65 The Committee further discussed the criteria for stopping TNF-alpha-inhibitor therapy in the context of NICE guidance for Crohn's disease. It noted that the guidance recommends that TNF-alpha inhibitors be given 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 to determine whether ongoing treatment is still clinically appropriate. Continuing treatment is recommended only if there is clear evidence of ongoing active disease. For all patients who are in stable clinical remission after 12 months of treatment, the guidance recommends considering a trial withdrawal from treatment. People who continue treatment should then 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. The Committee discussed with the clinical expert whether TNF-alpha inhibitors could be used in clinical practice for ulcerative colitis in the same way as they are for Crohn's disease, and heard that this type of stopping rule could work in patients with ulcerative colitis. It also heard that in most patients with Crohn's disease who stopped TNF-alpha-inhibitor therapy and subsequently experienced a disease

relapse, the disease responded well to reintroduction of TNF-alpha-inhibitor therapy. The Committee would have liked to consider further evidence that shows the treatment outcome in patients with ulcerative colitis who stop TNF-alpha-inhibitor therapy after entering into remission, but there was not any. Having heard that ulcerative colitis and Crohn's disease are associated with similar functional changes in the bowel (see section 4.63), the Committee concluded that the criteria for stopping treatment in [NICE's technology appraisal guidance on infliximab and adalimumab for the treatment of Crohn's disease](#) could also be applied for ulcerative colitis, which would align the treatment strategies for 2 conditions.

Clinical effectiveness

- 4.66 The Committee discussed whether the RCTs identified by the Assessment Group were generalisable to UK clinical practice. It heard from the clinical expert that the inclusion criterion for disease severity used in the RCTs (Mayo score of 6 to 12) represents patients who would be considered to have moderately to severely active disease in clinical practice in the NHS. However, the clinical expert pointed out that the trials typically excluded patients with ulcerative proctitis. They explained that this is a chronic condition with symptoms that do not respond to treatment but that it is not acute, so patients are not admitted to hospital even though their condition may be significantly disabling. In the clinical expert's opinion, it is important to consider clinical effectiveness in these patients because their disease seems to respond to TNF-alpha-inhibitor treatment and they are not usually suitable for colectomy because of how the disease is distributed in their bowel. The Committee noted consultation comments suggesting that most patients in the trials had moderate disease that was stable. In UK clinical practice, however, TNF-alpha inhibitors would be reserved for patients with more severe disease and for those whose disease is corticosteroid-refractory or corticosteroid-dependent. It heard from the clinical expert that in the trials 85% and 15% of patients had moderate and severe disease respectively, and that in clinical practice patients in whom TNF-alpha-inhibitor therapy would be considered are more likely to have severe, rather than moderate, disease. The Committee also noted that the average age of patients in the RCTs ranged from 37 to 42.5 years, whereas in clinical practice patients starting treatment would be younger because the peak incidence of

ulcerative colitis is between 15 and 25 years of age. The Committee appreciated that patients included in clinical trials may be fitter and have more stable disease than most people seen in clinical practice. However, it concluded that considering the clinical trial data was useful because these represented the key evidence on the clinical effectiveness of TNF-alpha inhibitors for ulcerative colitis.

- 4.67 The Committee considered the RCTs for adalimumab, golimumab and infliximab. It noted that the proportion of patients whose disease responded or remitted in the placebo groups of the RCTs indicated that a proportion of patients were still benefiting from drug therapy, and that the trials included patients in whom surgery was unlikely to be considered an acceptable option at that point in the treatment pathway. The Committee noted that in most RCTs the TNF-alpha inhibitors were associated with a statistically significant favourable effect compared with placebo. It therefore concluded that the TNF-alpha inhibitors were clinically effective compared with placebo in the RCTs.
- 4.68 The Committee considered the Assessment Group's network meta-analysis. It noted that this was based on the clinical trials that included a smaller proportion of patients with severe disease than would be seen in clinical practice (see section 4.66). The Committee heard from the Assessment Group that the trial evidence had been synthesised in the best way possible in the network meta-analysis. However, the Assessment Group stated that there was not enough evidence to estimate the relative treatment effect for moderate and severe disease separately, which the Committee considered to be a limitation of the analysis. The Committee noted that, although all TNF-alpha inhibitors had a statistically significant favourable effect compared with placebo for induction therapy, the difference for maintenance therapy was not statistically significant except for adalimumab for 1 maintenance outcome. It also noted that the credible intervals around the point estimates were wide, reflecting imprecise and uncertain estimates. The Committee heard from the clinical expert that, in their experience, all TNF-alpha inhibitors have the same effectiveness for moderately to severely active ulcerative colitis but patients may choose 1 over the other depending on their preferred method of administration. The Committee agreed that the uncertainty in the results of the network meta-analysis did not allow a conclusion to be drawn about the relative effectiveness of TNF-alpha inhibitors, but there was no positive evidence that they were different.

4.69 The Committee discussed the clinical effectiveness of infliximab in children and young people. It heard from the clinical expert that there was no biologically plausible reason for the effect of infliximab to differ according to the age of patients. The Committee considered the RCT evidence in children and young people noting that this consisted of 1 open label RCT that compared 2 infliximab regimens. The Committee was aware that the trial included patients with moderately to severely active ulcerative colitis, although infliximab is licensed in children and young people for severely active disease only. It heard from the clinical expert that although 50% to 60% of patients in the trial had been treated before with azathioprine, compared with 40% in the adult trials, the efficacy of infliximab was broadly similar in the 2 populations. The clinical expert considered this to have shown that infliximab had a favourable effect in children and young people who appeared to have more severe disease than patients in the adult trials. The Committee also heard that children are more likely to have a shorter duration of disease which is associated with better treatment outcomes. Acknowledging the limitations in the RCT for children and young people, the Committee concluded that infliximab was likely to be clinically effective in children and young people but it could not determine the size of the treatment effect from the available evidence.

Cost effectiveness

4.70 The Committee considered the Assessment Group's approach to modelling the effectiveness of TNF-alpha inhibitors. It noted that the Assessment Group extrapolated the results of its network meta-analysis to inform the modelling throughout the patients' lifetime. The Committee was aware that the network meta-analysis was based on the RCTs identified from the systematic review, which provided data over a maximum of 54 weeks. It was also aware that, although the network meta-analysis was well conducted, it estimated the effectiveness of TNF-alpha inhibitors for patients with moderate to severe disease and not for those with more severe disease who would start treatment at a younger age than patients in the trials. Furthermore, the wide credible intervals around the point estimates reflected uncertain results, and this uncertainty was propagated across the model by the extrapolation. The Committee concluded that the extrapolation of short-term trial data over a lifetime time horizon introduced further uncertainty about the health benefits of TNF-alpha inhibitors

estimated by the model.

- 4.71 The Committee considered the Assessment Group's model in which it was assumed that patients whose disease responds or remits on TNF-alpha-inhibitor therapy continue treatment until that benefit is lost. It noted that, as a result of this assumption, no patient in the model had a TNF-alpha inhibitor for longer than 3 years. The Committee heard from the clinical expert that, of patients who start on a TNF-alpha inhibitor, one-third to one-half are expected to continue therapy in the long term. It also noted that the patient experts who attended the meeting had been on a TNF-alpha inhibitor for longer than 3 years. The Committee recognised that some patients might have TNF-alpha-inhibitor therapy for prolonged periods and that these patients were not represented in the model. Without further evidence on the cost effectiveness of continuing or stopping TNF-alpha-inhibitor therapy in different clinical circumstances, the Committee concluded that the criteria in NICE's technology appraisal guidance on infliximab and adalimumab for the treatment of Crohn's disease could also be applied in this appraisal (see section 4.65). However, it appreciated that it would be difficult to model any such criteria given the lack of efficacy data for TNF-alpha inhibitors (including response and relapse rates) beyond the durations of the trials.
- 4.72 The Committee discussed the most appropriate sources of utility values for ulcerative colitis, noting that the results of the Assessment Group's model were highly sensitive to the utility values used, specifically to the difference between the values for patients having medical treatment and those having surgery. The Committee noted that the Assessment Group considered the utility studies by Woehl et al. and Swinburn et al. to be the most useful for this population. The Assessment Group indicated that it had chosen the study by Woehl et al. for its base case because this study used a preference-based measure of health-related quality of life and provided utility data for most states in the model. In addition, it stated that, based on expert opinion, the utility value after surgery should be similar to the utility value for mild disease, which was the case in Woehl et al. (post-surgery 0.71; mild disease 0.76) but not in Swinburn et al. (post-surgery 0.59; mild disease 0.80). The Committee heard from the clinical expert that, although the study by Woehl et al. included 180 patients, only 19 had ileostomies and 10 had pouches; this introduced uncertainty in the utility value after surgery estimated by this study. The Committee considered that if the utility after surgery is similar to the utility for mild disease, patients may be indifferent

between having surgery or medical treatment. However, it heard from patient experts that surgery is likely to be considered as a last line of treatment when all other options had failed. The Committee was aware that both studies by Woehl et al. and Swinburn et al. were available in abstract form only and provided little detail on the patient characteristics at baseline, which made the interpretation of the findings difficult. The Committee concluded that, although there was considerable uncertainty around the validity of the utility values reported in the studies by Woehl et al. and Swinburn et al., these studies represented the most relevant evidence on the quality of life of patients with ulcerative colitis.

- 4.73 The Committee discussed the data on health-related quality of life used in the economic analysis. It noted the consultation comments suggesting that the utility value for patients who had surgery was overestimated in Woehl et al. The Committee was aware that, in the model, the benefit of surgery was maintained until the patient dies, whereas for patients having TNF-alpha inhibitors the utility values varied over time as patients transitioned between the different states. Therefore, it was particularly important to capture the difference in utility between the 2 states accurately. The Committee heard from the clinical expert that several studies illustrated the poor quality of life of patients after surgery, resulting from post-surgical complications including reduced fertility and faecal incontinence (see section 4.60). Furthermore, the responses to consultation received from patients, either through patient groups or the NICE website, suggested that quality of life after surgery is worse than that reported by Woehl et al. The Committee was aware that patients with more severe disease (who, in clinical practice, are more likely to have TNF-alpha inhibitors) are likely to experience a greater change in their quality of life from treatment. This, in turn, would generate more QALY gains and improve the cost effectiveness of the treatment. The Committee concluded that the study by Woehl et al. is likely to have overestimated the utility value for patients who had surgery.
- 4.74 The Committee discussed whether the changes in health-related quality of life had been adequately captured in the economic analysis. It heard from patient experts that the emotional distress that patients experience when preparing for surgery is difficult to take into account in the QALY calculation, and so is the fact that some patients will want to avoid surgery. The Committee was aware that surgery is an irreversible step, with potential long-term complications and negative consequences on the patient's wellbeing, which can all affect the

patient's ability to live a normal life in various ways (see section 4.60). Because of this, the Committee agreed that it would be difficult to capture all aspects of the patient's quality of life after surgery in the descriptive system of the EQ-5D, particularly the emotional aspects and the long-term effects such as reduced fertility. The Committee concluded that these are important issues affecting the quality of life of patients with ulcerative colitis which should be taken into account, particularly for young people who may not cope well with the consequences of surgery and in whom the impact of surgery may be different. However, on this occasion, the Committee was not satisfied that they had been adequately captured in the economic analysis.

- 4.75 The Committee noted comments suggesting that the use of corticosteroids was assumed to be same in the model whether the patient was having TNF-alpha-inhibitor or conventional therapy, although in clinical practice, one of the aims of TNF-alpha-inhibitor therapy is to avoid using corticosteroids. The Committee noted that, although corticosteroids themselves are cheap, they are associated with multiple consequences that can be costly (see section 4.62), and these costs were not included in the model. The Committee concluded that the model should include higher rates of corticosteroid use among patients having conventional therapy than among those having TNF-alpha inhibitors, together with the cost of treating the side effects of corticosteroids. The Committee was also aware that a utility decrement would be associated with the side effects of corticosteroids, which would favour treatment with TNF-alpha inhibitors.
- 4.76 The Committee discussed the rate at which patients have surgery in the model, noting that the Assessment Group used a study by Solberg et al. to estimate this rate at 1.02% per year. The Committee heard from the clinical expert that this study was likely to have underestimated the rate of surgery because it included newly diagnosed patients and patients with any degree of disease severity. They thought that in clinical practice, 10% to 15% of patients are likely to have had surgery in their first year after diagnosis and up to 40% are likely to have had it at 10 years. The Assessment Group indicated that no study was ideal or reflected the more severe population that would receive TNF-alpha inhibitors in clinical practice, but that it had chosen the study by Solberg et al. because this study did not specifically relate to patients who had experienced a flare-up of ulcerative colitis. However, the Assessment Group agreed that the appropriate rate of surgery to include in the model was highly uncertain. The Committee noted that

the rate of surgery in the trials for TNF-alpha inhibitors ranged from 0.7% to 5.8% in the individual trial groups at 1 year, but heard from the clinical expert that these rates are lower than those observed in clinical practice where patients are likely to have more severe disease. The Committee noted that when the Assessment Group increased the rate of surgery, the ICERs for the medical options remained high because surgery was included in the model as a possible downstream intervention after all medical options and occurred at similar rates for patients who had a TNF-alpha inhibitor and for those who had conventional therapy. The Committee heard, however, that after TNF-alpha-inhibitor therapy, surgery rates are expected to be lower because TNF-alpha inhibitors are given with the intention to avoid surgery, and that observational studies showed that the growing use of TNF-alpha inhibitors reduced the need for surgery. The Committee concluded that the actual rate of surgery is likely to be higher in clinical practice and that different rates of surgery should be applied for patients who have a TNF-alpha inhibitor and those who have conventional therapy. The Committee, however, acknowledged the scarcity of the evidence on the appropriate rates of surgery for each of these cohorts.

- 4.77 The Committee considered the consultation comments suggesting that the cost of surgery was underestimated in the Assessment Group's model. The comments indicated that the Assessment Group assumed that patients have only 1 procedure, whereas on average they will have 2 or more procedures. The Committee understood that most patients in the UK will first have a colectomy with an ileostomy, and while some patients will keep their ileostomy in the medium to long term, others will have a second and third procedure to create an ileo-anal pouch. The Committee noted that maintaining the ileostomy in the medium to long term and caring for the stoma are associated with costs that were not included in the original model. Alternatively, the patient may have a colectomy with ileal pouch-anal anastomosis, which may require up to 3 procedures; first to remove the colon and create an ileostomy, then to remove the rectum and form the ileum into a pouch, then to close the ileostomy and reattach the small intestine to the pouch. The Committee also heard from patient experts that at some point after surgery the stoma may need to be revised or the pouch may need to be redone, but the expert could not estimate the proportion of patients who undergo such procedures. The Committee concluded that the cost of surgery was underestimated in the model; however, it agreed that there were insufficient data to model the number of procedures required for the

patient, and the frequency of, and costs associated with, each of these procedures.

4.78 The Committee discussed the cost-effectiveness estimates from the Assessment Group's and the companies' models. It agreed that, for most patients with ulcerative colitis, surgery was not a relevant comparator for TNF-alpha inhibitors. The Committee noted that the company's models for infliximab and golimumab did not include conventional therapy as a comparator. In the company's model for adalimumab, the base-case ICER for adalimumab compared with conventional therapy was £34,400 per QALY gained. This was revised to £23,000 per QALY gained in response to consultation on the assessment report; a revision not critiqued by the Assessment Group. The Committee noted that when the Assessment Group compared medical options only, infliximab was dominated by adalimumab, and golimumab was extendedly dominated by adalimumab and conventional therapy. The base-case ICER for adalimumab compared with conventional therapy was £50,600 per QALY gained. For children and young people, the Assessment Group estimated an ICER of £68,400 per QALY gained for infliximab compared with conventional therapy. The Committee took note of the range of ICERs presented in this appraisal and agreed that there was a high degree of uncertainty associated with the following aspects in the models:

- The assumptions about the sequencing and timing of conventional therapies in the pathway of care for ulcerative colitis.
- The effectiveness of TNF-alpha inhibitors in patients in whom these agents are likely to be used in clinical practice; that is, patients with more severe disease who would start treatment at a younger age than patients in the trials.
- The optimal duration of treatment with TNF-alpha inhibitors.
- The long-term benefits of TNF-alpha inhibitors (that is, beyond the trial durations).
- The appropriate rate of surgery.
- The benefit of TNF-alpha inhibitors in terms of avoiding or delaying surgery.
- The cost of surgery and post-surgical care.

- The utility values for patients at the different points in the pathway of care for ulcerative colitis, particularly for patients who had surgery.
- The effect of TNF-alpha inhibitors on reducing corticosteroid use, with the associated long-term cost and health benefits.

It was also unclear to the Committee if and how all the above would differ for children and young people because much of the evidence did not relate to this population. After considering the consultation comments and the views of the experts, the Committee concluded that all the models presented to it had shortcomings that inhibited the accurate estimation of the cost effectiveness of TNF-alpha inhibitors for ulcerative colitis.

4.79 The Committee discussed whether further analyses were warranted to address its concerns about the modelling. It noted that there was no explicit treatment pathway for ulcerative colitis because treatment tends to be individualised based on, among other factors, the patient's preferences and tolerability to treatments, as well as the duration and severity of the disease and how the inflammation is distributed in the colon. The choice of treatment also takes into account the patient's age and personal circumstances, and weighs the benefit of treatment against the potential long-term consequences on the patient's health and wellbeing. Because of this, the Committee agreed that it would be challenging to make accurate assumptions about the pathway of care for ulcerative colitis and to model the proportion of patients who would follow each possible pathway. In addition, there was limited evidence to inform the uncertain parameters in the model and it would be difficult to source robust data for these parameters. The Committee also noted that there was inherent uncertainty arising from extrapolating the efficacy of TNF-alpha inhibitors from trials with maximum follow-up of just over 1 year (56 weeks) over a lifetime time horizon, and that the trials themselves did not totally represent patients in clinical practice (see section 4.66). Therefore, the Committee took the view that the existing evidence would not allow the long-term benefits of TNF-alpha inhibitors to be estimated in such a way that could usefully inform the clinical and cost effectiveness of these agents in practice. Although the Committee would have liked to have seen robustly modelled ICERs for TNF-alpha inhibitors, in its judgement revising the model was, on the whole, unlikely to estimate cost effectiveness with significantly more certainty than currently available to the Committee, and further

analyses to explore the cost effectiveness of TNF-alpha inhibitors were unlikely to represent an efficient use of resources. The Committee concluded that further analyses were not warranted given the existing evidence.

4.80 The Committee discussed whether or not it could recommend the use of TNF-alpha inhibitors for ulcerative colitis. It noted that the uncertainty around the costs and QALYs for TNF-alpha inhibitors, in addition to the potential uncaptured QALY benefits (see section 4.74), meant that the costs are likely to be overestimated and the QALYs underestimated, which when taken together, would improve the cost effectiveness of TNF-alpha inhibitors. In addition, applying the criteria for continuing and stopping TNF-alpha inhibitors (see section 4.71) would further improve the cost effectiveness of treatment. The Committee was aware that, aside from the TNF-alpha inhibitors, there have been relatively few advances in the management of ulcerative colitis and the available treatment options remain limited. It acknowledged that TNF-alpha inhibitors represent a significant change in the management of ulcerative colitis by adding to the options available to clinicians to treat the condition, and that this was not adequately captured in the QALY calculation. The Committee noted from the clinical expert at the meeting and the professional groups that responded to consultation that often there are only subtle clinical differences between ulcerative colitis and Crohn's colitis and that, for this reason, clinicians would like the treatment strategy for the 2 conditions to be aligned. The Committee concluded that the costs were likely to have been overestimated and the QALYs underestimated. As a consequence, it was likely that TNF-alpha inhibitors could be considered a cost-effective use of NHS resources for treating active ulcerative colitis in patients whose disease has responded inadequately to conventional therapy, or who cannot tolerate, or have medical contraindications for, such therapy, particularly if the same criteria for stopping treatment as in NICE's technology appraisal guidance on infliximab and adalimumab for the treatment of Crohn's disease were applied.

4.81 The Committee was aware that biosimilar versions of infliximab are licensed for the same indications as the reference product, although they are not yet available in the UK. It discussed whether the guidance on infliximab should also apply to the biosimilars. The Committee noted that the European Medicines Agency was content that the pharmacokinetics, efficacy, safety, and immunogenicity profiles of the biosimilars were similar to those of the reference product. The Committee

concluded that its recommendations for infliximab could apply both to the reference product and to its biosimilars.

- 4.82 On the basis of the considerations in sections 4.79 and 4.80, the Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy, or who cannot tolerate, or have medical contraindications for, such therapy. For golimumab, this is only if the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme. The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available, taking into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).
- 4.83 The Committee also concluded that infliximab could be recommended for treating severely active ulcerative colitis in children and young people aged 6 to 17 years whose disease has responded inadequately to conventional therapy, or who cannot tolerate, or have medical contraindications for, such therapy.

5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has ulcerative colitis and the healthcare professional responsible for their care thinks that infliximab, adalimumab or golimumab is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members, guideline representatives and NICE project team

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 4 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.

Professor Iain Squire (Chair)

Consultant Physician, University Hospitals of Leicester

Dr Jane Adam (Vice-Chair)

Consultant Radiologist, St George's Hospital, London

Dr Graham Ash

Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Simon Bond

Senior Statistician, Cambridge Clinical Trials Unit

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant

GP, Swadlincote, Derbyshire

Mr Matthew Campbell-Hill

Lay member

Professor Aileen Clarke

Professor of Public Health & Health Services Research, University of Warwick

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University of Salford

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital, Bristol

Dr Ian Lewin

Honorary Consultant Physician and Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, Health Economics Research Group, Brunel University

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Dr Alec Miners

Senior lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Mrs Sarah Parry

Clinical Nurse Specialist, Paediatric Pain Management, Bristol Royal Hospital for Children

Mrs Pamela Rees

Lay member

Dr Ann Richardson

Lay member

Ms Ellen Rule

Director of Transformation and Service Redesign, Gloucestershire CCG

Dr Sharon Saint Lamont

Head of Clinical Quality, NHS England (North)

Mr Stephen Sharp

Senior Statistician, University of Cambridge Medical Research Council Epidemiology Unit

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital

Dr Peter Sims

GP, Devon

Mr Cliff Snelling

Lay member

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr David Thomson

Lay member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project

manager.

Ahmed Elsada

Technical Lead

Joanna Richardson and Fay McCracken

Technical Advisers

Bijal Joshi

Project Manager

7 Sources of evidence considered by the Committee

The assessment report for this appraisal was prepared by the School of Health & Related Research, The University of Sheffield:

- Archer R, Tappenden P, Ren S, et al. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262): Clinical effectiveness systematic review and economic model, June 2014

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). Companies, professional or expert and patient or carer groups, and other consultees, were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

Companies:

- AbbVie (adalimumab)
- Celltrion Healthcare (infliximab)
- Merck Sharp & Dohme (golimumab, infliximab)

Professional or expert and patient or carer groups:

- British Society of Gastroenterology
- British Society of Paediatric Gastroenterology, Hepatology and Nutrition
- Crohn's and Colitis UK
- Royal College of Nursing
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

Other consultees:

- Department of Health
- NHS England
- Welsh Government

Commentator organisations (without the right of appeal):

- Department of Health and Social Services and Public Safety, Northern Ireland (DHSSPSNI)
- Healthcare Improvement Scotland
- National Institute for Health Research Technology Assessment Programme
- Pfizer (sulfasalazine)
- School of Health & Related Research University Sheffield

The following individuals were selected from clinical expert and patient expert nominations from the 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, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262) by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr A Barney Hawthorne, Consultant Gastroenterologist, nominated by organisation representing British Society of Gastroenterology – clinical specialist
- Ms Julie Duncan, Clinical nurse specialist – Inflammatory Bowel Disease & Inflammatory Bowel Disease Network National Committee Chair, nominated by organisation representing Royal College of Nursing – clinical specialist
- Mr Mark Byrne, nominated by organisation representing Crohn's and Colitis UK – patient expert
- Mr Joseph Fitzgerald, nominated by organisation representing Crohn's and Colitis UK – patient expert

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

- AbbVie (adalimumab)
- Celltrion Healthcare (infliximab)
- Merck Sharp & Dohme (golimumab, infliximab)

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