NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Crohn's Disease – adalimumab and infliximab

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD 3)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Abbott	**Abbott's response to the Appraisal Consultation Document 3 of adalimumab and infliximab for the treatment of Crohn's disease** Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD3) prepared by the Committee for the appraisal of adalimumab and infliximab for the treatment of Crohn's disease. Abbott's comments are set out under section headings containing the questions NICE asks consultees to comment on for the ACD. **Executive Summary** Abbott considers that the recommendation that all patients should stop therapy at 1 year regardless of their clinical status is not an appropriate recommendation for the treatment of severe patients with Crohn's disease. The previous recommendation in ACD2 allowing the flexibility of clinicians and patients to discuss the need to continue therapy is pragmatic and appropriate as this would allow patients at high risk of relapse and hospitalisation or surgery to continue therapy based on a full consideration of the risks and benefits of treatment continuation. It should be noted that the Bodger *et al.* modelling study indicated that maintenance therapy with adalimumab and infliximab would reach a cost per QALY of £30,000 at 34 years continuous therapy and 4 years respectively. Despite being based on the Olmsted County cohort of mixed severity patients discussed extensively in previous correspondence, the results of this analysis indicate that maintenance therapy beyond 1 year would be cost effective. Therefore, Abbott considers that on cost effectiveness grounds restricting treatment to 1 year of maintenance therapy is unwarranted	Comment noted. The comments summarised here in the Executive Summary are addressed individually below.

Consultee	Comment	Response
	and overly restrictive. Abbott considers it unlikely that treatment of CD patients using infliximab would be less costly than treating patients with adalimumab, and that on average infliximab is likely to be significantly more costly. Based on an indirect comparison of the largest RCTs of maintenance for adalimumab and infliximab, the evidence is not supportive of a requirement for greater dose escalation for patients with adalimumab. The ACD3 currently states: "*Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active <u>non-fistulising</u> Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy.*" This recommendation is not in line with the adalimumab licence or the available evidence. The licence for adalimumab does not specify a sub-group of severe patients with non-fistulising disease; it instead encompasses all patients with severe disease, a proportion of whom will have fistulising disease. Therefore, Abbott requests that when the Committee prepares the Final Appraisal Determination, that the wording in paragraph 1.1 is amended to:" *Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe, active Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy.*"	

Consultee	Comment	Response
Abbott	**1. Do you consider that all of the relevant evidence has been taken into account?** As previously indicated in comments on the ACD2 for this appraisal, Abbott considers it unlikely that treatment of CD patients using infliximab would be less costly than treating patients with adalimumab, and that on average infliximab is likely to be significantly more costly[1]. Consultation received by the Institute on ACD2 highlighted that dose escalation with adalimumab may mean that infliximab may be the less costly treatment option. Section 1.1 below sets out supportive evidence not previously seen by the Committee that adalimumab is not associated with greater rates of dose escalation than infliximab and that therefore adalimumab is likely to be significantly less costly than infliximab. It also appears that there is a concern regarding the long term effectiveness and safety of anti-TNF agents. Section 1.2 highlights the available data for periods of treatment greater than one year with adalimumab.	Comment noted. The comments summarised here are addressed individually below.
Abbott	**1.1 Impact of dose escalation on comparative cost of adalimumab and infliximab** As highlighted in the ACD3 document, adalimumab is a lower cost treatment option than infliximab at the recommended maintenance dose of 40mg every other week compared to 5mg/kg for infliximab. However, comments made in consultation have questioned whether the cost difference would be reduced by a greater requirement to dose escalate in patients receiving adalimumab. There are a	Comment noted. The additional data on dose escalation submitted by both manufacturers in response to ACD3 was

[1] Abbott response to ACD2 of adalimumab and infliximab for Crohn's disease. 5 October 2009.

Consultee	Comment	Response
	number of important points that Abbott wishes to highlight in relation to this issue. It is unclear why the dose escalation rates available from the CHARM study of maintenance therapy have not been considered as this is the largest, randomised maintenance trial of adalimumab in Crohn's Disease (n=854) as is the most appropriate for comparison with the ACCENT I maintenance study for infliximab. In CHARM, 27% of patients escalated to adalimumab weekly dosing by week 56 compared to 30% of infliximab patients in the ACCENT RCT by week 54. Therefore, based on an indirect comparison of the largest RCTs of maintenance for adalimumab and infliximab, the evidence is not supportive of a requirement for greater dose escalation for patients with adalimumab. Two other aspects of the CHARM data are also worthy of further consideration when considering the likely dose escalation of the two anti-TNFs. Firstly, 49.6% of patients receiving adalimumab in the CHARM trial had been previously treated with infliximab[2]. Given the refractory nature of this segment of the patient population in CHARM compared to ACCENT, it would be expected that a greater proportion of adalimumab patients would dose escalate in CHARM compared to infliximab patients in ACCENT, which was not the case. Secondly, available data indicate that some patients in CHARM having a disease flare were able to regain disease control without escalating to weekly therapy. It is important to consider additional evidence on dose escalation rates with adalimumab and infliximab. A	sent to and discussed by the Appraisal Committee. For more information on the discussion of dose escalation by the Appraisal Committee, please see the FAD (sections 4.1.15, 4.2.16 and 4.3.16). For more information on the inclusion of dose escalation in the original economic analysis, please refer to the Assessment Group report.

[2] Colombel J, Sandborn W, Rutgeerts P, Enns R, Hanauer S, Panaccione R, Schreiber S, Byczkowski, Li J, Jent J, Pollack P. Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial. *Gastroenterology* 2007;**132**:52-65.

Consultee	Comment	Response
	survey of use of adalimumab in 61 patients across centres in England and Ireland indicated that 16% of patients required dose escalation with adalimumab[3]. An observational study has considered dose escalation rates with adalimumab and infliximab in privately insured CD patients in the US[4]. Importantly, this analysis was restricted to anti-TNF naïve patients for both drugs to allow a fair comparison of dose escalation rates. The study sample included 701 patients initiated on adalimumab and 873 patients initiated on infliximab. Based on 1-year follow-up using a Kaplan-Meier analysis, patients treated with adalimumab had a significantly lower rate of dosage escalation compared with patients treated with infliximab (24.3% vs. 55.1%; $p<0.01$). Cox regression analysis also demonstrated that adalimumab was associated with a significantly smaller risk of dose escalation (HR=0.57; $p<0.01$) compared with infliximab. One of the key strengths of this analysis is that it compares dose escalation rates in similar patient populations over a similar length of follow-up. However, the authors provide the caveat that payer restriction might be a reason for lesser dosage adjustment with adalimumab, because the opportunity to adjust is specified only in the label for infliximab in the US. In conclusion, taking into consideration the similar dose escalation rates observed in the CHARM and ACCENT studies despite the inclusion of a potentially more refractory disease population for patients receiving adalimumab, as well as the greater dose escalation rates observed in US clinical practice for infliximab, Abbott considers that the available evidence indicates that adalimumab is likely to be associated with lower rates of dose escalation than infliximab.	

[3] Russo EA, Iacucci M, Lindsay JO, Campbell S, Hart A, Hamlin J, Orchard T, Arebi N, Nightingale J, Jacyna MR, Gabe SM, O'Connor M, Harris AW, O'Morain C, Ghosh S. Survey on the use of adalimumab as maintenance therapy in Crohn's disease in England and Ireland. Eur J Gastroenterol Hepatol. 2009 Jun 12.

[4] Plevy S, Lu M, Yu AP, Sharma H, Chao J, Mulani PM. Observational Study of Treatment Patterns in Patients Newly Initiated With Adalimumab or Infliximab Therapy for Crohn's Disease. P287 Poster presentation at the American College of Gastroenterology Annual Scientific Meeting, October 23–28, 2009, San Diego, California.

Consultee	Comment	Response
Abbott	**1.2 Data on use of adalimumab for greater than 1 year in CD** During the 5th Appraisal Committee meeting on 22 October 2009, members of the Committee raised concerns around the risk: benefit profile of the anti-TNFs, particularly around the long-term safety and efficacy of these drugs. In Abbott's response to the WMHTAC in July 2008, Abbott provided evidence showing sustained efficacy of adalimumab for up to 2 years, as well as 2,374 patient years worth of safety data. Since these data were outlined, longer-term data have become available which show that patients with moderately to severely active Crohn's disease treated with adalimumab have sustained clinical remission for up to three years. Panaccione *et al* presented data from the ADHERE study (Additional Long-Term Dosing With HUMIRA to Evaluate Sustained Remission and Efficacy in CD), at the 2009 ECCO meeting[5]. ADHERE is the long-term extension study to the one year randomised study CHARM. A total of 467 patients enrolled in the open-label extension trial. Remission results for the 145 patients initially randomised to adalimumab who were in remission (CDAI < 150) at the end of CHARM are shown in Table 1.2.1. As can be seen from the table, 83% (120 of 145) of patients were in remission 3 years after enrolment in CHARM (Week 108 of the open-label extension) in the post-hoc LOCF analysis. **(Table 1.2.1 not reproduced here. Please refer to comments from manufacturer for more information)** Furthermore, no new safety signals were identified through the three years of adalimumab exposure in	Comment noted. The additional data submitted by the manufacturer on the efficacy and safety of adalimumab for treatment lasting longer than one year was sent to and considered by the Appraisal Committee. For more information on the discussion of long term efficacy and safety by the Appraisal Committee, please see the FAD (sections 4.1.14 and 4.3.15).

[5] Panaccione R, Colombel JF, Sandborn WJ, Rutgeerts P, Haens GR, Lomax KG, Li J, Pollack P. Adalimumab maintains long-term remission in moderately to severely active Crohn's disease through 3 years of therapy. Journal of Crohn's and Colitis Volume 3, Issue 1, February 2009, Pages S69-S70

Consultee	Comment	Response
	patients with Crohn's disease. In a recent review of the safety of adalimumab in the global clinical trials of Crohn's Disease, over 50% (1652/3160) of the patients had been followed for more than one year[6]. The authors concluded that the rate of adverse events observed in Crohn's disease patients were comparable to other approved indications for adalimumab spanning greater than 10 years of clinical observation. Another concern raised was the perception that concurrent steroids were a requirement for continued adalimumab treatment which is not the case. Indeed, there are also 3 year data showing continued steroid free remission in patients with moderate to severely active Crohn's disease[7]. This *post-hoc* sub-analysis evaluated data from the intention-to-treat population of patients receiving steroids at baseline who were randomised to adalimumab and assessed for steroid-free remission at 3 years from CHARM baseline. Remission rates were calculated using non-responder imputation (NRI) analysis. Results showed that at 2 and 3 years after CHARM baseline, respectively, 27% and 28% of these patients were in steroid-free remission (Table 1.2.2). **(Table 1.2.2: not reproduced here. Please refer to comments from manufacturer for more information)** Therefore, there is a considerable evidence base (newly documented in this response and previously supplied to the Institute) that demonstrates the safety and efficacy of adalimumab beyond one year of	

[6] Colombel JF, Sandborn WJ, Panaccione R, Robinson AM, Lau W, Li J, Cardoso AT. Adalimumab safety in global clinical trials of patients with Crohn's disease. Inflamm Bowel Dis. 2009 Sep;15(9):1308-19.

[7] Kamm MA, Hanauer SB, Panaccione R, Colombel JF, Sandborn WJ, Lomax KG, Pollack PF. Steroid free remission in patients with Crohn's disease who received adalimumab therapy for at least 3 years: long-term results from CHARM. European Crohn's and Colitis Organisation Annual Meeting, February 2009, Hamburg, Germany. Poster No. P83.

Consultee	Comment	Response
	treatment in patients with Crohn's disease that should help alleviate the Committee's concerns on long term safety and efficacy.	
	2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate? In paragraph 1.1 of the ACD3, the recommendations around treatment duration have changed from the wording that the Committee stated in the ACD2. In the ACD2, based on the available evidence, NICE recommended that "*maintenance treatment with adalimumab or infliximab (as indicated in 1.1 or 1.2) should continue until treatment failure (which includes the need for surgery), or until 12 months after the start of treatment, whichever is shorter. The person's disease should then be reassessed. Maintenance treatment should only then be continued if there is clear evidence of ongoing active disease, as determined by clinical symptoms and investigation, including endoscopy if necessary. People whose disease relapses after maintenance treatment is stopped should have the option to resume treatment for a further 12 months. They should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate*." In the ACD3 the wording is as follows: "*Treatment with infliximab or adalimumab may be a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People whose disease relapses after the planned course of infliximab or adalimumab is stopped should have the option to resume treatment for a further 12 months*." However, the summaries of clinical- and cost-effectiveness providing the evidence base for these recommendations have not changed in the move from the ACD2 to ACD3. Therefore, Abbott does not	Comment noted. The additional data submitted by the manufacturer on the efficacy of adalimumab for treatment lasting longer than one year was sent to and considered by the Appraisal Committee. Patient and clinical experts were invited back to attend the Appraisal Committee meeting prior to the FAD. For more information on the clinical and expert evidence, please see the FAD (section 4.1.13).

Consultee	Comment	Response
	understand why this change has been made, particularly as comments received from consultees and commentators, especially patients and clinicians, fully supported the recommendations in the ACD2 around treatment duration. This may be important given that when the discussions around treatment duration were raised again at the 5th Committee Meeting, there were no clinicians or patient experts in attendance to give their expert opinion, as had been sought previously for this issue at the 4th Committee Meeting in August 2009. Sections 4.1 in both ACD documents do not differ in their content. This section summarises data from the induction trials of adalimumab and infliximab, and also data from either 52 weeks (infliximab) or 56 weeks (adalimumab) maintenance treatment, all of which were provided in the original submission. Abbott would like to draw attention to the fact that considerable additional evidence has been submitted since the original evidence submission on 30 July 2007. As there was a delay to this appraisal, a significant amount of time elapsed before the release of the first and subsequent ACDs, in which a substantial amount of additional data from open-label extension trials have been presented and published. These data include information on fistula healing, mucosal healing, reduction in the risk of all-cause hospitalisation, sustained long-term remission data (up to 3 years), and long-term steroid free remission (up to 3 years) (see Abbott response to WMHTAC July 2008 and Section 1.2 above). Therefore, given the fact that the evidence base supporting the safety and efficacy of treatment with adalimumab beyond one year has increased, and that there is no documented new evidence in the ACD3 that supports the arbitrary change in the wording around treatment duration, Abbott considers that the recommendations should revert to the original wording in the ACD2 and allow the clinician discretion to stop treatment when they consider it appropriate.	For more information on the recommendations for continuing treatment with infliximab or adalimumab, please see the FAD (sections 1.1 and 1.4)

Consultee	Comment	Response
	3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS? Abbott considers that two aspects of the provisional recommendations do not constitute a suitable basis for the preparation of guidance to the NHS. Section 3.1 highlights the concern that the recommendations in ACD3 are not in line with the licensed indication for adalimumab for the treatment of severe active CD. Section 3.2 outlines critical concerns regarding an inflexible 12-month stopping rule for all patients. **3.1 The recommendation that adalimumab is only for non-fistulising disease is not in line with the licensed indication.** Both adalimumab and infliximab are licensed for the treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. According to the ACD3, patients fulfil the criteria for severe disease if they have a CDAI score > 300. The CDAI is a composite score comprising 8 categories describing the signs and symptoms of Crohn's disease. One of the eight categories of the CDAI index includes the following items: 'anal fissure, fistula or abscess; other fistula'. In order to obtain a CDAI score > 300 to qualify for anti-TNF treatment, it is highly likely that a proportion of patients will have fistulising disease forming a part of their total disease severity index measure. This is supported by the fact that 15.2% of patients in CHARM had fistulising disease both at screening and at baseline. Therefore, the definition of severe Crohn's disease stipulated within adalimumab and infliximab licences includes a proportion of severe patients who have fistulising	Comment noted. The Appraisal Committee considered indications for which each drug had received a marketing authorisation and consulted clinical experts on the populations defined in the ACD. The Committee considered it appropriate to amend the recommendations in line with the wording of the marketing authorisations (see FAD section 1.1).

Consultee	Comment	Response
	disease as part of their severe CD symptoms. There are also a proportion of CD patients who have predominantly fistulising Crohn's disease. Indeed, the literature shows that a patient can have fistulae years prior to the onset of luminal Crohn's disease itself[8]. These patients with fistulising disease often do not obtain CDAI scores > 300 because they do not manifest all the other symptoms related to the other 7 domains of the CDAI necessary to attain severe CDAI scores[9]. It is in these patients with fistula but not severe luminal disease as determined by the CDAI score that the wording in the infliximab licence around fistulising disease refers to: "Infliximab is licensed for use in active fistulising Crohn's disease". The median CDAI score in patients in the infliximab ACCENT II fistulising trial (forming the evidence base for the licence) was 180 and 41% of patients had a CDAI < 150 at baseline[10]. The infliximab licence therefore includes patients with severe Crohn's disease (some of whom will have fistulas), and also patients who do not have severe disease but do have the presence of fistulas and are therefore able to use infliximab. The ACD3 currently states: "*Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active <u>non-fistulising</u> Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy.*" The perception of this recommendation as it currently reads is not in line with	

[8] Nielson OH, Hahnloser D, Thomsen O. Diagnosis and management of fistulising Crohn's disease. *Nat Clin Pract Gastroenterol Hepatol* 2009 Feb;**6**(2):92-106.

[9] Yoshida EM. "The Crohn's Disease Activity Index, its derivatives and the Inflammatory Bowel Disease Questionnaire: a review of instruments to assess Crohn's disease". Can. J. Gastroenterol. 1999. 13 (1): 65–73.

[10] Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med. 2004 Feb 26;350(9):876-85.

Consultee	Comment	Response
	adalimumab licence or the available evidence. The licence does not specify a sub-group of severe patients with non-fistulising disease; it instead encompasses all patients with severe disease, a proportion of whom will have fistulising disease. Therefore Abbott requests that when the Committee prepares the Final Appraisal Determination, that the wording in paragraph 1.1 is amended to:" *Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe, active Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy.*" Furthermore, the recommendation in 1.3 for infliximab should be amended to *"Infliximab, within its licensed indication, is recommended as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy*." This would then be in line with both anti-TNF licences and the evidence supporting these.	
Abbott	**3.2 Need for individual consideration of risks and benefits of continuation of therapy beyond 1 year** Abbott considers that the recommendation that all patients should stop therapy at 1 year is not an appropriate recommendation for the treatment of severe patients with Crohn's disease. The previous recommendation in ACD2 allowing the flexibility of clinicians and patients to discuss the need to continue therapy is pragmatic and appropriate as this would allow patients at high risk of relapse and hospitalisation or surgery to continue therapy based on a full consideration of the risks and benefits of treatment continuation. It is unclear why the ACD3 has settled on a maximum of 1 year maintenance therapy for patients	Comment noted. The additional data submitted by the manufacturer on the efficacy of adalimumab for treatment lasting longer than one year was sent to and considered by the Appraisal

Consultee	Comment	Response
	receiving anti-TNF therapy. In this respect it should be noted that the Bodger *et al* modelling study indicated that maintenance therapy with adalimumab and infliximab would reach a cost per QALY of £30,000 at 34 years continuous therapy and 4 years respectively. Despite being based on the Olmsted County cohort of mixed severity patients discussed extensively in previous correspondence, the results of this analysis indicate that maintenance therapy beyond 1 year would be cost effective. Therefore, Abbott considers that on cost effectiveness grounds restricting treatment to 1 year of maintenance therapy is unwarranted and overly restrictive. Abbott acknowledges that there is uncertainty regarding the long term effectiveness and safety of anti-TNF agents for the treatment of Crohn's. However, as outlined in section 1 there are data for periods greater than 1 year to indicate that adalimumab remains an appropriate therapy option from a risk/benefit perspective. Further, the long term safety of adalimumab has been studied in patients with a variety of immune-mediated inflammatory diseases[11]. Conversely, there are no data available to indicate that all patients with Crohn's disease can be safely stopped at 1 year of anti-TNF therapy. Data from Louis *et al.* indicate that some anti-TNF patients on long term steroid-free remission can have their therapy discontinued and not relapse in the short term[12]. However, it is important to note that data for patients in long-term steroid-free remission cannot be extrapolated to indicate that all patients can have their anti-TNF therapy stopped at 1-year without suffering relapse. As noted in the ACD2 response by Schering Plough, no consideration has been made of prognostic factors that could help predict whether a patient is likely to relapse. The long term risk-benefit of continuing anti-TNF therapy will be best agreed between	Committee. The analysis by Bodger *et al.* has been considered by the Appraisal Committee in making their recommendations (see FAD section 4.2.15). The Appraisal Committee reconsidered the population included in the GETAID/STORI study published in abstract form by Louis *et al.* For the Committee discussion relating to this study please refer to the FAD (sections 4.1.13 and

[11] Burmester GR, Mease P, Dijkmans BA, Gordon K, Lovell D, Panaccione R, Perez J, Pangan AL. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis. 2009 Dec;68(12):1863-9.

[12] Louis E, Vernier-Massouille G, Grimaud J, et al. Infliximab discontinuation in Crohn's disease patients in stable remission on combined therapy with immunosuppressors: a prospective ongoing cohort study. Gastroenterology 2009;136:A-146.

Consultee	Comment	Response
	gastroenterologists and patients taking a pragmatic approach based on a consideration of prognostic factors for relapse and the personal circumstances of the patient. For example, consider a patient who has received 1 year of anti-TNF therapy about to start a 3-year university course. If this patient were not in long term steroid-free remission without signs of active disease, rigid application of a 1-year stopping rule as per the ACD3 recommendations would mean this patient should stop anti-TNF therapy before starting his or her university course. This patient would then be at risk of being hospitalised or requiring surgery during this period. If the guidance allowed the gastroenterologist and patient to agree a treatment period for greater than 1 year it may be that the patient would decide to remain on anti-TNF therapy during this period. Given the uncertainty of relapse and patients' fear of relapse and surgery weighed against considerations of long term safety of anti-TNF agents, Abbott considers it is appropriate that clinicians and patients should discuss the need for long term anti-TNF therapy based on a pragmatic consideration of risks and benefits rather than having an arbitrary stopping rule at 1-year. In conclusion, Abbott considers that the previous ACD2 recommendations that anti-TNF therapy could be continued if appropriate beyond 1 year is a more pragmatic recommendation that balances the needs for consideration of clinician and patient preferences with assessments of long term safety and cost-effectiveness. Given that gastroenterologists and patients were strongly in favour of the need for appropriate maintenance therapy Abbott considers that the recommendations in this appraisal should allow anti-TNF therapy for greater than 1-year when this is considered appropriate by clinicians and patients.	4.3.15) The Committee considered the additional evidence for continued treatment and thought it appropriate to amend the recommendations. For more information on the Committee's consideration of the additional evidence and the recommendations for the continuation of treatment with infliximab and adalimumab, please see the FAD (sections 1.1, 1.3 and 1.4).
Abbott	**4. Are there any equality related issues that may need special consideration?** None that Abbott is aware of.	Comment noted.

Consultee	Comment	Response
Schering-Plough	Schering-Plough welcomes the opportunity to comment on the third appraisal consultation document ("ACD3"), published on 19th November 2009, which sets out the appraisal committee's (the "Committee") recommendations on infliximab and adalimumab for the treatment of Crohn's Disease ("CD"). Schering-Plough welcomes the Committee's decision to allow eligible CD patients equal access to infliximab and adalimumab treatment within their licensed indications, and firmly supports this stance, believing it to be in the best interests of patients and clinicians. Nonetheless, we still consider some sections of ACD3 perverse in the light of available evidence and urge the Committee to reconsider the following three points: 1. The guidance to reflect the range of plausible treatment costs with infliximab and adalimumab 2. The guidance to acknowledge the broader evidence base and superior long term outcomes profile of infliximab compared to adalimumab; and 3. The guidance to exclude an obligatory treatment discontinuation rule as it is not based on robust evidence. Schering-Plough has outlined these concerns in detail in the following letter.	Comment noted. The comments summarised here are addressed individually below.
Schering-Plough	**Response to ACD content** ***1. 1 Incorrect representation of infliximab treatment cost in the ACD3*** Schering-Plough welcomes the Committee's acknowledgement of the uncertainty surrounding infliximab treatment costs and its comparison with adalimumab treatment costs, arising out of variations in patient	Comment noted. The additional data on dose escalation submitted by both manufacturers in

Consultee	Comment	Response
	body weight, administrations costs, vial sharing practices and local discounting agreements (section 4.3.11). The uncertainty regarding treatment costs is further augmented due to the higher induction dose used in clinical practice for adalimumab[13,14] and variable dose escalations required for both agents, albeit more frequently for adalimumab compared to infliximab (45.8%[15] vs 30%[16]). Current clinical evidence also suggests that the majority of patients receiving infliximab dose escalations are subsequently able to de-escalate back to 5mg/kg[17]. No such dose reduction evidence exists for adalimumab. Lastly, further real-world evidence suggest dose frequency escalation with adalimumab in the range of 30% to 65.4%.[18,19] Based on the available evidence, a range of plausible induction and maintenance costs estimated by varying some of the above parameters, is displayed in table 1 below. **(Table 1 not reproduced here. Please refer to comments from manufacturer for more information)** In light of the uncertainty regarding the treatment costs, Schering-Plough urges the Committee to acknowledge this in the guidance by presenting a range of plausible administrations costs (TAG 134; Section 4.11, page 14) and a range of plausible treatment costs such as £2,717-£3,556 for induction and £8,828-£14,828 for maintenance for infliximab and £1,546-£2,618 for induction and 9,295-£15,337 for	response to ACD3 was discussed by the Appraisal Committee. For more information on the discussion of dose escalation by the Appraisal Committee, please see the FAD (sections 4.1.15, 4.2.16 and 4.3.16). For more information on the inclusion of dose escalation into the original economic analysis, please refer to the Assessment Group

[13] Rutgeerts et al. Gastroenterology 2009; 136-5, Suppl 1:A-116 (DDW 2009, Abstract 751e)
[14] Hanauer et al. Gastroenterology 2006; 130:323-33.
[15] Sandborn et al. Gut 2007;56;1232-1239
[16] Rutgeerts et al. Gastroenterology 2004;126:402–413
[17] Schnitzler et al. Gut 2009; 58:492-500
[18] Ho et al. Alimentary Pharmacol & Ther 2009; Mar 1;29(5):527-34.
[19] Karmiris et al. Gastroenterology 2009, Aug 5 [Epub ahead of print]

Consultee	Comment	Response
	maintenance for adalimumab (sections 3.6 and 3.10 respectively).	report.
Schering-Plough	***1.2 Interpretation of cost-effectiveness evidence*** The Committee has taken a pragmatic decision to recommend equal access to CD patients for infliximab and adalimumab even though the supporting evidence is inconsistent and incomplete. Schering-Plough welcomes this decision in the context of providing equal access to eligible CD patients. Schering-Plough however, would like to reiterate its position on evidence generation and interpretation phase. The models submitted by the manufacturers, the model developed by the assessment group ("AG") and the economic analysis by an independent group (Bodger et al.)[20] used different structural and parametric assumptions. These models have never been never fully reconciled even though it was deemed essential by the Decision Support Unit ("DSU") to produce robust Incremental Cost Effectiveness Ratios ("ICERs") [DSU report 1 and DSU report 2]. In the absence of full reconciliation, ICERs presented to the Committee from several different analyses are not comparable with each other. In addition, even though multiple cost-effectiveness analyses are available, none of them compare infliximab directly with adalimumab and all of them have significant limitations leading to more conservative ICERs for infliximab than adalimumab. The cost-effectiveness estimates for infliximab are further hampered by use of incorrect infliximab costs and inappropriate assumption of therapeutic equivalence between the two TNF-α inhibitors. The infliximab ICERs thus obtained are conservative and should not directly be compared with adalimumab ICERs in these analyses.	Comment noted. The Appraisal Committee considered the clinical and economic evidence and was aware of the different model designs and assumptions. For more information on the consideration of the evidence, please refer to the FAD (sections 4.3.6 and 4.3.7). The Appraisal Committee considered the additional information submitted in response to ACD2 and ACD3 about the costs of infliximab and adalimumab. For more

[20] Bodger et al. Alimentary Pharmacol Ther 2009; 30:265-74

Consultee	Comment	Response
		information please refer to the FAD (sections 4.3.11 and 4.3.16).
Schering-Plough	***2 Recommendations based on inappropriate conclusion of therapeutic equivalence between the TNF-α inhibitors*** The Committee's present recommendations are based on the assumption of therapeutic equivalence between infliximab and adalimumab. Schering-Plough believes that this assumption is unsupportable and perverse, because: 1. There is no head-to-head trial data available to support this assumption. 2. No formal efficacy comparison has been made between infliximab and adalimumab in any of these analyses. Schering-Plough emphasised this point in our previous responses to the ACD and the DSU report, yet the Committee has not acknowledged or remedied this obvious weakness. 3. The available evidence clearly differentiates both the products, and TNF-α inhibitors in general. Infliximab has demonstrated significant in outcomes such as mucosal healing. Mucosal healing has various associated benefits, the most pertinent of which is a proven significant reduction of hospitalisations and surgeries – major cost drivers in CD.[21] Recent evidence has identified mucosal healing as the only clinical endpoint linked to long term remission. Importantly, Infliximab is the only biologic to achieve this clinical endpoint prospectively. Finally, Infliximab also has a broader indication covering fistulising and paediatric CD patients compared to adalimumab.	Comment noted. The Appraisal Committee considered all the available evidence on the efficacy and safety for the two drugs. For more information please refer to the FAD (section 4.3.4). In line with the different marketing authorisations for infliximab and adalimumab, there are separate recommendations for the fistulising and paediatric indications (see FAD

[21] Rutgeerts et al. (2006); Schnitzler et al. (2008b); Baert et al. (2008); Frøslie et al. (2007)

Consultee	Comment	Response
	Schering-Plough accepts the Committee's pragmatic decision to allow access to CD patients for both TNF-α inhibitors in the absence of any head to head analysis as this is in the best interests of patient and their providers. However, Schering-Plough would strongly urge the Committee to ensure that the above uncertainties are reflected in the final guidance.	sections 1.1, 1.3 and 1.4 for more information).
Schering-Plough	***3 Treatment discontinuation strategy*** Section 1.3 of ACD2 recommended treatment discontinuation from primary responders 12 months after the start of the treatment unless they show *"clear evidence of ongoing active disease"*. In response, Schering-Plough argued that this recommendation was unsupportable, as it was not based upon the best evidence that is currently available, was likely to lead to significant patient morbidity, and as such was not in the best interests of patients. Unfortunately, ACD3 is now even more stringent, stating that treatment may only continue until *"treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter."* Patients who relapse are subsequently allowed further treatment, following the development of symptoms. As previously discussed, due to the chronic progressive nature of active CD, any patient who suffers a relapse of their disease will suffer irreversible damage to their bowel, as a result. The successful withdrawal of treatment is a current area of active investigation, and as such knowledge	Comment noted. The Appraisal Committee reconsidered the population included in the GETAID/STORI study published in abstract form by Louis *et al.* For more information on the Committee discussion please refer to the FAD (sections 4.1.13 and 4.3.15). The Committee also considered the additional data submitted in the

Consultee	Comment	Response
	is constantly evolving. There are three pieces of evidence which we believe have bearing on this issue: 1. The prospective STORI study[22] (as discussed in our response to ACD2) has recruited 115 patients who are receiving infliximab. All were in remission for at least one year and off steroids for at least 6 months, prior to discontinuation of infliximab. During the first 12 months, 45 patients (39%) had relapsed. Various predictors of relapse were identified. 2. At the GASTRO 2009 conference, Armuzzi *et al*[23] presented a retrospective study of patients who had discontinued infliximab treatment following a "sustained clinical benefit" from infliximab for at least 12 months prior to discontinuation. 69 patients discontinued infliximab electively following prolonged steroid-free remission; of these, 30 (44%) relapsed within a median follow-up of 13 months. Mucosal healing was found to be a predictor of sustained clinical benefit following discontinuation (HR 2.7, 95% CI 1.3-6,6; p=0.009). 3. Schering-Plough has been given confidential pre-publication access to the forthcoming position statement from the World Congress of Gastroenterology (WCOG), which contains the following text[24]: **WCOG Statement 1.22 (This information is now in the public domain and is no longer considered to be of a confidential nature)** **Stopping biological therapy** Patients with ulcerative colitis or Crohn's disease who have responded to a year of anti-TNF therapy	study published by Armuzzi *et al.* and the (now published) statement from the WCOG. For more information on the Committee discussion please see the FAD (sections 4.1.13 and 4.3.15) The Committee considered it appropriate to amend the recommendations to allow a more individualised approach to treatment continuation and withdrawal (see FAD sections 1.1 and 1.4).

[22] Louis et al. Gastroenterology 2009; 136 Suppl 1:A-146
[23] Armuzzi et al. Gut 2009; 58(Suppl II) A466 (abstract P1803)
[24] Data on File, Schering-Plough – personal communication

Consultee	Comment	Response
	should have the benefits of continuing therapy weighed against the risks of discontinuation. Withdrawal of therapy is often appropriate in those who have both complete mucosal healing and no biological evidence of inflammation, although the previous pattern of disease, previous response to conventional or biological therapies and implications of a relapse, are essential considerations. In a similar approach to that taken by the two studies above, the experts' position is that treatment withdrawal may be appropriate in patients with no biological evidence of inflammation, and who have complete mucosal healing. The available evidence suggests a 12-month relapse rate, post-discontinuation, in the region of 39-44%, in patients who have been in stable steroid-free remission for 6-12 months prior to discontinuation. This is a critical point, as the strategy suggested in ACD3, involving an obligatory blanket discontinuation following 12 months of treatment irrespective of disease status, presence of remission, or known risk factors for relapse, will result in a *significantly* higher relapse rate than those reported. In conclusion, there is no current evidence which supports the treatment discontinuation strategy suggested in ACD3, and indeed, several pieces of evidence suggest that current best practice differs significantly from this approach. It is highly likely that this approach would be directly harmful to patients. As such, based on the evidence available, and with the interests of patients in mind, Schering-Plough strongly recommends that the Committee should remove the treatment discontinuation strategy, as it stands, from any future recommendations.	
Schering-Plough	**Summary** Schering-Plough acknowledges the paucity of head to head evidence between infliximab and	Comment noted. The comments

Consultee	Comment	Response
	adalimumab presented to the Committee upon which to make recommendations. However, in the context of the Committee recommending the least expensive drug to be used, Schering-Plough would urge the Committee to accurately represent the plausible ranges of treatment costs for both TNF-α inhibitors in the final guidance. Schering-Plough would also urge the Committee to acknowledge the broader evidence base available for infliximab, its stronger heritage and its established efficacy and safety profile including superior real-world outcomes in the final guidance. Finally, Schering-Plough would request the Committee to reconsider its position on the treatment discontinuation rule and to exclude it from the final guidance in absence of any strong supporting evidence. In summary, Schering-Plough would urge the Committee to consider its comments along with those of other consultees and commentators to ensure that the pragmatic approach that has been adopted throughout this last phase of the process allows for refinements to the points above to best reflect the latest evidence and so provide optimal care for patients within the resources of the NHS.	summarised here are addressed individually above.

Comments received from clinical specialists and patient experts

No comments were received

Comments received from commentators

Commentator	Comment	Response
British Society of Gastroenterology / Royal College	Many thanks for giving us the opportunity to respond to this new appraisal consultation document. Taking your questions in turn:	Comment noted.

Commentator	Comment	Response
of Physicians	1. Do you consider that all of the relevant evidence has been taken into account? Yes	
British Society of Gastroenterology / Royal College of Physicians	2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate? Yes.	Comment noted.
British Society of Gastroenterology / Royal College of Physicians	3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS? **Not without modification.** There are two main problems and two minor ones: (i) The statements in 1.1 and 1.3 regarding stopping treatment at 12 months are not workable as they currently stand and we are puzzled that the qualifications of these statements that were in the previous version of the appraisal have now been removed. The evidence base (GETAID study) only supports the cessation of treatment in patients who (a) have not required corticosteroids in the previous 6 months and (b) have no evidence of ongoing mucosal ulceration on colonoscopy (including ileoscopy). To address this we would strongly recommend reinsertion in both 1.1 and 1.3, in each case after "whichever is shorter" the following sentence: "The person's disease should then be reassessed. Maintenance treatment should only then be continued if there is clear evidence of ongoing active	Comment noted. The Appraisal Committee reconsidered the population included in the GETAID/STORI study published in abstract form by Louis *et al*. For more information on the Committee discussion please see the FAD (sections 4.1.13 and 4.3.15). The Appraisal

Commentator	Comment	Response
	disease, as determined by clinical symptoms and/or need for corticosteroids within the previous 6 months and investigations, including endoscopy if necessary". (ii) An additional statement should be inserted: "In persons who have had a good initial response to infliximab but have subsequently become non-responsive or intolerant a trial of adalimumab is reasonable providing this is discontinued if there has been no response within 8 weeks". (iii) 1.5 – "one or more of" should be inserted before "weight loss and sometimes fever …". Patients should not all be expected to have lost weight before becoming eligible for anti-TNF therapy. (iv) As we stated previously: The CDAI is cumbersome for use in clinical practice, requiring a one week patient diary and laboratory tests – we would recommend an insert (in italics) in para 1.5 last sentence: "This clinical definition normally but not exclusively corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more *(or to an equivalent Harvey-Bradshaw Score of 9 or more)*. We are pleased to see that access to both infliximab and adalimumab for adults with severe Crohn's disease will be equivalent.	Committee discussed the use of the CDAI and the Harvey-Bradshaw measures of disease severity. After advice from clinical experts, the Committee considered it appropriate to amend the wording of the recommendations to also allow the use of the Harvey-Bradshaw score to define severity (see FAD section 1.6).
British Society of Gastroenterology / Royal College of Physicians	4. Are there any equality related issues that may need special consideration? No We do hope that these issues get resolved quickly as the IBD community, patients and clinicians	Comment noted.

Commentator	Comment	Response
	alike, are becoming increasingly anxious about the current geographical variations in access to treatment that are resulting from lack of up-to-date guidance. We remain very grateful to the NICE Committee members for the attention that they have paid to the concerns about the previous inappropriate use of low relapse rates from the Silverstein cohort in economic modelling and to the scientific and medical concerns about the poor efficacy of episodic anti-TNF treatment.	
Royal College of Nursing	The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) of the technology appraisal of Tumour necrosis factor alpha (TNF a) inhibitors - infliximab (review and adalimumab) for Crohn's disease. This document was reviewed by nurses working in this area and in the IBD Network. The RCN's response to the four questions on which comments were requested is set out below: i) **Has the relevant evidence been taken into account?** There are no further comments to make this section as the relevant evidence seemed to have been taken into consideration. ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** With respect to the real cost of Infliximab v Adalimumab - it is important to note loss of response can occur in both infliximab and adalimumab, which may necessitate escalation of biologic therapy. This may be based upon a number of approaches, either progression to either 40mg weekly of adalimumab, a single dose of 10mg/k of infliximab to recapture and the reverting to 5mg/k afterwards	Comment noted. The Appraisal Committee previously discussed the issue of vial optimisation and also reviewed newly submitted data on dose escalation (see FAD sections 4.1.15, 4.3.11 and 4.3.16). The Technology Appraisal programme is only able to issue guidance on the clinical and cost effectiveness of a

Commentator	Comment	Response
	in addition some patients benefit for a reduction in the infusion intervals of infliximab. It is difficult to obtain precise numbers of patients who receive dose escalation of both adalimumab and infliximab in clinical practice; however the practice does seem to be wide spread suggesting that the true price of both therapies is much higher. We think that this is factored into the cost analysis. Wastage of Infliximab is an issue that may need to be explored. Vial optimisation is a practice taken up in some centres but not throughout the UK. This reflects recommendations of the NPSA, and the support for centres to develop infusion clinics which see multiple patients receiving infusions at the same time. This could ultimately reduce drug costs and provide support from other patients who receive biologic therapy. Also there does not appear to be any mention of the importance of smoking cessation in maximizing achievement remission. We believe that the promotion of smoking cessation services and ongoing smoking cessation support is vital to optimizing therapy. iii) **Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?** Ultimately, we consider that clinicians and patients should have a choice with respect to which anti-TNF Alpha product is used. This could be based upon individual clinical need and also on cost effectiveness issues. iv) **Are there any equality related issues that need special consideration that are not**	technology and it does not make recommendations on the appropriate management of people with various lifestyle choices (such as smoking).The Clinical Guideline or Public Health programmes at NICE would be best placed to make recommendations on smoking cessation services.

Commentator	Comment	Response
	covered in the ACD? There do not appear to be any equality issues that have been missed otherwise at this stage. **<u>Conclusion</u>** We would welcome the issuance of guidance to the NHS on the use of this health technology.	Comment noted.
National Association for Colitis and Crohn's Disease	**Do you consider that all of the relevant evidence has been taken into account?** Yes	Comment noted.
National Association for Colitis and Crohn's Disease	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?** Yes in broad terms. <u>However, we note that the interpretations and judgments of the Committee have been subtly altered to support the changed recommendations without, so far as we are aware, any new evidence having been submitted or considered by the Committee compared to the previous ACD.</u> For example, 4.3.5:The summary of the evidence from clinical specialists bullet point 3 which in the September 2009 ACD read “the evidence from clinical practice now strongly favoured maintenance therapy” becomes in the November 2009 ACD “the evidence from clinical practice now strongly	Comment noted. The Appraisal Committee reconsidered the population included in the GETAID/STORI study published in abstract form by Louis *et al*. For more information on the Committee discussion please see the FAD

Commentator	Comment	Response
	favoured a longer-term approach to treatment". We are certain that the clinician experts would have referred to maintenance and question the appropriateness of this change. An additional paragraph has been added to 4.3.5 in the November ACD which records that the committee concluded that the definition of maintenance treatment was unclear and agreed that the term 'planned course of treatment' was a clearer way of defining a longer-term approach to treatment for a *specified period of time*. (Our italics.) Whilst planned course of treatment may indeed be a reasonable substitute for maintenance treatment and perhaps preferable in its implicit emphasis on planning, the Committee has introduced a new concept not previously discussed or justified, namely that such treatment with antiTNFs should be for a specified period of time. This is a totally different approach to management than that in the September ACD where the decision of the Committee was to support current clinical practice – namely to have a formal review at 12 months and maintain continuity of treatment unless the patient is in full remission, in which circumstance the GETAID study suggests it is safe to stop treatment. Similarly, in the September ACD (para. 4.3.10) the Committee was unclear about the effectiveness of treatment over periods longer than 1 or 2 years, suddenly in the November ACD (para 4.3.9) the uncertainty is about periods longer than one year. No justification is given for this shortening of the time horizon. Also in para 4.3.10 the ACD reports the view of the Committee that it could not reliably identify a	(sections 4.1.13 and 4.3.15). Despite receiving additional data from the manufacturer of adalimumab, the Committee maintained that it was uncertain about the efficacy and safety of continued drug treatment for more than one year (see FAD sections 4.1.13, 4.1.14 and 4.3.15). The Committee considered it appropriate to amend the recommendations to allow a more individualised

Commentator	Comment	Response
	patient group with a sufficiently high rate of relapse that meant treatment should be continued after 12 months. It is the nature of Crohn's Disease that there is some uncertainty in the progression of the disease in each individual patient and therefore identifying patients at risk of relapse is the essence of the clinical review process accepted by the Committee in the September ACD. The clinician takes account of various indications of the progression of the disease and together with the patient decides on the most suitable treatment plan.	approach to treatment continuation and withdrawal (see FAD sections 1.1 and 1.4).
National Association for Colitis and Crohn's Disease	In summary, it seems that the Committee came up with a very different interpretation of the evidence and very different conclusions from exactly the same evidence base as it considered in the August 2009 meeting and published in the September ACD. NACC attended the October Committee meeting as an observer. We noted that one of the Committee members specifically raised points of discussion which he acknowledged he had raised before and that had been overruled. These points seem to us to relate quite closely to the subsequent changes in recommendations incorporated into the ACD. This is potentially important given that there were significant changes to the composition of the Committee – a new Chairperson and new Committee members. These members had not had the benefit of hearing patient or clinical expert comment – none were invited to be available at this meeting - and yet questions previously resolved at earlier Committee meetings seem to have been brought forward to be reconsidered by the Committee. This gives us great concern about the satisfactory continuity and consistency of the appraisal process, which as demonstrated by the contrast between the August and October meetings seems neither fair nor reasonable. If this ACD is	Comment noted. Both clinical and patients experts were invited to attend the Committee meeting in January 2010.

Commentator	Comment	Response
	confirmed in January it would seem a completely perverse outcome to a three-year process that has left many patients struggling to get access to anti-TNF treatment at local level.	
National Association for Colitis and Crohn's Disease	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** No. The proposed arbitrary time limit on treatment of 12 months has no basis in the evidence or in clinical practice in the UK or the rest of the world. For those patients in full remission at 12 months, the time limit will have no impact on their treatment – they would have stopped antiTNF therapy anyway under the review system proposed in the September ACD. For those patients not in full remission but who have not 'failed' and had treatment withdrawn, the reality at 12 months is that many are likely to be living as near normal a life as they can with symptoms that have been much improved by the antiTNF therapy, but that fall short of complete remission. Continued therapy will be enabling these patients to continue their education, their employment, and their family roles. Even for those patients who are not responding as well, the antiTNF will provide a period of symptom containment that allows for the next stage of treatment, often surgery, to be planned and undertaken as an elective. The revised recommendations in the November ACD condemn these patients to an arbitrary stopping of their treatment followed by a period of almost certainly worsening symptoms, additional	Comment noted. The Appraisal Committee reconsidered the population included in the GETAID/STORI study published in abstract form by Louis *et al.* For the Committee discussion see the FAD (sections 4.1.13 and 4.3.15). Despite additional data from the manufacturer of adalimumab, the Committee maintained that it was uncertain about the efficacy and

Commentator	Comment	Response
	hospital appointments and disrupted life until they 'requalify' for a further course of antiTNF therapy. We suggest the overall cost-effectiveness of this scenario is questionable and it is certainly not accepted good clinical practice. In terms of the individual patients and their families, we believe it is unethical to withdraw a treatment that is working, albeit imperfectly, and require the patient to suffer increased ill-health and impaired quality of life to 'requalify'. **The positive argument for the '12 month review' approach.** The newer committee members may not be aware that the proposal for a review at 12 months was put forward to the Appraisal Committee by the IBD community as our united view of what constitutes best practice, taking account of safety concerns, patient-well-being, service efficiency and cost-effective use of the antiTNF therapies. The review process addresses the issue of not allowing ever-increasing numbers of patients to be unthinkingly continued on these therapies and also addresses the concern of the Committee to identify which patients are most susceptible to relapse and who should be eligible for continued treatment. The wording of the September ACD with two possible changes would establish a very effective, fair and consistent pattern of clinical practice across England and Wales. The possible changes are: ➢ the minor adjustments to the review criteria proposed by the British Society of Gastroenterology and Royal College of Physicians	safety of continued drug treatment for more than one year (see FAD sections 4.1.13, 4.1.14 and 4.3.15). The Committee considered it appropriate to amend the recommendations to allow a more individualised approach to treatment continuation and withdrawal (see FAD sections 1.1 and 1.4).

Commentator	Comment	Response
	➢ the adoption of the term 'planned course of treatment' which we feel does emphasise the importance of a treatment plan provided it does not imply an arbitrarily defined period of treatment. The Review Process meshes very effectively with the approaches to multidisciplinary management of complex Crohn's Disease incorporated into the national IBD Standards published earlier in 2009 (www.ibdstandards.org.uk).	
National Association for Colitis and Crohn's Disease	**Other recommendations:** In our response to the previous ACD, we pointed out that the Committee has not made clear that patients who initially respond to an antiTNF but who subsequently lose response should be able to switch to a trial of the alternative antTNF. Trial evidence shows that this can be deliver successful outcomes for a significant proportion of these patients. We fully support the increased emphasis in the November 2009 ACD on the importance of the creation of a Register of IBD patients that will enable the outcomes of antiTNF therapy to be properly audited and evaluated. We regard this as important not only in terms of future assessment of cost-effectiveness, but also to monitor the long-term safety of these drugs. An important benefit of a Register of all IBD Patients would be to provide an alternative to the Silverstein data that has been such an issue in this appraisal. iv) Are there any equality related issues that may need special consideration? No.	Comment noted. The Committee heard from the experts about switching patients between anti-TNF therapies (see the FAD section 4.1.15). The Committee considered there to be insufficient submitted evidence to make recommendations on switching. For research recommendations see

Commentator	Comment	Response
		the FAD (section 6). Comment noted.

Summary of comments received from members of the public

Theme	Response
The reasoning behind the 12 month stopping rule for treatment is unclear. The committee changed their opinion and there is no clear reasoning.	Comments noted. The comments on withdrawal of treatment after 12 months and the impact on people with Crohn's disease were sent to and considered by the Committee. The Appraisal Committee reconsidered the population included in the GETAID/STORI study published in abstract form by Louis *et al*. For more information on the Committee discussion please see the FAD (sections 4.1.13 and 4.3.15). Despite additional data from the manufacturer of adalimumab, the Committee maintained that it was uncertain about the efficacy and safety of continued drug treatment for more than one year (see FAD sections 4.1.13, 4.1.14 and 4.3.15).
12 months is an arbitrary cut-off point to stop treatment.	
There is insufficient evidence to support stopping treatment after 12 months.	
There is no evidence of harm to patients who are treated for over 12 months.	
The committee appears to find this a cost effective treatment so it does not explain the 12 month stopping rule for treatment.	
Adalimumab falls within the guidelines for cost effectiveness so it is unclear why the treatment would be stopped after 12 months.	
The 12 month stopping rule removes clinical and patient input into the treatment decision.	
The recommendation to end treatment after 12 months is against clinical practice.	
Time limits are an inappropriate way to treat severe disease.	

Theme	Response
Treatment for diabetes, high blood pressure or epilepsy is not stopped after 12 months to see what will happen (e.g. heart attack, stroke, coma).	The Committee considered it appropriate to amend the recommendations to allow a more individualised approach to treatment continuation and withdrawal (see FAD sections 1.1 and 1.4).
Crohn's disease can take varying lengths of time to respond to treatment and to achieve remission.	Comments noted. The comments on withdrawal of treatment after 12 months and the impact on people with Crohn's disease were sent to and considered by the Committee. The Committee heard from clinical and patient experts on the variability of Crohn's disease (see FAD sections 4.1.13 to 4.1.15). The Committee considered it appropriate to amend the recommendations to allow a more individualised approach to treatment continuation and withdrawal (see FAD sections 1.1 and 1.4).
This recommendation assumes an obvious remission or failure at 12 months.	
Fistulae can take longer than a year to heal.	
Patients may respond and have symptoms controlled without being in remission.	
Crohn's disease is complex, varying and unpredictable. Every patient and flare-up is different.	
Patients have to wait for flare ups to be treated again which can do harm and disrupt life.	Comments noted. The comments on withdrawal of treatment after 12 months and the impact on people with Crohn's disease were sent to and considered by
Once off a programme it can be practically difficult to get back on one (e.g. having to wait to get an appointment, go through A&E or a doctor again).	

Theme	Response
There are complications associated with stopping and re-starting anti-TNFs.	the Committee. The Appraisal Committee reconsidered the population included in the GETAID/STORI study published in abstract form by Louis *et al.* For more information on the Committee discussion please see the FAD (sections 4.1.13 and 4.3.15). Despite additional data from the manufacturer of adalimumab, the Committee maintained that it was uncertain about the efficacy and safety of continued drug treatment for more than one year (see FAD sections 4.1.13, 4.1.14 and 4.3.15). The Committee heard from clinical and patient experts on the impact of disease relapse on people with Crohn's disease (see FAD sections 4.1.13 to 4.1.15). The Committee considered it appropriate to amend the recommendations to allow a more individualised approach to treatment continuation and withdrawal (see FAD sections 1.1 and 1.4).
Patients risk developing hypersensitivity/allergy/immunity due to stopping and starting treatment (evidence from the US – not specified).	
Patients want to avoid further surgery.	
There is a high likelihood of relapse, especially in young patients.	
The 12 month stopping rule is short-sighted. Remission can be temporary.	
There is a potential negative effect due to this recommendation.	

Theme	Response
This ignores the potential costs of allowing patients to relapse including surgery, hospitalisation, consultations, hospital visits, many ineffective treatments, dressings, draining, incontinence pads and other aids.	Comments noted. The comments on withdrawal of treatment after 12 months and the impact on people with Crohn's disease were sent to and considered by the Committee. The Appraisal Committee reconsidered the population included in the GETAID/STORI study published in abstract form by Louis *et al*. For more information on the Committee discussion please see the FAD (sections 4.1.13 and 4.3.15). Despite receiving additional data from the manufacturer of adalimumab, the Committee maintained that it was uncertain about the efficacy and safety of continued drug treatment for more than one year (see FAD sections 4.1.13, 4.1.14 and 4.3.15). The Committee heard from clinical and patient experts on the impact of disease relapse on people with Crohn's disease (see FAD sections 4.1.13 to 4.1.15).
This ignores the potential costs of allowing patients to relapse including anxiety about potential flare-ups, stress and depression (which consequently exacerbate the disease).	
Patients cost the NHS more when they are sick. These treatments are cost effective in the long term.	
The damage from flare-ups can be life changing and long lasting.	

Theme	Response
This doesn't consider the future drop in price when treatments become generic.	The Committee considered it appropriate to amend the recommendations to allow a more individualised approach to treatment continuation and withdrawal (see FAD sections 1.1 and 1.4). The Committee can only consider the list price of technologies unless a Patient Access Scheme is proposed by the manufacturer (see http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf).
Recommendation should be to review treatment after 12 months as in previous ACD2.	The comments on withdrawal of treatment after 12 months and the impact on people with Crohn's disease were sent to and considered by the Committee. The Committee considered it appropriate to amend the recommendations to allow a more individualised approach to treatment continuation and withdrawal (see FAD sections 1.1 and 1.4).
A 12 month review by a clinician, MRI and colonoscopy are reasonable to determine if continued treatment is appropriate.	
Clinicians should monitor patients regularly and review at 3 months for response.	
Patients are qualified to input into their own treatment decisions and make informed decisions balancing the risks and benefits.	
There is no explanation/provision to what happens after two courses of treatment.	The comments on withdrawal of treatment after 12 months and the impact on people with Crohn's disease

Theme	Response
Is the recommendation of 2 planned courses designed to take relevant patients through to the next proposed review by Guidance Executive?	were sent to and considered by the Committee. The Committee considered it appropriate to amend the recommendations to allow a more individualised approach to treatment continuation and withdrawal (see FAD sections 1.1 and 1.4).
There is no estimate of eligible numbers of patients who will qualify for this treatment.	In line with NICE's methods for technology appraisal, the Committee considers the clinical and cost effectiveness of individual technologies within their licensed indications (see FAD sections 4.3.3 and 4.3.4).
The number of patients severe enough to qualify for these treatments is actually quite small/there are varying levels of severity of disease.	
There is a lack of consideration by the committee of the social and personal cost/burden of the disease (especially in young people at an important time of their life) including impact on quality of life.	Comments noted. The Committee considered comments from people with Crohn's disease, their carers and members of the public in response to ACD3. The Committee heard from clinical and patient experts on the impact of Crohn's disease (see FAD sections 4.1.12, 4.1.13, 4.3.1, 4.3.2). NICE must issue guidance in the context of legislation on human rights, discrimination and equality (see http://www.nice.org.uk/media/916/6B/Guide_to_the_MTA-proof_8-26-10-09.pdf)
The impact of lethargy and tiredness should not be underestimated.	
Crohn's disease can stop people developing their career/education, working, contributing to society and paying tax.	
Crohn's disease affects young people under 30 years (50%) and so interferes with career development, education, work, well-being and other aspects of everyday life.	

Theme	Response
US insurance companies support these drugs even though they often refuse other expensive treatments.	In line with NICE's methods of technology appraisal, the Committee considers the clinical and cost effectiveness of technologies from an NHS and PSS perspective (see http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf).
These treatments are available in other countries.	
The committee should consider evidence from the rest of the world.	
Stopping treatment after 12 months is unethical.	
These are the first treatments that really work.	Comments noted. The Committee considered the evidence submitted by manufacturers, from clinical and patient experts, and other consultees on the clinical and cost-effectiveness of infliximab and adalimumab. Please see the FAD (section 4) for the evidence submitted and the consideration of the evidence. The Committee heard from the experts about switching
The effectiveness of steroids is limited and they are associated with side effects.	
A range of treatment options is needed. Treatments are not uniformly effective.	
This is a last option for many patients who have tried other treatments.	
Patients have experience of using these treatments and they work. Patients are 'amazed' at the response (which can be fast).	
The effect of these treatments starts to wear off before the next infusion/treatment (symptoms start to return).	
There is no cure for Crohn's disease so it requires long-term treatment and control of symptoms.	

Theme	Response
Patients should be able to take these treatments if they do not respond or are unable to take other treatments.	patients between anti-TNF therapies (see the FAD section 4.1.15). The Committee considered there to be insufficient submitted evidence to make recommendations on switching. In line with NICE's methods for technology appraisal, the Committee considers the clinical and cost effectiveness of technologies compared to standard practice in the NHS (see http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
Clinicians need to be able to amend dose according to response. High dose induction means less need for high dose maintenance, affecting cost. Vial sharing is a good idea.	Comments noted. The additional data on dose escalation submitted by both manufacturers in response to ACD3 was discussed by the Appraisal Committee. For more information on their discussion of dose escalation, please see the FAD (sections 4.1.15, 4.2.16 and 4.3.16).
More research is required into cheaper drugs (e.g. side effects with steroids).	Comments noted.

Theme	Response
More research is required into reducing the dose of treatments to optimise use.	For research recommendations see the FAD (section 6).
If implemented, research is required into the impact of stopping treatment after 12 months.	Comments noted. The comments on withdrawal of treatment after 12 months and the impact on people with Crohn's disease were sent to and considered by the Committee. The Appraisal Committee reconsidered the population included in the GETAID/STORI study published in abstract form by Louis *et al*. For more information on the Committee's discussion please see the FAD (sections 4.1.13 and 4.3.15). Despite receiving additional data from the manufacturer of adalimumab, the Committee maintained that it was uncertain about the efficacy and safety of continued drug treatment for more than one year (see FAD sections 4.1.13, 4.1.14 and 4.3.15). The Committee heard from clinical and patient experts on the impact of disease relapse on people with Crohn's
The data is difficult to evaluate as the results from different groups are so varied.	
Section 4.3.10 notes the limited evidence behind the subsequent recommendation.	
The evidence is limited and fragmented.	

Theme	Response
There is a need to research patients on maintenance not treating and stopping after 12 months.	disease (see FAD sections 4.1.13 to 4.1.15). The Committee considered it appropriate to amend the recommendations to allow a more individualised approach to treatment continuation and withdrawal (see FAD sections 1.1 and 1.4).
Planned course of treatment is a metaphor for controlling costs. Patients understand episodic and maintenance terminology.	Comment noted.
A gastroenterologist is required on the Appraisal Committee.	In line with the NICE process for Multiple Technology Appraisals, clinical experts are invited to the Committee meetings to advise the Committee on specialist issues.
Early treatment could help prevent severe disease.	The Appraisal Committee evaluates technologies within their licensed indications.
The recommendation needs to include Harvey-Bradshaw to determine severity and response.	The Appraisal Committee discussed the use of the CDAI and the Harvey-Bradshaw measures of disease severity. After advice from the clinical experts, the Committee considered it appropriate to amend the wording of the recommendations to also allow the use of the Harvey-Bradshaw score to define severity (see FAD section 1.5).

Theme	Response
Does the 12 month rule apply to children?	The recommendations for the treatment of young people aged 6-17 years are defined in the FAD (section 1.5)
Does guidance support the use of dose escalation?	NICE makes recommendations for technologies within their licensed indications. For further details, please refer to the SPC for each technology.
Was sequencing of treatments considered?	The Committee heard from the experts about switching patients between anti-TNF therapies (see the FAD section 4.1.15). The Committee considered there to be insufficient submitted evidence to make recommendations on switching.