NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

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)

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

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

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 NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Abbvie	*[Only the executive summary of AbbVie's response is reproduced below. For the full response, see the evaluation report.]* AbbVie welcomes the opportunity to comment on the Appraisal Consultation Document (ACD). We are disappointed with the preliminary decision not to recommend adalimumab, infliximab or golimumab for treating moderately to severely active ulcerative colitis (UC) after the failure of conventional therapy. We are committed to working with NICE in order to address the Committee's key uncertainties as outlined in the ACD and we hope NICE can work with us to find a solution that will enable appropriate UC patients to access anti-Tumour Necrosis Factor (anti-TNF) therapy. The negative recommendations for anti-TNF therapy are based on the ICERs not representing a cost-effective use of NHS resources. AbbVie disagrees with this conclusion and is concerned that the appraisal decision has been made without taking sufficient time to do so. We are also disappointed that the Institute has failed to take into consideration all the evidence provided by consultees in response to the Assessment Report. Consequently, the ACD lacks clarification on a number of critical issues raised in response to the Assessment Report. We will revisit the evidence that was provided, but not considered, in **Error! Reference source not found.**. As we believe that the impact of all the evidence on the estimates of cost effectiveness was not fully explored, we will also address the relevant issues. Lastly for section 1 and in Appendix 1, we will provide additional evidence on the efficacy of adalimumab and UC-related cost applicable to the NHS. We are also concerned that the summaries of clinical and cost-effectiveness evidence are not reasonable interpretations of some of the evidence and this will be addressed in **Error! Reference source not found.**. In this section we will also highlight our concerns relating to the presentation of the ICERs in the ACD and the	The Committee noted that the uncertainty around the costs and QALYs for TNF-alpha inhibitors, in addition to the potential uncaptured QALY benefits, 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. The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations For further details, see sections 4.80 and 4.82 of the FAD. The additional evidence was made available to the Committee (although not critiqued by the AG), and its key results are summarised in section 4.9 of the FAD.

Consultee	Comment	Response
Abbvie (cont.)	definitions of health states in the Assessment Group model. As an Appendix to this document, we have highlighted factual inaccuracies identified in the ACD. Therefore, we do not believe that the provisional recommendations are sound or a suitable base for guidance to the NHS. Anti-TNF therapy is a step change therapy for people who have failed conventional therapy and are left with no treatment options other than surgery. We consider it is important for patients to have the opportunity to receive anti-TNF therapy particularly as those who subsequently fail anti-TNF therapy will still be left with surgery as a last resort. In contrast, surgery is irreversible and patients consistently show a strong preference for exhausting all medical options first. Anti-TNF therapies such as adalimumab are considered as effective treatment options for people with moderate to severe UC who have failed conventional therapy and used in these patients as standard of care across Europe. Anti-TNFs are also widely reimbursed in major European countries. AbbVie believes that patients in the UK should have the opportunity to receive the same standard of care as in the rest of Europe.	Comment noted. Where appropriate, the factual inaccuracies identified in the ACD have been corrected in the FAD. The Committee 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. For further details, see section 4.80 of the FAD. The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD.
MSD	MSD believes that the preliminary recommendation in the Appraisal Consultation Document (ACD) is an inaccurate reflection of the totality of the evidence that was available for the Committee to consider, based around inadequacies in the process. We are disappointed that these shortcomings have resulted in a recommendation that prevents any adult or paediatric patient from accessing an alternative to surgery once conventional therapy has been deemed to fail by their clinician. The need for an alternative to surgery is particularly crucial for children, where data for medical therapies will always be limited, but the unmet need is arguably stronger. The marketing authorisations for TNF-α inhibitors stipulate that these medicines should be used only after the failure of conventional therapy e.g. “Simponi is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies”. The appraisal scope and the Assessment Group (AG) approach, by including conventional therapy as a treatment option where TNF-α inhibitors can also be used, have both assumed the potential for their off-label use. For the record, MSD does not support the use of our medicines outside of licence; with, additionally, this assumption being a key to the failings in the AG approach to evaluating these drugs.	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD. 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. For further details, see section 4.61 of the FAD. Having heard that conventional therapy is generally regarded as an ongoing option throughout the treatment pathway for ulcerative colitis, the Committee concluded that conventional therapy is an option at the same stage at which TNF-alpha inhibitors would be considered. It appreciated,

Consultee	Comment	Response
MSD (cont.)	MSD supports the valid role that NICE has in evaluating and making recommendations for drugs to be used by the NHS. However, one of the concerns that MSD has is around the potential for bias within the evaluation process. The majority of new therapies or new indications for currently available therapies are evaluated through the single technology appraisal (STA) process. This process, by having a manufacturer submission critiqued by an 'independent' AG and subsequently reviewed by the Committee, is relatively balanced. The multiple technology appraisal (MTA) process has the AG both build the reference case as well as critique any submission(s) by the manufacturer(s). When this process is combined with a lack of balance in what is presented to the Committee for discussion, with the discussion itself failing to cover the key issues, MSD believes that the intrinsic bias of the process has been significantly exacerbated.	however, that for some patients in whom conventional therapy had failed, continuing the same type of therapy may be suboptimal. For further details, see section 4.62 of the FAD. This appraisal was conducted as per the NICE Guide to the processes of technology appraisal.
	We believe that the only alternative to restarting the process is for a scenario analysis to be conducted within the AG model which better reflects the eligible population for TNF-α inhibitors. This analysis should then be presented to the Committee as an alternative to the current base case for discussion. We have elaborated on these key issues in the main body of this letter, and additionally summarise a number of inaccuracies which have been identified in the ACD.	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 were not warranted given the existing evidence. For further details, see section 4.79 of the FAD.
	Proposed scenario analysis Conventional therapy is not an appropriate comparator for TNF-α inhibitors given the marketing authorisations for these biologics. It is not apparent to MSD how the AG could adjust for this within their model without rebuilding the model. A potential solution could be to amend the current model so that patients receiving conventional therapy are assumed to have no response to that therapy. This would better reflect both the TNF-α inhibitor marketing authorisations and clinical practice in the UK, where TNF-α inhibitors are only considered for use where conventional therapy has failed (as an alternative to surgery).	The Committee concluded that conventional therapy is an option at the same stage at which TNF-alpha inhibitors would be considered. For further details, see section 4.62 of the FAD.
	If this issue can be corrected, the following aspects of the model also need to be considered as there is considerable uncertainty as to how appropriate they are for the 'new' population being assessed: **Surgery cost**: UK clinical experts and published literature support an increased cost for surgery than has been assumed by the AG (up to ~£24k opposed to ~£8k originally estimated by the AG). The low cost assumed by the AG is based on the	The Committee concluded that the cost of surgery was underestimated in the model. For further

Consultee	Comment	Response
MSD (cont.)	wrongful assumption that surgery is completed in one procedure. In reality, up to three procedures are required.	details, see section 4.77 of the FAD.
	Post-surgery cost: Similarly, MSD does not accept that the AG has correctly estimated the costs that occur following surgery i.e. costs associated with long-term stoma care. Our estimate for post-surgical management is £863 per 6-month cycle (opposed to £780 estimated by the AG). The cost of complications must also be considered in more depth.	The Committee noted that maintaining an ileostomy in the medium to long term and caring a stoma are associated with costs that were not included in the original model. For further details, see section 4.77 of the FAD.
	Post-surgery utility: As was stated in our response to the AG report and by clinical experts at the first Committee meeting, MSD believes that the utility value for the post-colectomy health state used in the AG model is excessively high and does not adequately reflect the considerable impairment and poor quality of life that persists following surgery. Further, the study from which this value is drawn is referenced incorrectly by the AG and may not be an appropriate source given that only a minority of patients received colectomy.	The Committee concluded that the study by Woehl et al. is likely to have overestimated the utility value for patients who had surgery. For further details, see section 4.73 of the FAD.
	Rate of progression to surgery: The rate assumed by the AG is very low and indicates that a more moderate population has been considered than reflects the decision problem, as patients with more severe UC who have failed conventional therapy could reasonably be expected to progress to surgery more frequently and/or rapidly (the value was obtained from a study which assessed newly-diagnosed patients whereas the average disease duration in the AG base case is 6 years).	The Committee concluded that the actual rate of surgery is likely to be higher in clinical practice. For further details, see section 4.76 of the FAD.
	Efficacy of TNF-α inhibitors: The AG network meta-analysis concluded that there were no significant differences between the three TNF-α inhibitors. Therefore, MSD sees value in a scenario analysis in which comparable efficacy for all TNF-α inhibitors is assumed. For completeness, three analyses should be performed in which the efficacy is set to that of Remicade, that of Simponi, and that of Humira.	The Committee concluded that further analyses were not warranted given the existing evidence. For further details, see section 4.79 of the FAD.
	Duration of TNF-α inhibitor therapy: We are aware that clinicians believe that TNF-α inhibitor therapy can be discontinued in stable patients. Given the need for a re-evaluation, it might be helpful to additionally model what this would look like.	The Committee appreciated that it would be difficult to model any criteria for stopping treatment given the lack of efficacy data for TNF-alpha inhibitors (including response and relapse rates) beyond the durations of the trials. The Committee concluded that the stopping criteria in NICE's technology appraisal guidance for TNF-alpha inhibitors for treating Crohn's disease could also be applied in this appraisal to align the treatment strategies for
	To summarise, MSD is concerned that the MTA process has the potential to present a one-sided case in that the 'independent' academic group both presents the base case and critiques any submission made by the manufacturer. Appropriate discussion and testing of this scenario analysis with clinical experts at the second Committee meeting would go some way to reassuring the manufacturer that the	

Consultee	Comment	Response
MSD (cont.)	potential challenges within the MTA (as opposed to the STA) process have been ameliorated. A simpler alternative would be to present the MSD base case for Simponi to the Committee for consideration. **<u>Issues identified with AG budget impact</u>** The AG assumes a 1 year net budget impact for Simponi of ~£200 million. This is far higher than realistic, equating to ~one third of total spend in England on all TNF-α inhibitors for all indications in 2012[i]. The AG estimate is based upon a population of 134,000 patients with UC, of which it is assumed that 14.5% (~20,000 patients) would be eligible for biologics. However, when only patients with moderate to severe UC, who are eligible for and receive TNF-α inhibitors, are considered; the budget impact is far lower at ~£20 million. This estimate better reflects the marketing authorisations than the AG scenario. **<u>Issues identified in ACD</u>** Key areas of uncertainty which have not been adequately addressed and information within the ACD which is inaccurate or has been misrepresented have been highlighted in the following table. *[This table has not been reproduced here. For details, see MSD's response in the evaluation report.]* *[References were provided but are not reproduced here.]*	the 2 conditions. For further details, see sections 4.65 and 4.71 of the FAD. Comment noted. Comment noted. Where appropriate, the factual inaccuracies identified in the ACD have been corrected in the FAD.
Crohn's and Colitis UK	*[Only the summary of Crohn's and Colitis UK's response is reproduced below. For the full response, see the evaluation report.]* • There is a clear and defined need for biological drugs to be available to people with moderate to severe Ulcerative Colitis, for whom conventional treatments have failed, using stopping rules which would bring this in line with the guidance for Crohn's Disease (TA187) • Neither surgery or conventional treatment are appropriate comparators for biological drugs as conventional treatment has, by definition, failed and, unless by patient choice, surgery should be considered a last resort when all	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD. The Committee concluded that conventional therapy is an option at the same stage at which TNF-alpha inhibitors would be considered. It appreciated, however, that for some patients in

Consultee	Comment	Response

Crohn's and Colitis UK (cont.)	appropriate medical options have been explored
	• Considerable uncertainties arise from the assumptions on which the modelling is based in terms of:
	  ○ lack of representativeness of the patient population being considered
	  ○ extrapolation of short-term data to a lifetime horizon
	  ○ lack of stopping rules
	  ○ full costs, complications and risks of surgery
	  ○ small sample on which health utility values are based
	  ○ selection of conventional therapy as a comparator, when this has already failed this group of patients
	• There are significant equality/diversity issues in terms of effectively compelling patients in this group to elective or potential emergency surgery, in particular for young people who have not begun a family and whose fertility may be affected, and for religious groups such as Muslims, for whom this may impact on religious practices and cause particular distress.
		whom conventional therapy had failed, continuing the same type of therapy may be suboptimal. For further details, see section 4.62 of the FAD.
		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. The Committee noted that the uncertainty around the costs and QALYs for TNF-alpha inhibitors, in addition to the potential uncaptured QALY benefits, 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. For further details, see sections 4.78 and 4.80 of the FAD.
		Because the Committee recommended TNF-alpha-inhibitors for all patients, in line with their marketing authorisations, it did not consider that this potential equality issue warranted further discussion.

Consultee	Comment	Response
British Society of Gastroenterology	The BSG has considered the initial ACD document and the revised report sent in Sept following the committee meeting Aug 28th, noting the specific questions that you ask: • Has all of the relevant evidence been taken into account? • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The response to all three of these questions is an emphatic 'no'. The results of the appraisal to date give a grossly misleading and inappropriately high ICER for anti-TNF therapy, principally because the ScHARR model used by NICE does not translate the trial data into a form that adequately reflects the use of these drugs in clinical practice in the UK. This is because of the use of a network meta-analysis combining the different drug trials that introduces wide confidence intervals, further amplified by the model itself. The model is very insensitive to changes in most parameters, and (as acknowledged in the committee meeting), there is a lack of robust data around many of these key parameters, including expected rates of surgery in patients with moderate to severe UC failing conventional therapy; costs of surgery and post-surgery care; and health utilities in steroid-dependent patients with chronic active disease who cannot have surgery. There is a large disparity in ICERs between the company and the ScHARR models. The model outcomes differ substantially to those for anti-TNF therapy in Crohn's disease (TA187), when it would be expected that results would be very similar for two diseases with substantial common features, aetiology and treatment. It is noteworthy that the original model for Crohn's disease, by the University of Birmingham (Use of tumour necrosis factor alpha (TNF α) inhibitors adalimumab and infliximab for Crohn's disease, produced by: West Midlands Health Technology Assessment Collaboration, for NICE, July 2008) had similar flaws. The BSG and others challenged that model: the revised model was used in the final report TA187. Specifically, the confidence intervals were extremely wide; the time horizon was too long; and there was no discussion about stopping rules. The BSG provided data from the STORI paper that had been presented and published in abstract form, but had not been considered by the review. STORI informed guidelines on stopping anti- TNFs in CD. NICE accepted that stopping rules would be useful and the models were re-run. TA187 was published with recommendations about a review at 12 months to determine whether anti-TNFs can or should be stopped. TA187 quoted	The Committee noted that the uncertainty around the costs and QALYs for TNF-alpha inhibitors, in addition to the potential uncaptured QALY benefits, 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. For further details, see section 4.80 of the FAD.

Consultee	Comment	Response
British Society of Gastroenterology (cont.)	the STORI study. The BSG wishes to bring to the attention of NICE three studies similar to the STORI paper that report stopping anti-TNFs in UC (Major point 1, below). These data should not be ignored. They should instead inform the discussion about the time horizon and the recommendation of an annual review of anti-TNF therapy with a view to stopping the drug, as per Crohn's disease. **Specific comments:** **Major points:** 1) **Rigorous stopping rules should be evaluated in the economic assessment.** Sections 4.62 and 4.67, of the ACD, report the Appraisal Committee's consideration of evidence regarding stopping rules. In particular we note the following comment in section 4.67, "The Committee would have liked to consider further the stopping rules for patients with ulcerative colitis who had a TNF-alpha inhibitor then entered into remission, but there was no robust evidence in this regard." However, the BSG does not believe all the relevant evidence has been taken into account. There is growing evidence that the majority of patients entering deep remission on anti-TNF therapy will remain in remission if anti-TNF drugs are stopped at 1 year or later: - Molander et al (IBD 2014;0:1-8) showed that 22/34 UC patients remained in remission after cessation, and 94% of those relapsing responded to retreatment - Steenholdt et al (Scand J GE 2012; 47: 518–527) showed that of 28 UC patients stopping whilst in clinical steroid-free remission, 75% remained in remission at 1 year and 5/7 (71%) responded to retreatment. - Farkas et al (Scand J GE 2013;48:1394-1398) followed 51 patients who stopped infliximab after one year, and 65% remained in remission at one year after cessation, with the majority of relapses responding to retreatment. - Villafranca et al (JCC 2014;8:S234-235) prospectively studied UC patients given one year of infliximab. 12 with mucosal healing at one year stopped the drug, and 75% remained in remission over 2 years follow-up. The 3 relapsing responded well to retreatment. These data suggest that review at one year (in order to stop anti-TNF therapy in patients who are in remission) is likely to be a clinically and cost-effective treatment strategy, with further treatment only in those who subsequently relapse, and would	The Committee noted the observational evidence cited to support stopping TNF-alpha-inhibitor therapy in patients who go into remission 1 year after starting treatment, with further treatment only in those whose disease subsequently relapses. 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 for TNF-alpha inhibitors for treating Crohn's disease could also be applied in this appraisal. For further details, see sections 4.64 and 4.71 of the FAD.

Consultee	Comment	Response
British Society of Gastroenterology (cont.)	bring the UC recommendations into line with those for Crohn's disease. It seems unreasonable to model continuous anti-TNF therapy in all patients maintaining a response over the long-term when increasingly this does not reflect UK clinical practice. This assumption inevitably drives the cost-effectiveness estimates for anti-TNFs but substantially overestimates the true cost of treatment. Furthermore it seems odd to reject stopping rules on the basis of limited evidence since this is clearly inconsistent with modelling clinical effectiveness over a lifetime horizon on the basis of 1 year follow-up evidence. We argue that there is without question sufficient evidence to at least explore the impact of stopping rules on the cost-effectiveness estimates. Ruling against any use of anti-TNF therapy in moderate to severe ulcerative colitis without any consideration of stopping rules is unfair and not an appropriate reflection of current clinical practice. 2) **Many patients who receive anti-TNF will not have responded at the end of the induction period.** Patients who do not respond should have to their anti-TNF therapy stopped and they will be offered surgery, or occasionally novel therapies in a drug trial. Clear stopping rules could and should be applied after induction for these primary non-responders. This is not fully considered in the model. 3) **Some patients will lose response during the first year of therapy.** For those who lose response (secondary non-responders) drug and anti-drug antibodies levels should be used to determine whether switching to an alternative anti-TNF should be considered, or if surgery is preferable. This is not considered in the model. 4) **The trial populations covered patients with moderate to severe disease and do not reflect expected UK usage.** Inevitably patients with more stable moderate disease are easier to recruit to these studies and are likely to represent the majority of trial subjects; in ACT1 only 45 (12.4%) of patients had severe disease (Mayo score 11 or 12) while 317 (87.1%) had moderate disease (Mayo score 6-10); in PURSUIT 93.3% had moderate disease, vs 6.7% with severe. **Clinical practice in the UK is to reserve these salvage treatments for more severe disease, and those with steroid-refractory or steroid-dependent disease.** The effect, in clinical practise, is that this group will have lower response and remission rates if not given anti-TNF drugs, and are much less likely to respond to conventional therapy (and thus be much more likely to undergo surgery) once anti-TNF drugs fail. The parameters used in the model reflect trial data, which are not representative of clinical practice, and the models should be used to explore this. It is likely that the	In the Assessment Group's model, all patients started in the induction phase. 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. For further details, see section 4.43 of the FAD. The Committee discussed measuring drug and drug-specific antibody levels in the blood to determine whether or not to re-treat the patient with a TNF alpha inhibitor, but heard that these tests are not yet in routine use in the NHS. For further details, see section 4.64 of the FAD. The Committee appreciated that patients included in clinical trials may be fitter and have more stable disease than most people seen in clinical practice. It considered 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) to be uncertain. For further details, see sections 4.65 and 4.78 of the FAD.

Consultee	Comment	Response
British Society of Gastroenterology (cont.)	ICERs will be far more favourable with a more severe population. Abbvie has recently completed an open label study to gather data on the use of, and response rate to, Adalimumab for moderate-severe UC in the UK. Similarly, MSD are currently recruiting patients with refractory moderate UC for treatment with golimumab. These two studies are likely to better inform discussions about the potential use in the UK. 5) **The rate and role of surgery is misrepresented**. We understand that the Scope was set in stone before the review. We feel the final Scope misrepresents the view of professional and patient experts. Surgery is the alternative for patients with UC that is refractory to conventional therapy if they are not rescued by biologic agents such as anti-TNFs. These patients have already failed conventional therapy so decisions based on comparisons of anti-TNF therapy with conventional therapy are senseless and have no meaning when we are trying to make patients better. When using surgery as a comparator, the outcomes described after surgery (complications and mortality) are different to medical outcomes (relapse and remission) so do they represent a valid comparator? For utility values post-surgery (which are needed to capture QALY) there is very little data and wide variation for the same health state (see below). Furthermore, there is no long term follow-up data on these patients so this uncertainty must be considered when incorporating values into the model. Therefore the utility values used in the models are not reliable. The surgery rate used in the assessment group model has been assumed to be constant at 0.0051 per treatment cycle (=6 months) (ie about 1% per year). This is based on Solberg et al (IBSEN data Sc J GE 2007). This study was a population-based cohort of all patients diagnosed with UC over a set time-period from Scandinavia, and does not represent the specific subgroup of patients with failure to respond to conventional therapy with moderate and severe disease in this appraisal. In these patients rates of surgery will be significantly higher (40-50% over the next year). Patients with moderate-severe UC who fail anti-TNFs will either be recruited to trials of new biologic agents aimed at those not responding to anti-TNFs, or will undergo surgery. They will **NOT** simply return to the conventional therapy that they had failed before.	Having heard that conventional therapy is generally regarded as an ongoing option throughout the treatment pathway for ulcerative colitis, the Committee concluded that conventional therapy is an option at the same stage at which TNF-alpha inhibitors would be considered. It appreciated, however, that for some patients in whom conventional therapy had failed, continuing the same type of therapy may be suboptimal. For further details, see section 4.62 of the FAD. The Committee concluded 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. For further details, see section 4.60 of the FAD. 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. For further details, see section 4.72 of the FAD. The Committee concluded that the actual rate of surgery is likely to be higher in clinical practice. For further details, see section 4.76 of the FAD.

Consultee	Comment	Response
British Society of Gastroenterology (cont.)	6) **The Quality of Life of patients undergoing surgery is ignored.** A colectomy for UC is not the same as an appendicectomy for appendicitis: patients will have to live with an incontinent stoma (ileostomy) or a pouch. Pouch surgery provides a solution to the cosmetic issues, but most people with a pouch open the bowels 6-8 times per day with episodes of incontinence by day or night. This is **NOT** a cure for colitis. The draft only quotes the abstract (Woehl et al) and although there were 180 patients, only 10 had pouches and 19 ileostomies. There are other sources that illustrate the poor quality of life of patients who have undergone surgery: Probert et al (Arq Gastro 1996) reported that faecal incontinence occurred in 33% patients with a pouch. Tiainen (Scand J Gastro 1999) reported fecal incontinence, more than 10 bowel movements per day, and chronic pouchitis were all associated with reduced QoL score (using SF-36): median number of bowel movements per 24 h was six. Soiling at night occurred in 32%, and inability to differentiate pouch contents in 24% cases. 24% used a pad occasionally, and 9% every day. Berndtsson I and Oresland T (Colorectal Disease 2003) found the QOL of patients undergoing pouch surgery for UC had not changed one year after surgery compared with that before surgery. Cohen et al (IBD 1999) noted that medical (Cyclosporin) management of refractory UC was associated with a better ability to sleep ($p = 0.002$; VAS), better stool consistency ($p < 0.001$; VAS), less abdominal or rectal pain ($p = 0.009$, VAS), and fewer daytime ($p < 0.001$; Oresland), nighttime ($p = 0.006$; Oresland), and daily trips to the toilet ($p < 0.001$; VAS) than the 46 surgical patients.	The Committee concluded that the study by Woehl et al. is likely to have overestimated the utility value for patients who had surgery. For further details, see section 4.73 of the FAD.
	7) **Patients at risk of colectomy tend be young adults**. Education, socialising, employment and relationships are all important aspects of young lives that will be adversely affected if patients are forced into 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. For further details, see section 4.61 of the FAD.
	8) **The Network Analysis is impenetrable**. Health economists commissioned by the BSG as well as HE experts within the Society describe the uncertainties surrounding the ScHARR model are enormous and raise serious questions about the value of this approach using a life-time horizon, and basing many of their parameters on the network meta-analysis. A good example of the uncertainty is the confidence interval around the probability of adalimumab treatment in responders to induction therapy achieving remission in cycle 2 – 0.22 [0.005-0.72] For infliximab it is 0.41 [0.029-0.89]. (ScHARR Assessment report June 2014, Table 66). Most of the	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. For further details, see section 4.68 of the FAD.

Consultee	Comment	Response
British Society of Gastroenterology (cont.)	data used is similar in wideness of confidence intervals. This is a strikingly similar to the flawed report from Birmingham, prior to TA187, that was overturned when due consideration was given to the confidence intervals and the stopping rules.	
	9) **The economic model did not include indirect costs.** We would argue that ulcerative colitis, with a peak age of onset at 15-25, is a condition where indirect costs are particularly relevant and cannot be ignored in assessment of drug treatment. When health state was measured by a Visual Analogue Score (0-10) IBD patients with VAS score 0–2.5 had 71% productivity loss (WPAI questionnaire) and those with VAS score 2.5-5 had 48% loss, compared to 8% loss for those with VAS 7.5-10 (Gay et al Crohn's, Colitis and Employment – from Career Aspirations to Reality. Crohn's and Colitis UK, 2011). Patients with poorly-controlled disease, steroid-dependence, or needing multiple operations also stand to miss out on school and higher education that will have a life-long impact on their employment. Therapy that can control disease well at this critical time, even if postponing an operation for 1-2 years, can enable patients to complete qualifications that will benefit them over many years.	The NICE reference case stipulates that the perspective on costs is that of the NHS and personal social services. For further details, see sections 5.1.9 and 5.1.10 of the Guide to the methods of technology appraisal 2013.
	10)**The effect on young people is ignored**. Surgery in children and teenagers that will involve stomas can have a dramatic impact on relationships, and often leads to severe psychological morbidity, and the impact of pelvic surgery on fecundity is significant, (resulting in the need for future fertility treatment for some), and ileoanal pouch formation is often delayed for years in this group, and indeed subsequently often does not take place at all.	The Committee concluded that the decision to have surgery may be different for children and young people compared with adults. For further details, see section 4.61 of the FAD.
	The effect on young people is disproportionate. Young patients are more likely to respond to anti-TNF therapy than older patients, as they generally have a shorter duration of disease.	The Committee concluded that infliximab was likely to be clinically effective in children and young people. For further details, see section 4.69 of the FAD.
	11)Corticosteroid-dependency and/or chronic disease activity has a significant adverse effect on health utility that is not adequately reflected in the model used. Many patients who decline a colectomy will be in a state of chronic moderate disease activity, often with ongoing dependence on corticosteroids, that is not in any way reflected in the model used.	The Committee was aware that a utility decrement would be associated with the side effects of corticosteroids, which would favour treatment with TNF-alpha inhibitors. For further details, see section 4.75 of the FAD.
	12)**The cost of surgery is underestimated.** We acknowledge that surgery looks cheaper that medical therapy, but the surgical costs are between £11,000 and £23,000: (usually including three separate procedures:	The Committee concluded that the cost of surgery was underestimated in the model; however, it agreed that there were insufficient data to model

Consultee	Comment	Response
British Society of Gastroenterology (cont.)	*[Tables with the tariffs for the common surgical procedures were provided but are not reproduced here.]* 13)**Cost of ancillary equipment after colectomy with ileostomy have been ignored although the BSG provided data.** The costs range from £1,240.08 per year (good quality stoma bags with swabs) to £2,682.24 per year (stoma bags with rings, skin protective wipes, hydroframe and adhesive remover). The costs of daily high dose loperamide, for life, have also been ignored. 14)**The effect of disease distribution is ignored**. Most patients have left-sided colitis, many with disease limited to the distal colon or even the rectum. Removing the whole colon is the only surgical option for patient with colitis. The impact of colitis is similar in all patients, the quality of life is impact when the rectum is diseased. Proceding to colectomy and thus removing a large proportion of normal colon is challenging for patients and clinicians. Patients with limited disease arguably have the most to gain from anti-TNF therapy. 15) The ACD reports an ICER of £50,624 for adalimumab compared to conventional therapy (ACD section 4.51) for patients in whom colectomy is not an option. However, the ScHARR model assumes that these patients nonetheless proceed to surgery once they have failed conventional therapy or anti-TNF treatment. For patients in whom colectomy is not an option in the longer-term and therefore where it does not feature as an outcome, we estimate a base-case ICER of approximately £45k/QALY for adalimumab compared to conventional therapy. While this may still fall outside the range of acceptable ICER for NICE, we argue that there is an accumulation of exclusions/uncertainties which appear to bias against the biologics. If these were resolved it appears likely that the biologics would be cost-effective. These include: stopping rules, substantial uncertainty over the effects of surgery and the side effects of conventional therapy not being captured. Minor points 1) The monthly cost of infliximab of £210 on p.9 is wrong, and should be significantly more 2) On p.11 it states that none of the trials considered in the appraisal included patients who had been treated before with corticosteroids and 6-mercaptopurine or azathioprine. This is incorrect, as the majority did include this patient group **International Status** The use of anti-TNF induction and maintenance therapy in this patient population is	the number of procedures required for the patient, and the frequency of, and costs associated with, each of these procedures. For further details, see section 4.77 of the FAD. 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. For further details, see section 4.77 of the FAD. The Committee heard that it is important to consider clinical effectiveness in patients with ulcerative proctitis because their disease seems to respond to TNF-alpha-inhibitor treatment and they are not usually suitable for colectomy. It concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see sections 4.66 and 4.82 of the FAD. 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. It noted that the uncertainty around the costs and QALYs for TNF-alpha inhibitors, in addition to the potential uncaptured QALY benefits, 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. For further details, see sections 4.78 and 4.80 of the FAD. Comment noted. These factual inaccuracies have been corrected in the FAD.

Consultee	Comment	Response
British Society of Gastroenterology (cont.)	standard practice in Europe (The second European Consensus on the diagnosis and management of ulcerative colitis: current management. Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis SPL, Van Assche G, for the European Crohn's and Colitis Organisation (ECCO). *J Crohns Colitis* 2012;**6:**991-1030) and the USA. The conclusions of this ACD are in complete contrast to this and must prompt a thorough review and revision of the tools used to make this assessment. **Treatment in the UK will be at odds with the rest of the developed world**. **Discussion with patient groups** NICE funds several cancer drugs with ICER of up to 120,000/QALY. NICE should consider raising the threshold for UC for subgroups eg declined surgery after discussion with surgeon, high risk surgery, psychological issues. Without some such discussions, young adults will feel devalued and bitter instead of becoming valued members of society able to pursue their studies, support our economy and retain their fertility for the future of the country. **Discussion with Industry** We would encourage a dialogue between NICE and the pharmaceutical industry. Risk-sharing schemes have been agreed for supporting access to beta-interferon in MS and Velcade for multiple myeloma. For refractory UC patients, such a scheme could permit patients to receive induction therapy with anti-TNF therapy, if there is no response industry pays but if there is a response then the NHS will pay. *In conclusion, we feel that the assessment group model does not take all relevant evidence into account, and does not fairly reflect the clinical- and cost-effectiveness of these drugs as used in clinical practice in the UK. The stark contrast between this ACD recommendation and those for Crohn's disease and anti-TNF therapy are non-intuitive. Only a minority of UC patients have moderate to severe treatment-refractory colitis. Of these about half will respond well to anti-TNF drugs, and most in remission at one year will remain well after stopping. This group (often young and at a crucial time of education, forming relationships or starting a family) will be hugely disadvantaged by being subjected to unnecessary surgery, or forced to tolerate long-term steroid use and chronic ill-health as a result of being denied these therapies. We urge the committee to revise their recommendations to accommodate these concerns.*	

Consultee	Comment	Response
British Society of Paediatric Gastroenterology, Hepatology & Nutrition	Please find a response on behalf of the British Society of Paediatric Gastroenterology, Hepatology & Nutrition (BSPGHAN) in our role as a registered stakeholder and following on from a formal request from NICE for comments following publication of the consultation document recently. The IBD working group of BSPGHAN have reviewed the document and wish to provide written feedback to NICE on the MTA. We are extremely disappointed in the initial recommendations and think they will unfairly deny access to infliximab in children with chronic active Ulcerative Colitis (UC) as outlined below: *[Section 1.2 of the ACD was included in the response but is not reproduced here.]* We fully support the document submitted by the British Society of Gastroenterology (BSG) highlighting the reasons why severely restricting access for adults with chronic active UC is also misguided and as such will not seek to repeat these points but will merely restrict our comments to those most pertinent to children. • Has all of the relevant evidence been taken into account? The IBD WG believe that not all of the specific evidence relating to paediatrics has been indeed been considered. There is a lack of recognition that paediatric UC is different and that models applied in adults cannot be translated into making assumptions about care of paediatric patients. There is no recognition of the different phenotype of UC in children with significantly higher rates of pancolitis seen in children compared to adults.(1) This directly impacts on disease behaviour with higher admission rates for acute severe colitis and higher colectomy rates.(2) The colectomy rate in children is double the equivalent rate in adults after the same time period from diagnosis.(1) • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The group does not believe that the interpretations take all of the relevant factors into account. As stated in the previous section, translation of annual colectomy rates from the IBSEN cohort into a model for colectomy rates in UK children is not valid. Using a 15 year old to model for all paediatric patients also is inaccurate: *[Section 4.73 of the ACD was included in the response but is not reproduced here.]*	The Committee heard that young people tend to present with more extensive and severe disease, which is more likely to need surgery. It also heard that children are more likely to have a shorter duration of disease which is associated with better treatment outcomes. For further details, see sections 4.61 and 4.69 of the FAD. The Committee understood that the rate of surgery is higher among children and young people than adults. For further details, see section 4.61 of the FAD. 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. It was also unclear to the Committee if and how the uncertain aspects in the model would differ for

Consultee	Comment	Response
British Society of Paediatric Gastroenterology, Hepatology & Nutrition (cont.)	The model offered no weight for the patient so the costing calculations cannot be worked out accurately in the base case provided. Given the mg/kg dosing of infliximab, different costing calculations would need to made at different ages due to the massive weight differential and subsequent cost differential between the ages of 6 and 17 – a one age fits all is neither appropriate nor accurate. The failure to consider the unique nature of childhood and adolescence is also not addressed. The delaying of colectomy by using infliximab in children with UC has been demonstrated in previous paediatric studies.(3) The benefit of giving an adolescent in education the chance to undertake their examinations with use of an anti-tnf even if this is only delaying surgery to a later and more appropriate time has a profound impact on the young person's future education and earning potential. This has not been factored into any modelling. This clearly challenges the validity of the conclusion "There are no specific groups of people for whom the technology is particularly cost effective."	children and young people because much of the evidence did not relate to this population. For further details, see section 4.78 of the FAD. The Committee heard that 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. It concluded that TNF-alpha inhibitors are important treatment options that could allow patients to avoid surgery. For further details, see section 4.61 of the FAD.
	• Are the provisional recommendations sound and a suitable basis for guidance to the NHS?	
	The current recommendations are not, in their present form suitable, and as such if implemented they will have a profound and significant impact on all paediatric gastroenterology teams treating children with UC in the NHS. There will be no other option for these children but to have a colectomy. The suggestion that these children could be maintained on "conventional" therapy is incorrect especially as anti-tnf therapy is considered only when they are failing this treatment. Surgery does not provide a cure and there are significant complications and consequences both acute and longer term. The psychological impact of the disease is most profound in this age group and there is no recognition of the negative impact of having a stoma (even if temporary) in a child or teenager. In addition, the longer term impact of surgery on fecundity is not considered or it would seem costed. The recommendation as is would put the UK paediatric IBD care significantly outside the care offered in other European countries and would be against the recommendations of the European guidelines for the care of children with UC.(4) The recognition that the price of this treatment dropping significantly with the launch of biosimilar infliximab in February 2015 in the UK has also not been factored in. The failure to consider optimising treatment response by trough level and antibody measurement means the guidance is not really reflective of current UK practice. The	The Committee concluded that infliximab could be recommended for treating severely active ulcerative colitis in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy, or who cannot tolerate, or have medical contraindications for, such therapy. For further details, see sections 1.3 and 1.4 of the FAD.

Consultee	Comment	Response
British Society of Paediatric Gastroenterology, Hepatology & Nutrition (cont.)	fact that there are so few medical options for this group of patients who have more extensive and severe disease makes this proposed guidance all the more challenging. Of note the recent licence of Vedolizumab for adults in the UK is not likely to be translated to a paediatric licence for around 7 years based on previous time lags between adult and paediatric trials for other biologics and in keeping with the companies currently proposed paediatric investigational plan.(5;6) This decision would therefore condemn a generation of children with UC to higher rates of ill health and colectomy given the lack of any new therapies on the horizon. In conclusion, the current guidance does not accurately or fairly summarise all of the relevant evidence, the assumptions used to model the costings are flawed and it does not reflect current UK paediatric practice. We would suggest children be allowed access to an induction course of infliximab for chronic active UC with the option for responders only to carry on treatment with reassessment at one year in line with the current NICE guidance on infliximab for paediatric Crohn's disease. *[References were provided but are not reproduced here.]*	
Royal College of Nursing	The Royal College of Nursing (RCN) welcomes the opportunity to review the Appraisal Consultation Document of this appraisal. Comments and recommendations have been submitted by the RCN IBD (Inflammatory Bowel Disease); Adult patients, British Society of Paediatric Gastroenterology, Hepatology & Nutrition (BSPGHAN); Paediatric IBD, British Society of Gastroenterology (BSG) and the RCN Gastrointestinal (GI) Nurse Forums on behalf of the Royal College of Nursing i) **Has the relevant evidence been taken into account?** We fully support the comments submitted by the forum highlighting the reasons why access for adults with chronic active UC is misguided as indicated in this response and as such will not seek to repeat these points here but will merely restrict comments to those most pertinent to children. The response to the above question is no, relevant evidence has not been taken into account as there is a lack of recognition that paediatric UC is different and that models applied in adults cannot be translated into making assumptions about care of paediatric patients. There is no recognition of the different phenotype of UC in children with significantly higher rates of pancolitis seen in children compared to adults.(1) This directly impacts on disease behaviour with higher admission rates for acute severe colitis and higher colectomy rates.(2) The colectomy rate in children is	The Committee heard that young people tend to present with more extensive and severe disease, which is more likely to need surgery. It also heard that children are more likely to have a shorter duration of disease which is associated with better treatment outcomes. For further details, see

Consultee	Comment	Response
Royal College of Nursing (cont.)	double the equivalent rate in adults after the same time period from diagnosis.(1) **ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No they are not. As stated, translation of annual colectomy rates from the IBSEN cohort into a model for colectomy rates in UK children is not valid. Using a 15 year old to model for all paediatric patients also is inappropriate. *[Section 4.73 of the ACD was included in the response but is not reproduced here.]* No consideration of patient weight was taken in these models. Paediatric patients are dosed using a 'mg/kg' dose. Clearly, there is a significant difference in the weight of a 6yr old and a 15yr old (as used in the NICE model) and this would obviously have a subsequent effect on costings. A 'one age fits all' approach is neither appropriate nor accurate. In addition, the failure to consider the unique nature of childhood and adolescence is also not addressed. Delaying colectomy through the use of infliximab in children with UC has been demonstrated in previous paediatric studies. (3) The benefit of giving a young person in education the chance to undertake their examinations with use of an anti-TNF even if this is only delaying surgery to a later and more appropriate time has a profound impact on the young person's future education and earning potential. This has not been factored into any modelling. In particular, this challenges the conclusion that "There are no specific groups of people for whom the technology is particularly cost effective." We feel this appraisal has not fully explored the direct and indirect costs such as loss of earnings, loss of education and the longer term socioecomic effects of these; and it may have underestimated the impact of poorly treated disease on health. Additionally, as healthcare professionals who have significant contact with people diagnosed with Inflammatory Bowel Disease (IBD) we have identified that patients with Ulcerative Colitis (UC) feel their treatment options are unequal to those with Crohns disease (CD). We are concerned that the current Appraisal Consultation Document does not address medical options after failure of conventional therapy. It appears to assume that patients will respond to a re-trial of medications to which they have previously been refractory. Clinical experience tells us this is not the case. Therefore the current document does not provide options for patients' refractory to conventional therapy that are unsuitable for, or unwilling to have, surgery.	sections 4.61 and 4.69 of the FAD. The Committee understood that the rate of surgery is higher among children and young people than adults. For further details, see section 4.61 of the FAD. 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. It was also unclear to the Committee if and how the uncertain aspects in the model would differ for children and young people because much of the evidence did not relate to this population. For further details, see section 4.78 of the FAD. The Committee heard that 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. It concluded that TNF-alpha inhibitors are important treatment options that could allow patients to avoid surgery. For further details, see section 4.61 of the FAD. The NICE reference case stipulates that the perspective on costs is that of the NHS and personal social services. For further details, see sections 5.1.9 and 5.1.10 of the Guide to the methods of technology appraisal 2013. The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. It also concluded that infliximab

Consultee	Comment	Response
Royal College of Nursing (cont.)	It is likely that this cohort will require management with on-going steroids. The overarching aim of ulcerative colitis management is steroid-free remission. Repeated or long-term exposure to steroids is associated with potentially irreversible complications including osteoporosis, diabetes, hypertension, increased susceptibility to serious infection, adrenal insufficiency and hepatic and ophthalmologic effects. We are not clear that the economic models used have taken these factors, and costs treating them, into account. The modelling tool also does not appear to have considered the financial impact when patients are unwell such as the loss of earnings, lack of productivity, loss of education and general impact on family life. People with chronically active disease may be unable to work, or work full time due to severity of symptoms, such as urgency, faecal incontinence or fatigue. Patients with ulcerative colitis are at an increased risk of colorectal cancer. That risk increases with duration, anatomical extent and activity of disease. Therefore people who have chronically active, poorly controlled disease are at significantly increased risk of developing bowel cancer. These are a group who may require annual surveillance colonoscopies with associated costs, impact on service and, importantly, morbidity. We also have concerns regarding the lack of weight given to the effects of pelvic surgery on fertility. The economic model made the presumption that 47.3% and 5% of patients going to colectomy will develop transient or chronic post-surgical complications respectively. With regards to colectomy and Ileo-anal pouch procedure (IAAP), the British Society of Gastroenterology Guidelines (2011) state that complication rates can be significant and pouchitis remains a persistent and difficult problem following surgery, therefore incurring on-going costs through complex medical and often surgical management and follow-up. The ACD goes further to state fecundity of young women may be reduced by 40-50% following IAPP, probably as a result of pelvic surgery and subsequent pelvic adhesion and that an exploration of alternative medical or surgical options should be undertaken in women of childbearing potential before IAPP. The European evidenced-based consensus on reproduction in inflammatory bowel disease (2010) report that pelvic surgery may lead to impotence or ejaculatory problems in men and that those who undergo ileoanal pouch surgery for UC, may experience retrograde ejaculation and erectile dysfunction. Pelvic surgery for IBD increases the incidence of subfertility in females and previous systematic reviews including the ECCO guidelines (2010), conclude that the fertility of women with UC was reduced after restorative proctocolectomy. A meta-analysis	could be recommended for treating severely active ulcerative colitis in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy, or who cannot tolerate, or have medical contraindications for, such therapy. For further details, see sections 4.81 and 4.82 of the FAD. 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. It concluded that these are important issues which should be taken into account, particularly for young people. However, on this occasion, the Committee was not satisfied that they had been adequately captured in the economic analysis. For further details, see section 4.74.

Consultee	Comment	Response
Royal College of Nursing (cont.)	found that ileal pouch-anal anastomosis (IPAA) conferred a three-fold increased risk of infertility compared to medical management. It is essential for this to be considered in greater depth within the appraisal as the long-term effects of colectomy and IAAP must be considered against the use of Anti-TNF treatment for prevention of hospital admission and colectomy. The draft ACD states that “conventional therapy was an on-going option throughout the treatment pathway for moderately to severely active ulcerative colitis because most patients are unlikely to consider surgery until later (unless the patient has acute disease, which is not covered by this appraisal)”. The European evidenced-based consensus on reproduction in inflammatory bowel disease (2010) state there are no data to support the approach of subtotal colectomy with rectal stump and ileostomy during childbearing years and then creating an IPAA later in life to help reduce infertility rates. They note the drawbacks of the latter procedure include ileostomy complications during pregnancy such as obstruction and stoma related problems. The aims of IBD management is to significantly improve the quality of life for patients, eliminate or reduce costs associated with emergency admissions, repeated endoscopies, conditions associated with the use of long term steroids, major surgery and follow-up care. In our experience, the provision of anti-TNF (infliximab) therapy in appropriate patients: • Impacts on disease prevention by reducing the risk of complications and co-morbidities associated with severe ulcerative colitis • Impacts on health inequalities through equitable treatment access (to people with CD) • Improves outcomes, quality and/or safety • reduces the risk of complications and co-morbidities associated with severe ulcerative colitis • Improves patient experience. The treatment can potentially reduce the need for repeated hospital admissions for the patient group in question, thereby improving quality of life and allowing them to be managed in an outpatient setting • Improves cost efficiency by reducing admissions, in -patient care, reducing diagnostic endoscopies and avoiding surgery	

Consultee	Comment	Response
Royal College of Nursing (cont.)	Surgery may require a 3-stage procedure: a sub total colectomy, followed by a second operation at 6 months for stoma and pouch formation and a third operation at 12 months for stoma reversal. There is a 40% risk of pouchitis which requires further intensive intervention and monitoring. These are all factors which should be considered within the economic modelling.	The Committee concluded that the cost of surgery was underestimated in the model. For further details, see section 4.77 of the FAD.
	iii) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?	
	No. This will have a profound and significant impact on all paediatric gastroenterology teams treating children with UC in the NHS. There will be no other option for these children but to have a colectomy. The suggestion that these children could be maintained on "conventional" therapy is incorrect particularly if it has failed before. Surgery does not provide a cure and there are significant complications and consequences both acute and longer term. The psychological impact of the disease is most profound in this age group and there is no recognition of the negative impact of having a stoma (even if temporary) in a developing child or teenager. In addition, the longer term impact of surgery on fecundity is not considered or it would seem costed. The recommendation as is would put the UK paediatric IBD care significantly outside the care offered in other European countries and would be against the recommendations of the European guidelines for the care of children with UC.(4) The recognition that the price of this treatment dropping significantly with the launch of biosimilar infliximab in February 2015 in the UK has also not been factored in. The failure to consider optimising treatment response by trough level and antibody measurement also means the guidance is not reflective of current UK practice. The fact that there are so few medical options for this group of patients who have extensive and severe disease makes this proposed guidance all the more challenging. This decision would therefore condemn a generation of children with UC to higher rates of ill health and colectomy given the lack of any new therapies on the horizon. There is a psychological risk to patients who reluctantly have a colectomy if they feel they have no other choice. People often wish to exhaust all possible medical option before contemplating major surgery.The idea of an ileostomy to some is unthinkable and can impact on the ability to form and maintain relationships. Patients are increasingly aware of variations in treatments for their UC across the country and internationally. It is unacceptable to patients with UC that patients with	The Committee concluded that infliximab could be recommended for treating severely active ulcerative colitis in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy, or who cannot tolerate, or have medical contraindications for, such therapy. For further details, see sections 1.3 and 1.4 of the FAD.

Consultee	Comment	Response
Royal College of Nursing (cont.)	Colonic Crohns disease can access Anti-TNF, yet patients with Ulcerative Colitis cannot, despite the similarities between the two diseases. We note that the draft guidance does highlight that there are patients who require biological therapy for a period of time before surgery. The advantage of this is to decrease/stop the steroids as well as allowing the patient to mentally be prepared for surgery. These two things have a positive effect on the surgical outcome. Surgery is not always the most appropriate course of action, particularly in patients who have received high dose corticosteroids, such as those with acute exacerbations of refractory ulcerative colitis. Corticosteroids steroids give more potential risk of post-operative complications. First-stage surgery for refractory ulcerative colitis is a sub total colectomy and ileostomy. According to national guidelines, a large proportion of patients with moderate to severe active UC patients have left sided disease. While the draft guidelines explain that surgery in proctitis is not considered due to disease distribution, the same must be said of left sided disease. Following initial stage of surgery, patients are left with a rectal stump in preparation for the second stage and pouch formation. There are variations of the stump size depending on the surgical findings and individual surgeons. Post-surgical complication of diversion proctitis and inflammation of the rectal stump can occur. This may be a contraindication for the final completion stage of the pouch, as described in the draft guidelines but can have on-going costs associated with further surgical intervention, medical management and patient distress and quality of life issues. We also express great concern over the initial recommendations and think they will unfairly deny access to infliximab in children with chronic active ulcerative colitis (UC) as outlined below: *[Section 1.2 of the ACD was included in the response but is not reproduced here.]* In conclusion, the current guidance does not accurately or fairly summarise all of the relevant evidence, the assumptions used to model the costings are flawed and it does not reflect current UK paediatric practice. We would suggest children be allowed access to an induction course of infliximab for chronic active UC with the option for responders only to carry on treatment with reassessment at one year in line with the current NICE guidance on infliximab for paediatric Crohn's disease. iv) **Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of race, gender, disability,**	

Consultee	Comment	Response
Royal College of Nursing (cont.)	**religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** **General Comments** The emphasis of the use of anti-TNF therapy in UC has been placed on the patient with severe disease requiring hospitalisation. We would suggest that in the current climate where the role of the specialist nurse is to reduce admission rates and length of stays for patients with IBD, as a result patients with moderate/ severe disease are being kept out of hospital for longer periods than previously with regular reviews in outpatients. The proposed guidance does not support this practice and has the potential to increase hospitalisations to provide patients with access to these therapies. We believe there are other exceptional circumstances that need to be highlighted. For example, we see at least 5 patients per year who are hospitalised on their first presentation of ulcerative colitis and who historically would have undergo a colectomy during this period of hospitalisation. The availability of biologic therapies in this scenario is invaluable, in that patients are given time to absorb their diagnosis and the implications of diagnosis which although may only delay surgery gives patients the time and opportunity to psychologically adjust to their change in health and longer term are more accepting of surgery. Throughout the document there is reference to Ulcerative Proctitis, this is one of the most challenging presentations of UC to manage in that only 40% of the dose of oral medical therapies are able to promote healing within this affected this area. We would suggest that a substantial number of patients require immunomodulating therapy and this is a mainstay of treatment of this patient group beyond the implied topical steroids advocated in the document. This group of patients have immense problems after colectomy in that their retained rectal stumps/ mucus fistula remains problematic with rectal bleeding and loss of mucus remaining a problem. This longer term influences surgical management. **Conclusion** In light of the comments and recommendations above the Royal College of Nursing do not support recommendations provided within the ACD of the above appraisal.	Comments noted.

Consultee	Comment	Response
Royal College of Physicians	The RCP is grateful for the opportunity to respond to the above ACD consultation. We wish to fully endorse the submissions made by the BSG and Crohn's and Colitis UK (CCUK). In addition, we would like to add a supporting statement from the UK IBD audit. The UK IBD audit collects data on people with inflammatory bowel disease (Crohn's and Ulcerative colitis). Patients newly starting on biological therapies are included in the national audit. These drugs have a potentially positive impact, they are a vital part of treatment and if withdrawn could be detrimental to the quality of life of patients. It is likely the cost of these drugs will decrease with the imminent introduction of biosimilars.	The Committee concluded that infliximab could be recommended for treating severely active ulcerative colitis in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy, or who cannot tolerate, or have medical contraindications for, such therapy. For further details, see sections 1.3 and 1.4 of the FAD.
UK Clinical Pharmacy Association	Response to the specific questions that you ask: • Has all of the relevant evidence been taken into account? • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? **Has all of the relevant evidence been taken into account?** • It has been felt that patients view has not been taken into account at an adequate and proportional level. It is acknowledged that there is not sound clinical evidence of the long-term impact of uncontrolled disease and/or surgery on patient quality of live, but ignoring patients views clearly voiced through Crohn's and Colitis UK and other patient representatives groups is in our view not acceptable. • In view of the impact that uncontrolled disease and/or surgery has on the patient reviewing short term outcomes based on current trials only does not represent patients reality. • Surgery as an event rather than comparator seems to be acceptable as acknowledged during the scoping workshop, data on the long-term effect of surgery is scant and it seems that the major impact of surgery on this young patient group at the beginning of their lives is ignored. • Pouch surgery, as reported by the pouch registry, had major impact on the quality of patients' lives in view of reduced female fertility by 40-50%, unacceptable high number of daily defaecation rates, high occurrence of pouchitis (50%) and recurrent need for surgery. • It is unclear why for the modelling it was chosen to enter the patient at age of 40 as the main manifestation of UC is between the ages of 15 and 25.	The Committee discussed with patient experts the nature of the condition and their experience with treatment. It also considered the value placed on the benefits of infliximab, adalimumab and golimumab by patients. For further details, see section 4.58 of the FAD. The Committee heard that 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. For further details, see section 4.61 of the FAD. The Assessment Group assumed that patients

Consultee	Comment	Response
UK Clinical Pharmacy Association (cont.)	Trials do not represent normal population but are trying to prove that they work at any age. So basing the model on an artificially aged patient group is not acceptable. • Crohn's and Colitis showed in 2011 that uncontrolled disease has an 50-70% productivity loss for the most sever affected patients. Educational attainment is curtailed, carrier options restricted and starting work life curtailed. This comes at a considerable cost to society which is difficult to quantify but of considerable size. Just to ignore this hidden cost due to difficulties of modelling is not acceptable. • It is debatable if conventional therapy is appropriate as a comparator. As UK patients would have failed conventional therapy prior to starting biologics it can safely be assumed that they would need continuous or repeated tretemtns with steroids incurring considerably long-term adverse effects of this therapy option. Alternatively it would mean surgery with the long-term impact outlined above. Surgery is not a cure but a therapy option with considerable detrimental impact on patients' lives and negative long-term outcomes. The current modelling does not take this into account as it assumes that patients would continue with conventional therapy and behave in the same way as the initial patients group. The right comparator would be patients failed on conventional therapy not treated with biologics. • Stopping rules may not have evidence from RCTs but there is enough evidence to show that stopping biologics once patient is in deep remission is an effective treatment strategy. (Molander, IBD 2014, Steenholdt Scand J GE 2012, Farkas Scand J GE 2013, Villafranca JCC 2014). STORI data has been shown to stratify patients successfully in Crohn's disease and similar studies show that stopping rules can be developed for UC. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** It is felt that extrapolating trial data from international trials to the reality of UK practice is not useful. In the UK only patients having failed conventional therapy would be offered biologics. Trials include treatment naïve and patients failed on conventional therapies. It is very likely that treatment failure patients behave differently to patients who would have responded to conventional therapy but were offered biologics straight away. We are not yet in the situation where we can predict which patients respond to certain therapies but it is evident that there are distinct patient subgroups that behave differently and have a different disease progression and response to treatment.	enter the model at the age of 40 years, in line with the patient characteristics in the RCTs. The Committee was aware that the effectiveness of TNF-alpha inhibitors in the model related to patients with moderate to severe disease, and not to those with more severe disease who would start treatment at a younger age than patients in the trials. For further details, see sections 4.43 and 4.70 of the FAD. The NICE reference case stipulates that the perspective on costs is that of the NHS and personal social services. For further details, see sections 5.1.9 and 5.1.10 of the Guide to the methods of technology appraisal 2013. Having heard that conventional therapy is generally regarded as an ongoing option throughout the treatment pathway for ulcerative colitis, the Committee concluded that conventional therapy is an option at the same stage at which TNF-alpha inhibitors would be considered. It appreciated, however, that for some patients in whom conventional therapy had failed, continuing the same type of therapy may be suboptimal. For further details, see section 4.62 of the FAD. The Committee noted the evidence on stopping rules. Without further evidence on the cost effectiveness of continuing or stopping TNF-alpha-inhibitor therapy in different clinical circumstances, it concluded that the criteria in NICE's technology appraisal guidance for TNF-alpha inhibitors for treating Crohn's disease could also be applied in this appraisal. For further details, see sections 4.64 and 4.71 of the FAD. All 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. For further details, see section

Consultee	Comment	Response
UK Clinical Pharmacy Association (cont.)	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** It is felt that too many maybe difficult to assess factors have been neglected or omitted in the final modelling that the model as it stands is neither representing the reality of the patient population nor the current UK practice and assumptions based on inappropriate data sources have been used to populate the model. Recommendation 1.3 is ambiguous as it is not clear which patient group is meant with current. It could be interpreted as patients started on infliximab under TAG 163 then could continue with the treatment as they were started within the NHS. In addition by adopting these MTA the UK would be at odds with the international IBD community ignoring consensus statements and guidelines such as ECCO 2102 and American College of Gastroenterology UC guidelines 2010. We would like to ask the committee to take the concerns about the appraisal process into consideration when finalising the guidance.	4.2 of the FAD. 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. The Committee noted that the uncertainty around the costs and QALYs for TNF-alpha inhibitors, in addition to the potential uncaptured QALY benefits, 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. For further details, see sections 4.78 and 4.80 of the FAD.

Comments received from commentators

There were no comments from commentators.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1 Conflict – yes		I have been a Consultant Gastroenterologist for over 12 years and working in a unit with a large population of patients with UC have dealt with many cases of moderate to severe UC. It is perhaps difficult to articulate the distress and disruption that this condition causes to people. Education is interrupted, employers lose patience and patients lose employment, relationships with friends and families are stretched to breaking point.	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

I have received an educational grant to attend European Gastroenterology week this year from Abbvie		Thankfully, nowadays, very few people die as a consequence of their disease but many many lives are adversely affected and many days of useful employment are lost. While for many individuals a colectomy with or without subsequent restorative (pouch) surgery is a good option when conventional therapy fails or isn't tolerated, this seldom results in restoration of normal physiological function and further inmpairment of quality of life and educational and employment potential results. Many colectomised patients are deeply traumatised by their surgery and would have given anything for the opportunity to avoid it. It is simplistic to see colectomy as an end point especially when looking at long term health related QoL. The effects of surgery on days off work, impaired social functioning continue well beyond the immediate post operative recovery period. Gretaer emphasis needs to be given to the deleterious effects of surgery on long term QoL	The Committee heard that surgery, although potentially curative, does not fully restore the patient's quality of life. The Committee concluded 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. For further details, see section 4.60 of the FAD.
		It is deeply iniquitous to deny access to a group of highly effective drugs to UK patients when experience of their use and utility continues to build up in other civilised countries in Europe, North America and beyond	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD.
		Already we are seeing a situation where patients from other EU countries are coming to live and work in the UK already established on anti TNF therapy for their UC	Comment noted.
		Many patients have struggled on with ineffective conventional therapy, putting up with unpredictable, frequenct loose stools, abdominal pain and incontinence, running the risk of chronic poor health, reduced social functioning and the risk of bowel cancer because of the absence of any middle ground between conventional therapy and surgery. I will be deeply disappointed to have to spend the next few years of my working life dealing with these problems in the knowledge that such an alternative exists but cannot be used in the UK because of an economic model which does not take account of all the factors involved in this illness	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD.
NHS Professional 2	General	I am extremely concerned that NICE have once again taken the decision to deny anti-TNF drugs to patients with moderate-severe ulcerative colitis (UC). Not only is this is out of step with European and American practice it is also against UK clinical experience with these drugs in this setting. In essence anti-TNF drugs are being compared against colectomy which is	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82

		not a fair or valid comparison. Many patients who have UC which is not responsive to so called conventional therapy or who are unable to tolerate these drugs very reasonably do not want to have a colectomy especially when knowing that they might derive significant benefit from an anti-TNF agent. Indeed some will refuse colectomy and carry on with debilitating symptoms, more frequent hospital contact, absence from work and ongoing steroid use with all the associated long term side effects. This is an intolerable and cruel situation when drugs are available from which some of these patients will derive life-changing benefit. The decision from NICE appears to be based on cost-benefit modelling, not lack of efficacy. Consequently patients who have ongoing symptomatic disease, unresponsive to currently â€˜recommended treatments, have to be told, in the clinic, that while there are drugs available that might literally transform their lives and allow them to keep their colons NICE have said that they cant have them because its apparently cheaper, based on a mathematical model, to offer a colectomy. Of course not all patients with UC will respond to anti-TNFs. But some do. Denying these patients a chance of a symptom free, steroid side effect free, life, based on a mathematical model of an unpredictable disease whose course varies enormously between different patients is not only ludicrous but unconscionable.	of the FAD. The Committee heard that conventional therapy is generally regarded as an ongoing option throughout the treatment pathway for ulcerative colitis. For further details, see sections 4.59 and 4.62 of the FAD. The Committee noted that the uncertainty around the costs and QALYs for TNF-alpha inhibitors, in addition to the potential uncaptured QALY benefits, 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. For further details, see section 4.80 of the FAD.
NHS Professional 3 Conflict – yes I do not work for the manufacture of these medications but Abvie (adalimumub) do sponsor educational events that I attend and have sponsored		"it is difficult to extrapolate from seemingly uniform clinical trials, with rigid inclusion criteria, to assess the impact of TNF-alpha-inhibitor therapy on patients quality of life compared with surgery." Just because it is hard to compare this information it doesn't mean it needs to be unregognised. Instead efforts to find out this information should be sort. I am unsure if you have taken into account the cost of complications due to surgery, cost of possible depression when trying to adapt to body image issues and being unable to face work. I appreciate that unless you have got the condition or work with patients that have the condition it is hard to appreciate the full benefit of having the above medications available instead having to go through major life changing surgery. With this in mind I am also puzzled to the fact that in the titles I would have thought you would have had gastroenterology consultant involvement on the apraisal committee I can not see any gastroenterology consultants listed. In my experience, some patients do choose collectomies, they feel they can deal with a stoma but for others - to take away the chance to retain	The Committee 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. For further details, see section 4.66 of the FAD. The Committee was not satisfied that all aspects of the patient's quality of life after surgery had been adequately captured in the economic analysis. For further details, see section 4.74. The Committee considered evidence on the nature of ulcerative colitis and the value placed on the benefits of infliximab, adalimumab and golimumab by patient and clinical experts.

meetings at my work place.		their body image and gain control of their symptoms by having the stated medication seems wrong.	
NHS Professional 4	General	This is an incredibly dissapointing and short sighted decision on behalf of NICE. My working day is taken up with caring for these patients, many of whom have a very poor quality of life. This decision means there is nothing else to offer them when Aza/6MP fail/are intollerant too. This results in either risking their health on long term steroids or major surgery, and for some this last option is the worst possible scenario. I implore you to put the patient at the heart of the decision and to consider the effect your decision will have, by taking away a potentially life changing treatment option from them.	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD.
NHS Professional 5		The impact on a patients quality of life of active Ulcerative colitis should not be underestimated, often the severe urgency resulting in incontinence and severe fatigue result in patients living a hermits existence. many will do badly in GCSEs and A levels detrimentally affecting the rest of their careers, they may not go to university as planned as a result and suffer huge loss of potential earnings. Many will have to give up work and do not leave the house and so have no social life often resulting in depression. The impact of these costs on the person involved and on the economy in general must not be underestimated.	The Committee heard that symptoms of ulcerative colitis can profoundly affect the patient's quality of life and disrupt their education, employment and family and social life. For further details, see section 4.58 of the FAD.
		For those who will not consider colectomy, or in whom it is contraindicated due to co-morbidities or extent of disease (i.e. proctitis) long term steroids are often the only option. These have major potential health implications such as osteoporosis, glaucoma and diabetes all of which have major cost implications.	The Committee noted that corticosteroids are associated with multiple consequences that can be costly, and these costs were not included in the model. 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. For further details, see section 4.75 of the FAD.
		I would ask the committee to put themselves in the patients shoes, can they imagine being told in your teenage years or early twenties that you need to have major surgery and a colostomy bag. These patients are just embarking on education, work life and building relationships. They are just discovering who they are as a person and building their self esteem, body image and self confidence. For many the idea of a colostomy is an unthinkable scenario and they cannot imagine how they would function or meet new people with a colostomy in situ.	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD.
NHS	General	The overall conclusions seem reasonable, although the continued	The Committee concluded that the economic

Professional 6 nothing to disclose		emphasis on the economic costs of colectomy are disappointing. What seems to be missing in this document, especially related to service provision effects, is the interactions with clinical research networks. As the document states the optimal management for thiopurine non-responding patients is not certain and whilst the ant-TNF drugs are theoretically an option, it must be agreed they are no that effective at all. There are many ongoing clinical trials supported by the Gastroenterology Research network of novel agents, the majority of these seem to be considerably more effective that any of the anti-TNFs in inducing both clinical remission and improvement. The whole point of the NIHR infrastructure was to support clinical research and increase the availability of clinical trials to potential patients. The correct option for the patients surely should not be have anti-TNFs of modest efficacy and great cost, or a colectomy but to enter a clinical trial, which actually offers greater chance of benefit? By not driving a increase in clinical trial participation in this important group, the NICE guideline group are condoning less than optimal practice and disadvantaging the patients. There is already too much reluctance to refer patients elsewhere, perhaps for better care, and certainly insufficient patients are referred to centres recruiting patients to trials. This then clearly creates post-code prescribing: patients in the local area of research active units, get better drugs and better results. Those patients local but not quite local enough, will just get a colectomy.This guidance is very much a missed opportunity to reinforce the benefits of clinical trial participation and involvement in the research network, when this will be a clear benefit to individual patients.	analysis had tended to underestimate the cost effectiveness of TNF-alpha inhibitors. It further thought that the cost effectiveness of TNF-alpha inhibitors could improve by applying a stopping rule similar to that recommended in NICE's technology appraisal guidance for TNF-alpha inhibitors for treating Crohn's disease. The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see sections 4.80 and 4.82 of the FAD.
NHS Professional 7 Conflict – yes I have received honoraria for speaking and served on advisory boards for manufacturers of		I have significant concerns that the recommendations as stated are based upon inappropriate evidence / assumptions and that the previously highlighted issues have not been taken into consideration. As it stands this guidance will cause huge harm to patients with ulcerative colitis and mandate patients with otherwise treatable disease to undergo mutilating surgery which is associated with a significant burden of side effects. These patients are often adolescent / young adults, and the implications for their social and work productivity are immeasurable 1) The model as it stands is unintelligible to most clinicians / patient groups, and the outputs seem to bear no relation to the clinical trial data as I understand it. 2) The patient groups included in the analysis are taken from the clinical trials which include patients who have simply failed a 5ASA. UK practice would be to treat patients with more severe disease (who have more to	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. The Committee noted that the uncertainty around the costs and QALYs for TNF-alpha inhibitors, in addition to the potential uncaptured QALY benefits, 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. For further details, see sections 4.78 and 4.80 of the FAD.

this technology		gain from therapy). 3) The side effects and costs of surgery are underestimated by a significant margin. Patients often have 3 major surgeries after colectomy. Costs of complications post surgery are not adequately considered. Nor are the costs of stoma appliances etc 4) Patients who fail anti TNF therapy do NOT simply go back to conventional therapy many will undergo surgery and others will remain with chronic un treated disease (and its associated appalling quality of life) in order to avoid this. 5) Patients who respond to anti TNF induction therapy have a much better long term outcome would it be possible to approve use for patients in the category? I would urge you to re-consider this decision	
NHS Professional 8	General	within our trust we do not use maintenance therapy for our UC patients. the acute and sub acute follow the same pathway. 2 doses of Infliximab, a repeat sigmoidoscopy then +/- a 3rd dose. if no improvement after 2nd dose they are then referred to the surgeons. Bridging with Infliximab for sub acute patietns allows us to introduce immunosuppressent therapy which can take up to 12/52 to have full effect. patients feel better faster and can return faster to their work/school or homelife. we undertook a prospective study looking at our UC patients that had been treated with Infliximab and the results were as follows: Efficacy of infliximab therapy in acute and sub-acute ulcerative colitis: A single centre retrospective study Cheema D, Harrison E, Nizamuddin M, Slater J, Wood L, Ishaq S, Cooper SC, de Silva S Abstract: Background: Ulcerative colitis (UC) is a chronic relapsing and remitting disease with almost a third of acute severe cases needing rescue therapy. Infliximab is NICE approved in the UK for treating acute severe UC and moderate to severely active UC that is non-responsive to conventional therapy, however limited data exists with respect to long term outcomes. Methods: We conducted a single centre retrospective review of patients with UC who received infliximab between July 2006 August 2013. Patients were grouped according to whether they had received infliximab for either an acute or sub-acute exacerbation. Data gathered included all treatment, colectomy rates, CRP and platelets at presentation and smoking status.	Comment noted.

		Fishers exact or Mann-Whitney U analyses were performed. Results: 50 patients received 1-6 doses of infliximab in the 85 month period studied, 23 for acute and 27 for sub-acute UC. 70% received 3 loading doses only, then up to 3 further maintenance doses if indicated. In the acute group 15 patients (65%) avoided colectomy, with a median follow-up of 38 months. 73% of the acute patients who avoided colectomy were immuno-naive. In the sub-acute group 21 patients (78%) avoided colectomy, with median follow-up of 29 months. All patients in the sub-acute group had previously been exposed to immunomodulators. Conclusions: Infliximab has potential benefits in the treatment of both acute and sub-acute UC. Immuno-naive patients with acute ulcerative colitis are more likely to benefit from infliximab than those patients previously exposed to immunomodulator therapy (p=0.04). This supports the use of infliximab in these groups of patients with UC. this study is continuous so more data has been collated and currently being written up. admitting every patient to hospital for inflxiimab is not cost effective for the Trust due to pressures on beds but also for the impact on the patients loss of earnings/education and social life all of which can have longer term implications. loss of education can lead to reduced capacity to get a job and so they may become more financially dependent upon society. for those patietns who do not wish to have a colectomy this could have long term consequences on their disease activity, increased disease activity and being diagnosed at a young age can both lead to an increased risk of colon cancer.	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD.
NHS Professional 9	General	Very disappointing. 1: I don't think patients will accept this. 2: The cost of surgery seems to have been vastly underestimated and the assumption made that it is a panacea - what about pouchitis, peristomal hernia, high output problems - all are costly and involve admission to hospital. 3: Finally, the report is written in unintelligible language with the findings hidden in obscure, poorly worded sentences. Since when has 'dominated' been part of the scientific lexicon when considering the efficacy of	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD. The Committee concluded that the cost of surgery was underestimated in the model. For further details, see section 4.77 of the FAD.

		medicines?	
NHS Professional 10 Conflict – yes I have contributed to ad boards for MSD, Abbvie and also delivered lectures regarding biological therapies to IBD Nurses at Bradford University.		Most patients are diagnosed in their late teens, early twenties before they are settled in a career, university or within a relationship. The unpredictability of the disease blights their career prospects, university attendance and causes self-esteem problems that make it difficult to establish a settled relationship. Faecal incontinance is common.	The Committee heard that symptoms of ulcerative colitis can profoundly affect the patient's quality of life and disrupt their education, employment and family and social life. For further details, see section 4.58 of the FAD.
		Steroids are not recommended as a long term treatment for Ulcerative Colitis.	The Committee acknowledged that some patients would rather not have corticosteroids because of the potential long-term consequences on their health. For further details, see section 4.62 of the FAD.
		Surgery can be complex and may result in a permanent ileostomy which has it's own financial and emotional costs. Poor pouch function following surgey affects 10% of patients with a pouch. Fertility can be affected and most women are advised to complete their family prior to opting for pouch surgery.	The Committee heard that surgery, although potentially curative, does not fully restore the patient's quality of life. For further details, see section 4.60 of the FAD.
		For those patients who either refuse surgery or are not suitable due to other co-morbidities, long term steroid use often results in osteoparosis, diabetes and hypertension increasing the risk of strokes and cardiac events.	The Committee appreciated that, as the peak age of onset of ulcerative colitis is 15–30 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. For further details, see section 4.58 of the FAD.
NHS Professional 11	General	We believe that antiTNF biologic therapy should be available to patients with moderate to severe disease, for whom failure of established medical therapy currently mandates colectomy. This is important as there are other novel therapies in development that patients who have conserved their colon might respond to; whereas a colectomy is a finite treatment with risk, following which novel treatments that may be effective and less expensive would not be possible to use.	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD.
NHS Professional 12 Conflict – yes		I do not feel that the complications (specifically Surgical Site infection and adhesions) post-surgery have been given enough consideration. Surgical site infections in bowel surgery and are underestimated my national surveillance schemes at approx 9%. These schemes look only at inpatient data and high quality surveillance undertaken as part of research studies put the rate at 27% (Tanner J, Khan D, Aplin C, Ball J, Thomas M,	The Committee concluded that the cost of surgery was underestimated in the model. For further details, see section 4.77 of the FAD.

My daughter has UC. Biologics have transformed her quality of life		Bankart J. Post-discharge surveillance to identify colorectal surgical site infection rates and related costs. Journal of Hospital Infection. 2009;72(3):243-50.) The cost associated with these SSIs was Â£ 10, 523 per case. The cost associated with abdominal pain and adhesions requiring further surgery also should be considered.	

NHS Professional 13	General	6th October 2014 Dear NICE Today we had a meeting of the British Society of Gastroenterology Inflammatory Bowel Disease (IBD) Clinical Research Group. At the end of the meeting many opinion-leading IBD gastroenterologists (including Doctors Mansfield (Newcastle}, Lees [Edinburgh], Bloom [UCH, London], Lindsay [Barts and the London], Probert [Liverpool], Moran [Nottingham], Ahmad [Exeter], Raine [Cambridge], and Hart [St Marks, London]) expressed substantial concern at the draft NICE guidance relating to the use of anti-TNF therapy in ulcerative colitis. In particular was concern at the complexity and tangential relevance of the modelling used to interrogate costs and benefits (making the analysis all but impenetrable even to experts in IBD management highly familiar with the literature on this topic) and the flawed assumptions on which it seems to be based, seemingly failing to recognise that: 1. The patients included in the published studies of anti-TNF therapy were NOT representative of the patients who would be considered for this treatment in the UK [ie mild disease refractory just to mesalazine treatment vs â€˜end of the line patients often refractory to steroid and azathioprine and in whom surgery is the only remaining option] 2. A smarter treatment algorithm could be implemented, for example allowing patients an induction course of anti-TNF therapy and only allowing maintenance in those who clearly make a complete response having a dramatic impact on the cost-benefit analysis 3. The arrival of bio-similars in Q2 2015 will inevitably reduce the costs associated with anti-TNF therapy and substantially alter assumptions made in the current cost-benefit analysis 4. Critically, many patients who undergo colectomy for ulcerative colitis are NOT cured and do NOT return to a normal quality of life. 39%1 are incontinent of faeces overnight and 26% suffer some daytime incontinence2. 20% suffer from sexual dysfunction3 with only 56% being able to conceive at 2 years4. 20% of patients have on-going problems relating to inflammation in the pouch at 1 year5. Many of these are managed with anti-TNF therapy and 13% require further surgery to remove the pouch2. Thus the evidence from the literature and the large	1. The Committee noted that most patients in the trials had moderate disease that was stable, whereas in UK clinical practice, patients in whom TNF-alpha-inhibitor therapy would be considered are more likely to have severe, rather than moderate, disease. For further details, see section 4.66 of the FAD. 2. In the Assessment Group's model, all patients started in the induction phase. 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. For further details, see section 4.43 of the FAD. 3. The Committee concluded that its recommendations for infliximab could apply both to the reference product and to its biosimilars. For further details, see section 4.81 of the FAD. 4. The Committee heard that surgery, although potentially curative, does not fully restore the patient's quality of life. It also heard that several studies illustrated the poor quality of life of patients after surgery, resulting from post-surgical complications including reduced fertility and faecal incontinence. For further details, see sections 4.60 and 4.73 of the FAD.

		collective experience of our panel is that the traditional assumption â€˜colectomy = cure is deeply flawed, and that a modelled dysutility value for post surgery of 0.75 based on the paper by Woehl presents a hugely optimistic assessment. Accurate assessments of the costs and morbidity associated with post-surgical complications and care must be included in the model. We would strongly urge your committee to reconsider its analysis and the details of its modelling, and further engage experts in the gastroenterology and IBD community to input into the process. Otherwise we fear a grave injustice being done to this predominantly young and economically active patient group which would put UK practise at variance with the rest of Europe and North America, and which risks undermining confidence in the undoubted strengths of NICE. Thank you for taking these views into consideration Yours truly Chair, British Society of Gastroenterology IBD Clinical Research Group 1. de Buck van Overstraeten A, Wolthuis AM, et al. Long-term functional outcome after ileal pouch anal anastomosis in 191 patients with ulcerative colitis J Crohns Colitis. 2014 Oct 1;8(10):1261- 2. Wheeler JM, Banerjee A, Ahuja N, Jewell DP, Mortensen NJ. Long-term function after restorative proctocolectomy. Dis Colon Rectum. 2005 May;48(5):946-51. 3. Chapman JR, Larson DW, Wolff BG, Dozois EJ, Cima RR, Pemberton JH, et al. Ileal pouch-anal anastomosis: does age at the time of surgery affect outcome? Arch Surg 2005;140(6):5349 4. Hueting WE, Gooszen HG, van Laarhoven CJ. Sexual function and continence after ileo pouch anal anastomosis: a comparison between a meta-analysis and a questionnaire survey. Int J Colorectal Dis 2004;19(3):2158. 5. Hahnloser D, Pemberton JH, Wolff BG, Larson DR, Crownhart BS, Dozois RR. Results at up to 20 years after ileal pouch anal anastomosis for chronic ulcerative colitis. Br J Surg2007;94(3):33340.	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD.

NHS Professional 14		I have read the document in some detail and I am afraid that I believe many of the assumptions made are incorrect such that the conclusions drawn are unsafe. One of the biggest flaws relates to the outcome after failure of anti-TNF. As I understand, it is assumed that the majority of such patients will simply go back onto conventional therapy and that it will work. This is ludicrous. The only remainiing option currently after failure of anti-TNF is surgery. Returning to conventional therapy is not a treatment option in this situation. The fact that some patients choose to refuse surgery at that time prefering to live with chronic ill health, often with ongoing steriod exposure is simply a reflection of tthe unwillingness of patients to undergo surgery. As a treating physician, there is currently no other NICE approved therapy in this situation although if vedolizumab was approved, this would be an apppropriate traement at that time. To suggest that only 1% of this cohort go to surgery is grossly misleading. Again, one could argue that 1100% of such patients should go to surgery - I would imagine that probably 50-70% actually choose surgery within 12 months in this situation.	The Committee agreed that there was a high degree of uncertainty associated with the assumptions about the sequencing and timing of conventional therapies in the pathway of care for ulcerative colitis. For further details, see sections 4.59 and 4.78 of the FAD. The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD.
		As far as I can tell, the costs of chronic active disease and ongoing steroid dependency in the group mentioned above are not accurately considered. Chronic active disease is associated with an increased risk of malignancy, with very poor quality of life with disease related complications such as poor nutrition, aextraintestinal manifestations, an increased risk of thromboembolism, reduced fertility, osteoporosis etc. In addition, many of these patients will also be steroid dependent increasing the risk of chroinc disease including diabetes, hypertenision, osteoporosis and cataracts. Has this been introduced into the costing model?	The symptoms of ulcerative colitis should be captured in the QALY estimates. The Committee agreed that there was a high degree of uncertainty associated with the utility values for patients at the different points in the pathway of care for ulcerative colitis, particularly for patients who had surgery. For further details, see sections 4.73 and 4.78 of the FAD. Neither the cost of corticosteroids nor the costs of their consequences were 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. For further details, see section 4.75 of the FAD.
		It would appear that the costs of surgery are not fully considered. Most surgery is done as a 3 stage procedure (occasionaly to stage). But this is not a cure for the disease. Pouchitis is common and often recurrent. Pouch failure occurs. Increased use of fertility treatment as well as	The Committee concluded that the cost of surgery was underestimated in the model. For further details, see section 4.77 of the FAD. The Committee was not satisfied that all aspects of

		treatemnt for erectile dysfunction needs to be considered. Admission with intestinal obstruction also needs to be considered	the patient's quality of life after surgery had been adequately captured in the economic analysis. For further details, see section 4.74.
		As far as I can tell, no consideration has been given to the possibility of discontinuing thearpy with anti-TNF. In general, as for Crohn's disease, it would not be unreasonable to consider a model in which treatment is reconsidered in patients in remission after 1 year of therapy	The Committee concluded that the criteria in NICE's technology appraisal guidance for TNF-alpha inhibitors for treating Crohn's disease could also be applied in this appraisal. For further details, see sections 4.65 and 4.71 of the FAD.
		Ulcerative colitis is a young person's disease. The cost to society of preventing people from reaching their full educational achievement through school and tertiary education as well as work absence cannot be forgotten. Whilst I accept that this may be difficult to model, ignoring this important matter discriminates against young people and people with UC	The NICE reference case stipulates that the perspective on costs is that of the NHS and personal social services. For further details, see sections 5.1.9 and 5.1.10 of the Guide to the methods of technology appraisal 2013.
		I find it difficult to understand how the ACERs can be so drastically different to Crohn's disease. Whilst the trials are somewhat different, the differences in response and effects on disease activity and quality of life are not in reality so great. This suggests that there must be something wrong with the models	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. For further details, see section 4.78 of the FAD.
NHS Professional 15		Committee agrees that there is evidence for clinical effectiveness of all three anti TNF agents in this group of patients with moderate to severe UC. Cost analysis is flawed - conventional therapy as a comparitor is fundamentally a flaw as by definition these are patients who are failing on conventional therapy - if the conventional therapy was working they would not need anti-TNF. I understant the committee is not strictly using surgery as a comparitor but would like to state that it must not be seen as an alternative to anti TNF as many patients refuse this and would not consider it, also costs of surgery grossly underestimated (drug cost of zero, single surgery rather that 3 visits (pouch), cost of onging post surgical care (stoma issues, pouchitis etc) not adequately included. I would argue that a subgroup of patients should be allowed anti-tnf - those who refuse surgery and in whom conventional therapy (steroids, mesalasines, thiopurines and sometimes calcineurin inhibitors) have failed to work (on going need for high dose steroids, no mucosal healing with severe symptoms.	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. The Committee noted that the uncertainty around the costs and QALYs for TNF-alpha inhibitors, in addition to the potential uncaptured QALY benefits, 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. For further details, see sections 4.78 and 4.80 of the FAD.
NHS Professional	General	I am concerned that patients who fail conventional treatment will be denied bio logics which do have evidence for their effectiveness. tHis could lead to patients becoming dependant on steroids, increasing their risk of long	The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely

16		term side effects such as diabetes and osteoporosis which will Impact on the health economy. they will have to endure poor health, poor quality of life, and be unable to work. Patients will require more hospital follow ups. There will probably be an increase in patients requiring colectomy, which is mutilating surgery for this group of patients who are generally of a younger age, there will most likely be an increase in patients requesting ileoanal pouch reconstruction, therefore more investment into centres that provide this surgery will be required. There will also be an massive increase in the individual funding requests to the clinical commissioning groups, adding extra work load to the clinicians involved with these patients	active ulcerative colitis, in line with their marketing authorisations. For further details, see section 4.82 of the FAD.
NHS Professional 17 Conflict – yes Received honoraria to speak from MSD.		I am concerned that the models are flawed, the 100-year time horizon is too long and that to condemn all patients who fail to respond to conventional therapy to surgery is grossly unfair.	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. For further details, see section 4.70 of the FAD.
NHS Professional 18	General	As a health professional and a sufferer of UC I am saddened to read this document and the conclusions. As a health professional I have seen numerous UC patients improve and thrive on these biologics, not only in regards to their medical health but also their QOL. From a personal point of view I have received Infliximab and adalimumab which have provided me with an excellent QOL and enabled me to continue my working role in the NHS. I received 4 infusions of Infliximab 4 years ago and remained in remission until a surveillance colonoscopy triggered a moderate to severe flare this year. I was very fortunate to be enrolled on a humira trial for 6 months this year and the response was immediate. I am now in remission and did not miss 1 day of work, avoided a hospital admission and avoided an increase in my medications. I did not need to see my GP nor consultant about my UC during the trial and only saw the trial doctor as per trial protocol. Surgery is not an option for me, ever. I find it hard to believe in todays medical world that biologics are not the most cost effective way forward. As a health professional with an interest	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. The Committee noted that the uncertainty around the costs and QALYs for TNF-alpha inhibitors, in addition to the potential uncaptured QALY benefits, 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. The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations.

		in IBD I have read numerous international papers demonstrating a medical benefit, cost benefit and QOL benefit. From my case alone I have proved how cost effective it can be which compares well with what research is demonstrating. This is a very sad step backwards for IBD patients and to see NICE choosing to restrict UC patients to surgery (or at best 3 infusions of Infliximab) if second line treatment fails is very upsetting and prejudice to this group of patients. This will lead to poorer patient-doctor relationship and increased stress in this patient group due to the limited options available. Yes, I know that side effects are expected with most drugs. However the 1st and 2nd line treatments for UC are not without their own devastating side effects which impact upon QOL e.g. steroids and their known negative impact on bone health as well as development of diabetes in some patients both of which are also costly for the NHS. To conclude, I am immensely disappointed in NICE from both a patient perspective but also as a health professional who strives to first do no harm, puts patients first and takes on board patient choice and overall well being. This proposed guidance will do harm, does not put patients first, removes patient choice and will lead to reduce QOL and well being. It is in short shameful.	For further details, see sections 4.78, 4.80 and 4.82 of the FAD.

Summary of comments received from members of the public

Theme	Response
The positive experience of patients with TNF-alpha-inhibitor treatments	The Committee heard from patient experts about the nature of the condition and the experts' experience with treatment. It also considered the value placed on the benefits of infliximab, adalimumab and golimumab by patients. The Committee concluded that the economic analysis had tended to underestimate the cost effectiveness of TNF-alpha inhibitors. It further thought that the cost effectiveness of TNF-alpha inhibitors could improve by applying a stopping rule similar to that recommended in NICE's technology appraisal guidance for TNF-alpha inhibitors for treating Crohn's disease. The Committee concluded that infliximab, adalimumab and golimumab could be recommended for treating moderately to severely active ulcerative colitis, in line with their marketing authorisations. For further details, see sections 4.58, 4.80 and 4.82 of the FAD.

[i] Health & Social Care Information Centre. Hospital Prescribing: England 2012. 13 November 2013. Available at http://www.hscic.gov.uk/catalogue/PUB12651/hosp-pres-eng-2012-rep.pdf. Accessed 14/10/2014.