BRITISH SOCIETY OF GASTROENTEROLOGY

Multiple Technology Appraisal (MTA)
Appraisal Consultation Document
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 on behalf of the 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 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 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 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.

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.

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.

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 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.

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 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.

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.

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:

Subtotal colectomy

HRG code	HRG name	Combined day case / ordinary elective spell tariff (£)
FZ08A	Complex Large Intestine Procedures with Major CC	11,536
FZ08B	Complex Large Intestine Procedures without Major CC	7,408

Ileoanal pouch formation

HRG code	HRG name	Combined day case / ordinary elective spell tariff (£)
FZ67A	Major Small Intestine Procedures 19 years and over with CC	5,349
FZ67B	Major Small Intestine Procedures 19 years and over without CC	3,828

Reversal of ileostomy

HRG code	HRG name	Combined day case / ordinary elective spell tariff (£)
FZ67A	Major Small Intestine Procedures 19 years and over with CC	5,349
FZ67B	Major Small Intestine Procedures 19 years and over without CC	3,828

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 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.

14th October 2014