DSU responses to comments received on DSU Crohns Report 2.
10 August 2009

Schering Plough	DSU response
No reference was made in the DSU report about the new evidence presented to the Committee (Bodger et al. analysis) and its relevance in this reconciliation exercise.	The DSU provided comments on key structural issues in our previous report. However, there are several reasons why the replication in our second report does not consider the Bodger paper: 1. We did not have access to the electronic version of this model in order to review it. 2. We were unable to replicate the transition matrices either for standard care or for the treatment arms, using the information supplied in the publication. 3. The paper is of limited relevance to the decision problem faced in this appraisal since it does not consider episodic treatment as an alternative to maintenance therapy. ICERs for maintenance therapy in most scenarios in the DSU report, and the original Leeds modelling work, are calculated compared to episodic, not standard care. 4. The focus of the paper is maintenance therapy with a stopping rule (1,2 yrs in the base case. It is not clear how such a stopping rule relates to the decision problem faced by NICE or how such stopping rules could be administered in clinical practice. Despite differences in the analyses it is worth noting the similarity of results between the Bodger and DSU amended version of the Leeds model. Table 3 (Bodger et al.) shows infliximab for 4 years generates an ICER of £30k. Table 11 (DSU report) shows an ICER for 5 yrs maintenance of £34k (change 12, compared to standard care). It is also worth noting that adalimumab dominates infliximab in the Bodger et al analysis.
One of the important structural limitations is the inability of the AG model to fully account for treatment benefits in patients responding to TNF-α inhibitors who have not yet achieved remission.	The DSU agrees that the model does not reflect these benefits. This is a limitation that is shared with the SP model. Hence the reconciliation retains this limitation.
Therapeutic equivalence between adalimumab and infliximab in both episodic and	DSU has made not made the assumption of therapeutic equivalence. Results are

maintenance treatment was assumed	provided in the DSU report that demonstrate the resultant ICERs if the cost of adalimumab is substituted into the revised Leeds model. Coincidentally, the original Leeds model used the same point estimate of effectiveness for both infliximab and adalimumab (0.56). These estimates came from the CHARM and ACCENT trials respectively. The AG cited heterogeneity between the studies as a reason for not conducting an indirect comparison (see page 145 of the HTA report for detailed discussion). The same rationale was cited by Bodger et al: "We considered combining indirect evidence in a mixed treatment comparison, but heterogeneity in the trials precluded this. (p.268 Bodger)
Drug acquisition cost the mean number of vials used in clinical practice is 3.5	The DSU did not re-examine the evidence on the distribution of weight amongst CD patients. Leeds calculated the cost of 4 vials at £1,678 (4 x £419.62 net price of 100mg vial). This is used in their estimate of the drug acquisition cost of a course of treatment. Leeds estimated the mean weight of patients from four trials (CHARM, CLASSIC, GAIN and Targan) as 71.5kg. Therefore a course of treatment (5 mg/kg) for a 71.5kg patient would require 357.5mg, or 4 x 100mg vials. SP debate the mean weight of patients that Leeds estimated, and provide unpublished patient data on the distribution of weights and vials used for 185 patients with fistulating and non-fistulating CD. They believe that the weight of a patient with severe CD is likely to be lower than 71.5kg. The mean of the distribution of vials used in this cohort of patients is 3.50 (i.e. the mean amount used once vials have already been rounded up). In the DSU report, we have incorporated this change as part of the model reconciliation (change 4, section 4.1.5). In fact, the results are based on a mean of 3 vials that was in the original SP submission, not 3.5 vials referred to in subsequent rounds of consultation.
Drug administration cost £258 per infusion throughout the analysis. This is inaccurate. The estimated cost of an infliximab infusion, based on current clinical practice, is £99.25 per infusion. This figure is based on a day case in an IBD ward costing £397, during	The DSU did not re-examine the evidence on the unit costs of drug administration in our report. The Leeds model uses a value of £257.50 for the cost of an infliximab infusion from the Psoriatic Arthritis TA (TA104).

which time there can be as many as 4 infusions (2 hours/infusion). Infliximab treatment costs based on this administration cost were not challenged by the Committee during their appraisal of infliximab in acute ulcerative colitis (TA 163). This figure also is well within the range of plausible administration costs for infliximab accepted by the Committee in a previous appraisal of infliximab in psoriasis (TAG 134; Section 4.11, page 14).	Schering-Plough argue that this estimate is inaccurate, and provide a new estimate of £99.25, based on a day case IBD ward cost of £397 divided by 4. We have two queries regarding this calculation: i) there is no rationale given for the assertion that "there can be as many as 4 infusions" ii) We were unable to find the £397 estimate by Schering-Plough in the reference cost data. Day case HRG code F56 Inflammatory Bowel Disease" is £474. SP claim the same costs were used in TA163 Ulcerative Colitis. Yet in TA163 the manufacturer submission states: "For drug administration, we used the cost of a "Consultant led face to face adult follow‐up" attendance data in medical gastroenterology, i.e. £94, which was considered as an aggregate incorporating all tests, assessments and staffing costs associated with the infusion (NHS reference costs 2006‐07). This administration cost has already been deemed appropriate in a previous NICE appraisal (TAG 134)." (page 48, SP submission TA163). In the DSU report, we have incorporated this change as part of the model reconciliation (change 4, section 4.1.5). The results are based on an administration cost of £96.
Episodic treatment cost The AG assumed that the cost of treating CD patients episodically with infliximab is equivalent to a full induction dose (week 0, 2 and 6) at the beginning and at the time of every relapse, thus resulting in a treatment cost of £5,809 per relapse (£4,066 per relapse according to Schering-Plough calculations). This neither is in accordance with the current SPC for infliximab nor is in line with the current clinical practice in the UK.	SP are correct that the AG model estimates the cost of episodic treatment when a patient relapses is the same as the full induction dose (week 0,2 and 6). They are also correct that the SPC does not endorse this treatment regimen when a patient relapses, and instead are to only get a "further dose of 5 mg/kg if signs and symptoms recur." To address this issue we have amended the Leeds model further by changing the cost for episodic treatment subsequent to the first induction dose to £1355.19 (3 vials of infliximab plus £96 administration cost). We also changed the cost of the initial induction dose to reflect dosing at wks 0 and 2 (£2710.38) instead of 0,2 and 6 (4065.57). This was run in the reconciled DSU model (Change 12 – incorporating 2a). **Table 1 - Cost-effectiveness of infliximab with revised episodic treatment cost** SC 52,773 2.7868

	<table><tr><td>Epi</td><td>54,149</td><td>2.8254</td><td></td></tr><tr><td>Main</td><td>56,940</td><td>2.9111</td><td></td></tr><tr><td></td><td></td><td></td><td></td></tr><tr><td>Epi vs SC</td><td>1,376</td><td>0.039</td><td>35,648</td></tr><tr><td>Main vs SC</td><td>4,167</td><td>0.124</td><td>33,524</td></tr><tr><td>Main vs EPI</td><td>2,791</td><td>0.086</td><td>32,567</td></tr></table> This modification sees an improvement in the ICER from £118k to £36k. It should be noted that this is based on the original SP costs including 3 vials instead of 3.5. When 3.5 vials are assumed the ICER exceed £50k.
RCN	No DSU comment
BSG/RCP	
We note with approval that the previous problems arising from reliance on probabilities derived largely from the Silverstein study have been tackled.	
We would like to reiterate that there is now very clear evidence showing that maintenance therapy is more effective than episodic therapy, including reduced rates for hospital readmission and surgery and the UK is now, we believe, the only country where episodic anti-TNF therapy is still practiced for this condition. It follows from 4 above that there is a strong argument for comparing the cost-effectiveness of maintenance anti-TNF therapy with standard therapy rather than with episodic anti-TNF therapy. This lowers the ICERs still further.	Comparisons should be made with the next best alternative, not necessarily to standard care.
We would recommend that NICE also take into account the recent peer-reviewed and published cost effectiveness evaluation by Bodger et al (Alimentary Pharmacology and Therapeutics 2009;30:265-74; see attached pdf) which reports ICERs for 1 year maintenance therapy versus standard therapy of £19,050 and £7190 for infliximab and adalimumab respectively and, for 2 years maintenance, £21,300 and £10,310 respectively.	See previous comments to SP
Abbott	

. We believe the estimates that the Leeds Model, as well as the Schering Plough (SP) Model and amended Leeds Model used for surgery and relapse state costs are biased downwards. This is because either they are not CD-specific but rather are general costs for inflammatory bowel diseases, as per the Leeds Models; or are derived from data published more than ten years ago, as per the SP Model. Abbott's model uses the more appropriate, CD-specific estimate for the costs available from Bassi et al. (2004),[i] a NHS hospital-based, peer-reviewed micro-costing study. Bassi et al provided details of regression model coefficients, from which costs for CD-only patients could be estimated.	It was not within our remit to review the evidence or construct a new model. We have tried to reconcile the models and inevitably focussed on the SP approach given the closer structural approach with Leeds.
NACC	
➢ We were disappointed that a detailed discussion of the work of Dr Bodger and colleagues, which was informally submitted to the Committee in 2008 and referred to in the interim DSU report in January 2009, was not included in the final DSU Report although it has been published in the interim. This is a significant missed opportunity to provide the Committee with all the available evidence to take into account in making their decision.	See previous comment to SP above
1. The adapted AG Model only considers as a benefit the state of full-remission, yet we know that one third of patients respond but do not achieve full remission. This response is still of real clinical benefit in managing the disease and offers a quality of life improvement to patients. This benefit is not captured in the AG Model and therefore undervalues the benefit of treatment. We consider this to bean error in the preparation of the Schering-Plough Model also. It is interesting to note that this partial benefit is taken into account both in the Abbott model and in the model created by Dr Bodger and colleagues. The latter paper found both adalimumab and infliximab to be cost-effective in NHS terms. The fact that partial benefit is taken into account in both these models is, we believe, contributing to the ICERs for infliximab being above the threshold.	The conclusions of the Bodger paper are not as represented in these comments. As noted above, the Bodger paper demonstrates that maintenance infliximab ceases to be cost effective at a threshold of £30k after 4 yrs therapy, compared to standard care, not episodic care.
2. The Silverstein cohort models the course of disease and standard care for a	As detailed in the DSU report (section 4.1.10), the rates of surgery for patients on

	whole IBD population. Their rate of surgery is likely to be significantly lower than the population of patients who are considered for treatment with biologics. We find it very difficult to know whether this has been fully taken into account and whether the assumptions on surgery reflect clinical reality.	biologic treatments have been taken directly from the transition probabilities used by the Schering Plough model, to reconcile the differences between the Leeds and Schering Plough. For most transitions the probability of moving to the surgery state is lower that the original Leeds, Silverstein based approach. The exception is the transition from post surgical remission to surgery which is higher in the revised model.
3.	The assumed weight of the average patient is obviously one determinant of the cost of therapy. We believe that the DSU adapted model retains the assumption that the average patient is 80kgs. If so, this has been disputed previously in responses from consultees.	Please see the previous response to comments made by SP

[i] Bassi A., Dodd S., Williamson P., Bodger K. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. *Gut* 2004; 53:1471-1478.