Meindert Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
10 Spring Gardens
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15th October 2014

Dear Meindert,

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.

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.

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.

Kind regards,

[redacted]

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).

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 wrongful assumption that surgery is completed in one procedure. In reality, up to three procedures are required.

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.

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.

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).

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.

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.

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 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.

Issues identified with AG budget impact

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[1]. 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.

Issues identified in ACD

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.

Page number (section)	Text	Issue
4 (2.1)	"toxic megacolon (trapped gases in the colon causing it to swell)"	This statement does not appropriately convey the potentially life-threatening nature of toxic megacolon.
4 (2.3)	"The modified Truelove and Witts severity index is widely used to classify the severity of ulcerative colitis"	The clinical expert attending the first Committee meeting indicated that the Truelove and Witts scale is used more frequently and more appropriately in the classification of acute severe UC.
5 (2.4)	"The management of mildly to moderately active ulcerative colitis"	The management of mild UC is not relevant to this appraisal although we acknowledge that conventional therapy for moderate to severe UC can be similarly defined. We note that the only options described here are conventional therapy, TNF-α inhibitors, and colectomy which highlights the paucity of remaining options once conventional therapy has failed.
6 (3.4)	"the monthly cost of adalimumab maintenance therapy is £704"	This cost is based on list price. If the dose escalation that is permitted within the Humira marketing authorization and was observed in the pivotal clinical trial and other studies is considered, the cost would be increased.
8 (3.7)	"the monthly cost of golimumab maintenance therapy is £763"	This has been described incorrectly; this cost relates to a 4-week not a month long period.
9 (3.10)	"the monthly cost of infliximab maintenance therapy is £210"	This is incorrect; the cost of infliximab maintenance therapy should be £909 not £210. It may also be more appropriate to describe it as 4-weekly (as the drug is administered on an 8-weekly basis).
9 (3.11)	"Biosimilar versions of infliximab (Inflectra, Hospira; Remsima, Celltrion) have a marketing	As the final guidance is scheduled to be published prior to the patent expiry for Remicade it would be

Page number (section)	Text	Issue
	authorisation in the UK for the same indications"	helpful to note that these biosimilar versions are not available for use until that date.
11 (4.3)	"The Assessment Group noted that none of the trials included patients who had been treated before with corticosteroids and mercaptopurine or azathioprine, even though adalimumab, golimumab and infliximab are licensed for patients whose disease has had an inadequate response to, or who are intolerant to or have medical contraindications for, such therapies"	This statement is incorrect; for example, in PURSUIT the majority of subjects (99.8%) had an inadequate response to, were intolerant of ≥1 of the specified conventional therapies, +/or demonstrated corticosteroid dependence (71.9% had an inadequate response to, intolerance of, or dependence on corticosteroids; 52.0% had an inadequate response to or intolerance of 6-MP/AZA; 94.7% had an inadequate response or intolerance of 5-ASAs [among subjects randomised following implementation of protocol amendment 1 - for this amendment entry criteria were modified to allow subjects who were only refractory to or intolerant of oral 5-ASAs to be considered eligible to enter the study. A 10% enrollment cap was placed on this criterion and only 5.5% of randomised subjects met this criterion]).
11 (4.4)	"The primary endpoint in all the RCTs was clinical response or remission at pre-specified time points"	This is incorrect; the primary endpoint in the PURSUIT Maintenance trial was continuous clinical response.
11 (4.10)	"the Assessment Group indicated that the results of PURSUIT-Maintenance may be biased"	It is not clear why bias has been suggested. PURSUIT was designed as a randomised withdrawal study to be more reflective of clinical practice and to address an important question around the impact of maintenance treatment following induction. It is important to acknowledge that PURSUIT has a rigorous primary endpoint (continuous clinical response) which is more difficult to achieve and is not directly comparable with the efficacy endpoints at designated time points in trials of other TNF-α inhibitors. Further, both the placebo and the Simponi arms were exposed to Simponi induction. Therefore, the absolute difference in efficacy between the two arms is still a relevant indicator of efficacy.
15 (4.11)	"the rate at which patients had serious adverse events or stopped treatment because of an adverse event was higher in the 100 mg group"	This statement does not acknowledge the impact of the longer follow-up time in the 100mg group, nor the fact that patients were not randomised to the two strengths based on their weight in the study as they would be in clinical practice.
18 (4.17)	"maintenance of clinical response or remission at week 32 for patients starting with a clinical response at week 8"	As stated previously in our response to the AG report, we believe it is more appropriate to assess response/remission over the entire maintenance period. The current approach disadvantages Simponi compared to the other biologics due to the more stringent requirements for response to Simponi.

Page number (section)	Text	Issue
21 (4.22)	"(38.1% compared with 18.2%; p-values not reported)"	The p value is reported in the Hyams *et al*. publication (0.146).
24 (4.28)	"Patients who had infliximab stated that the side effects of corticosteroids, notably rounded face and severe acne"	While the listed side effects are important, this statement does not capture the full extent of side effects e.g. osteoporosis, diabetes, hypertension (which not only result in poor quality of life but will also demand healthcare resource use for monitoring and management).
28 (4.39)	"but deviated from the final scope in that conventional therapy was not included as a comparator"	Conventional therapy is not an appropriate comparator for TNF-α inhibitors given the marketing authorisations for these biologics. MSD believes that the inclusion of conventional therapy as a comparator is one of the key flaws underlying the AG approach.
28 (4.39)	"Furthermore, it stated that the company – having assumed that patients can only have corticosteroids or colectomy after TNF-alpha therapy fails – modelled a treatment pathway associated with severe disease, not moderate to severe disease for which further medical treatment would still be considered"	As the marketing authorisations for TNF-α inhibitors stipulate that they can only be used when conventional therapy has failed; there are no other effective medical treatments that can be considered after the failure of TNF-α inhibitors (although some patients may persist with sub-optimal conventional therapy). The only remaining new option is colectomy, and this is true regardless of disease severity. On the advice of UK clinical experts MSD modelled a period of relapse management in which IV corticosteroids are used to stabilise the patient in the *short term* as preparation for surgery (note that these IV corticosteroids would not be considered as part of conventional therapy). This treatment pathway is aligned with that described in the NICE UC Clinical Guideline, which also states that colectomy can be considered at any time, not only for severe disease.
28 (4.39)	"the company did not describe its network meta-analyses in sufficient detail"	This criticism has already been addressed in our response to the AG report, where additional information on the MSD NMA was provided to the AG.
28 (4.39)	"The 2 company models used different sources for the utility values and made different assumptions about resource use"	As explained in our response to the AG report, the two sets of utility values used reflect the fact that two models were submitted by MSD, one for Remicade (utilising utility data from ACT1/2) and one for Simponi (utility data from PURSUIT). Further, it is not clear what the AG are referring to when they state that MSD made different assumptions about resource use in each model as we did not take this approach.
28 (4.39)	"The Assessment group indicated that in an incremental analysis, infliximab should be compared with golimumab"	It is not clear why the AG have concluded this. MSD believe it is equally as valid and relevant to the decision problem to compare Simponi against Humira (and they are both subcutaneous agents) or

Page number (section)	Text	Issue
		to colectomy.
29 (4.40)	"for moderate to severe ulcerative colitis that had failed at least 1 previous therapy"	The way the population is described in the ACD is outside the licensed indication for each of the TNF-α inhibitors. It also differs from the way the population is defined in the appraisal scope: "People with moderately to severely active ulcerative colitis (excluding those with acute severe ulcerative colitis, as defined in the background section), whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant of or have medical contraindications to such therapies".
30 (4.42)	"Patients who started on conventional therapy and those who started on a TNF-alpha inhibitor but then moved to conventional therapy continued conventional therapy in the maintenance phase whether or not their disease responded or remitted, but they could have colectomy if their disease remained active"	In additional to the fundamental issue that conventional therapy should not be included as a comparator in the AG model, it does not seem appropriate for patients in the model to remain on conventional therapy regardless of whether they respond or not. ECCO guidelines[2] state that "Continued medical therapy that does not achieve a clear clinical benefit is not recommended". In the AG model patients may proceed to surgery while receiving conventional therapy; however, the rate at which this occurs is very low (as discussed earlier in this response). For patients receiving TNF-α inhibitors who fail, it is inappropriate for those patients to proceed to conventional therapy as they should have failed conventional therapy previously in order to be considered for treatment with TNF-α inhibitors. These patients are also not able to move directly to surgery without receiving more conventional therapy, whether they respond to it or not.
30 (4.43)	"To derive the rate at which patients have colectomy, the Assessment Group used a study by Solberg et al. estimating that every 6 months 0.51% of patients have colectomy"	The Solberg study describes the colectomy rate in all UC patients from time of diagnosis but does not categorise patients by severity. Patients are also newly-diagnosed with UC. Therefore, Solberg cannot be said to focus on the moderate to severe UC population who have failed conventional therapy. In addition, the colectomy rate reported by Solberg et al. was 3.5% at 1 year so it is not clear how the AG derived a rate of 0.51% every 6 months. MSD suggests that the rate of surgery should be informed by the approach taken in the MSD model, in which the estimated colectomy rates were closer to those reported in observational studies of Remicade than the AG estimates were.

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31 (4.45)	"The Assessment Group stated that the studies by Woehl et al. and Swinburn et al. were the most useful to source utility values in the model because they were UK-based, included reasonably large number of patients (n=180 and n=230 respectively)"	It is important to record that the Woehl reference stated in appraisal documentation to date is incorrect (the reference listed at #109 in the AG report is for an abstract, in Crohn's disease, which does not contain the relevant data). The other Woehl reference listed in the AG report (#162) does contain the correct data so referencing must be corrected. The correct Woehl study includes data from 180 patients; however, only a minority of these patients underwent colectomy (described further in section 4.68 of the ACD). MSD believes that the utility value for the post-colectomy health state used in the AG model (0.70) is excessively high and does not adequately reflect the considerable impairment and poor quality of life that persists following surgery. MSD suggests that the utility values reported in Swinburn *et al*. and in the HODaR UK dataset which is used in the MSD model would be more appropriate (e.g. Swinburn reports a post-colectomy value of 0.59, closer to a mid-point between reported mild and severe disease values).
33 (4.46)	"For conventional therapy, the Assessment Group assumed that in both the induction and maintenance phases, 100% of patients have corticosteroids and aminosalicylates, 80% have mercaptopurine, and 20% have azathioprine"	These assumptions may be unrealistic, particularly the assumption that 100% of patients will tolerate corticosteroids and aminosalicylates. In UK clinical practice use of azathioprine is more common than assumed; also, a proportion of patients will not tolerate either of these therapies.
37 (4.57)	"The Assessment Group listed the following as the main limitations in its model"	MSD does not believe this list of limitations to be complete. As stated above, in additional to the fundamental issue that the model examines TNF-α inhibitors use outside of their marketing authorisations, there is also considerable uncertainty around the assumptions that have been made, and the appropriateness of model inputs for the population being assessed.
38 (4.59)	"colectomy would be avoided if possible"	This section contains a detailed description of the limitations of surgery and the poor quality of life that may be associated with surgery. The AG's use of a high utility value for the post-colectomy health state (which is close to published values for a mild disease state) is contradictory to this information.
39 (4.59)	"The Committee concluded that conventional therapy was an ongoing option throughout the treatment pathway for moderately to severely active ulcerative colitis because most patients are unlikely to consider surgery until later"	MSD would like to understand whether the Committee's conclusion acknowledges that patients may be tolerating ineffective treatment with conventional therapy for prolonged periods and accept the associated poor quality of life as this is still preferable to surgery. If this is confirmed by the clinical experts, then we would assume that

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		quality of life was siginificantly worse than for patients who are controlled on conventional therapy.
41 (4.62)	"the clinical expert was not aware of any evidence from randomised controlled trials (RCTs) that shows what happens to patients with ulcerative colitis when treatment with a TNF-alpha inhibitor is stopped"	MSD acknowledges that there is limited evidence but there are a number of studies which examine remission in UC once patients withdraw and the associated outcomes (Steenholdt *et al*. 2012[3], Farkas *et al*. 2013[4], Molander *et al*. 2014[5]).
41 (4.62)	"The Committee also heard that when patients with Crohn's disease stop TNF-alpha-inhibitor treatment, a small proportion would be expected to remain in total remission, but in 50% of patients their symptoms will worsen and they will need to change treatment"	Regarding patients with Crohn's disease who relapse upon stopping treatment with TNF-α inhibitors, it is important to mention that re-treatment with TNF-α inhibitors has been shown to be successful in the majority of cases (STORI trial[6]).
42 (4.63)	"The Committee concluded that the RCTs were otherwise representative of patients in clinical practice"	This is not in agreement with the advice offered to the Committee by the clinical expert who referred to patients in RCTs as being stable patients whereas in the real world they tend to be younger patients and often less stable.
42 (4.65)	"The Committee agreed that the network meta-analysis did not allow a conclusion to be drawn about the relative effectiveness of TNF-alpha inhibitors"	As we have stated in this response, the AG NMA did not discern any significant differences between TNF-α inhibitors and therefore a scenario analysis in which comparable efficacy is assumed for all TNF-α inhibitors may be helpful.
43 (4.66)	"Acknowledging the limitations in the study by Hyams et al., the Committee concluded that infliximab was likely to be a clinically effective treatment in children and adolescents, but it could not determine an estimate of the size of the effectiveness from the available evidence"	MSD acknowledges that there are limited data available for paediatric patients; however, guidelines produced by ECCO/ESPGHAN may be helpful in shaping the recommendation for this group of patients. It is also important to remember that the evidence will always be inadequate in this population although they are arguably the group most in need of an alternative to surgery.
43 (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"	This was also an issue in TA187 (Remicade and Humira for Crohn's disease), however, a 12-month review rule was accepted using the data that were available (abstract by Louis *et al*., Armuzzi *et al*. 2009). In the absence of RCT data, the Committee may be able to consider observational data that exist such as Steenholdt *et al*. 2012.
44 (4.67)	"Without any other evidence, the Committee concluded that the Assessment Group's approach to modeling the stopping rules was appropriate for the purpose of its decision-making in this appraisal"	It is not clear from the AG report what work, if any, they have performed to understand the impact of a stopping rule and whether this is possible in the existing AG model. MSD believes that it would be valuable to explore this in more depth.
44 (4.68)	"The Committee concluded that the utility values from Woehl et al. could be considered appropriate"	It is not clear how the Committee has reached this conclusion, especially given the description of surgery and the poor quality of life that can be associated with it that is presented elsewhere in the ACD (section 4.59).

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45 (4.70)	"The Committee concluded that the actual rate of surgery may be higher in clinical practice"	As we have stated in this response, we believe that this must be discussed further by the Committee, particularly as the Solberg study may not be appropriate for the population being considered in this appraisal.
46 (4.72)	"The Committee noted that when the Assessment Group doubled the cost of surgery in a sensitivity analysis, this did not change the relative cost effectiveness of TNF-alpha inhibitors. The Committee concluded that the cost of surgery was not a key driver of cost-effectiveness in the model"	As we have stated in this response, we do not believe that doubling the cost of surgery is sufficient. UK clinical experts and published literature support an increased cost for surgery when all required procedures are accounted for (up to ~£24k opposed to ~£8k estimated by the AG). We believe that this issue would benefit from further discussion before the Committee reaches a final conclusion.

[1] 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.

[2] Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M *et al*. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis. 2012 Dec; 6(10):991-1030. doi: 10.1016/j.crohns.2012.09.002. Epub 2012 Oct 3.

[3] Steenholdt C, Molazahi A, Ainsworth MA, Brynskov J, Østergaard Thomsen O, Seidelin JB. Outcome after discontinuation of infliximab in patients with inflammatory bowel disease in clinical remission: an observational Danish single center study. Scand J Gastroenterol. 2012 May; 47(5):518-27. doi: 10.3109/00365521.2012.660541. Epub 2012 Mar 1.

[4] Farkas K, Lakatos PL, Nagy F, Szepes Z, Miheller P, Papp M *et al*. Predictors of relapse in patients with ulcerative colitis in remission after one-year of infliximab therapy. Scand J Gastroenterol. 2013 Dec; 48(12):1394-8. doi: 10.3109/00365521.2013.845906. Epub 2013 Oct 16.

[5] Molander P, Färkkilä M, Salminen K, Kemppainen H, Blomster T, Koskela R *et al*. Outcome after discontinuation of TNFα-blocking therapy in patients with inflammatory bowel disease in deep remission. Inflamm Bowel Dis. 2014 Jun; 20(6):1021-8. doi: 10.1097/MIB.0000000000000052.

[6] Louis E, Mary JY, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D *et al*. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology. 2012 Jan; 142(1):63-70.e5; quiz e31. doi: 10.1053/j.gastro.2011.09.034. Epub 2011 Sep 22.