Abbott's response to the Appraisal Consultation Document of adalimumab and infliximab for the treatment of Crohn's disease

Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) prepared by the Committee for the appraisal of adalimumab and infliximab for the treatment of Crohn's disease. Abbott's detailed comments from page 3 onwards are set out under section headings containing the questions NICE asks consultees to comment on for the ACD.

Executive Summary

- Abbott welcomes the appraisal committee's consideration that adalimumab maintenance or episodic therapy is likely to be cost effective versus non-biologic standard care.
- Abbott considers that the cost effectiveness of adalimumab maintenance therapy versus episodic therapy has been underestimated in the WMHTAC model, due to a modelling error and underestimation of the relapse rate in severe patients.
- Abbott considers it to be perverse that adalimumab maintenance therapy has been restricted and infliximab episodic therapy has been recommended when the WMHTAC model analyses have shown adalimumab maintenance therapy to be associated with similar or lower average cost compared to infliximab episodic therapy and associated with similar QALY gains.

Abbott welcomes the appraisal committee's consideration that adalimumab is likely to be cost effective versus non-biologic standard care. However, Abbott considers that the cost effectiveness of adalimumab maintenance therapy has been improperly characterised on the basis partly of a modelling assumption for the relapse 2 state in the WMHTAC model and a significant underestimation of the rate of relapse for severe Crohn's Disease (CD) patients.

The WMHTAC model includes a "Relapse 2" state for the IND (episodic) arm, during which patients receive no adalimumab over a four week period; yet, patients receive adalimumab health benefits when transitioning out of the state. This "Relapse 2" Dosing/Benefit difference is asymmetric with the rest of the model, and is not supported by any evidence.

Abbott considers that adalimumab maintenance therapy is likely to be cost-effective versus episodic therapy when clinical trial data for severe patients or alternative literature-based estimates are used for the parameter, sc_relapse. NICE and WMHTAC acknowledged the sensitivity of the cost effectiveness results to this parameter, which is the four-week probability of a patient moving from remission to relapse when receiving standard care. Therefore, Abbott has applied two methods to calculate valid estimates of the sc_relapse parameter for which it asks the Appraisal Committee to consider:

1) After demonstrating that CHARM placebo (IO/RI) patients are a more reasonable proxy for episodic patients than those in the WMHTAC model, the four-week transitional probability of moving from remission to non-remission was estimated using trial data for these patients. The estimated transitional probabilities range from 0.399 to 0.456. Abbott asks that the impact of these alternative probabilities should be considered in revised modelling analyses.

2) The sc_relapse sensitivity analysis performed by WMHTAC that used Abbott's systematic literature review and meta-analysis, which found that adalimumab maintenance therapy dominates adalimumab episodic therapy is further explored (Table 10, PDF page 459 of the Evaluation Report). Abbott considers that the systematic literature review and meta-analysis previously presented is valid based on

prior independent research by Su *et al.* and that the arguments for not using these data are not supported by the evidence.

Finally, evidence is summarised regarding the cost effectiveness profile of adalimumab compared to infliximab. The majority of the evidence base indicates that adalimumab maintenance therapy is likely to be dominant versus infliximab maintenance therapy. Furthermore, it is unclear why adalimumab maintenance therapy has been restricted and infliximab episodic therapy has been recommended when the WMHTAC model analyses have shown adalimumab maintenance therapy to be associated with similar or lower average cost compared to infliximab episodic therapy. Applying a greater rate of relapse for severe patients than the 9-year base case median time to relapse will lead to greater QALY benefits for adalimumab maintenance therapy versus infliximab episodic therapy at similar or lower average cost for adalimumab maintenance therapy.

On the basis of the evidence, Abbott considers that NICE should recommend adalimumab for maintenance therapy for the severe, refractory patients who are indicated for its use. This would be in accordance with clinician and patients' preference for management of this serious chronic relapsing condition.

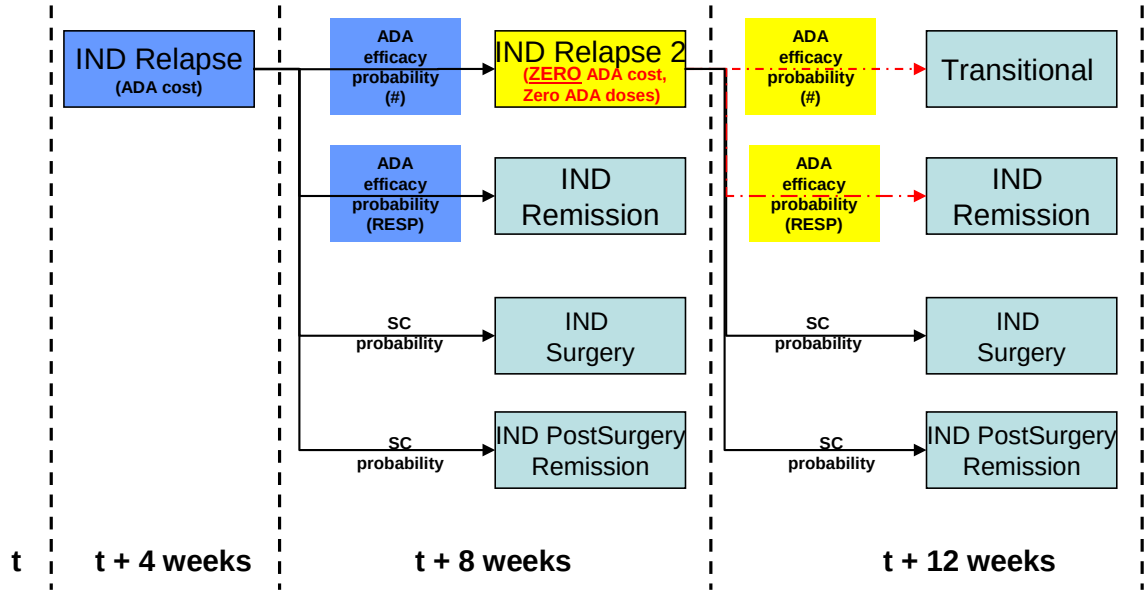
1. Do you consider that all of the relevant evidence has been taken into account?

1.1 WMHTAC modelling error: "Relapse 2 dosing/benefit" asymmetry

Abbott considers that the WMHTAC model contains an error, which results in the benefits of intermittent adalimumab therapy being overstated, therefore influencing the recommendations given in the ACD. Abbott suggests that if this factor were taken into account, it may affect the overall recommendations in the ACD. The WMHTAC's model includes a "Relapse 2" state for the episodic therapy (IND) arm, during which patients receive no adalimumab; yet, patients receive adalimumab health benefits when transitioning out of the state four weeks later. This "Relapse 2" Dosing/Benefit difference is asymmetric with the rest of the model, and is not supported by evidence.

The diagram in Figure 1.1.1 below demonstrates this problem. Episodic (IND) patients who go into relapse (blue box) at the end of time t remain in that state for 4 weeks, from t to t + 4 weeks. They consume (and incur costs for) adalimumab induction doses while in the relapse state. The transitional probability, which instantaneously reallocates them into one of the next cycle's states, uses the RESP probability of remission, which indicates the therapeutic effect of adalimumab. When patients who started in "IND Relapse" relapse again and accordingly go to "IND Relapse 2" (yellow box), the error in the construction of the model occurs. Specifically, such patients do not consume or incur costs for adalimumab in this four-week time period from the end of t + 4 weeks to the end of t + 8 weeks. However, upon exiting "IND Relapse 2" after t + 8 weeks, the patient still realises the adalimumab therapeutic effect (indicated by the red arrows) despite having discontinued adalimumab at least four weeks earlier (6 weeks according to a real world dosing schedule), after t + 4 weeks. As such, the patient receives adalimumab's higher probability of remission (RESP), despite not having consumed any adalimumab drug in the previous transitional state.

Figure 1.1.1: "Relapse 2" Dosing/Benefit Error: Patients receive their final IND doses over the t + 4 week interval, then no doses over the t + 8 week interval, but still receive ADA therapeutic efficacy between t + 8 and t + 12 weeks.



The effect of this structural issue, whereby IND (episodic) patients do not use adalimumab but do get its full therapeutic benefit, is to overstate the benefits of adalimumab for patients receiving episodic therapy.

This structural issue implies a technical design flaw. In the rest of the WMHTAC model, there are no other instances where, for example, a patient utilising (and deriving costs for) adalimumab in a state faces standard care transitional probabilities when exiting that state, or a patient utilising standard care in a state faces adalimumab transitional probabilities when exiting. The simple correction to this would be to use standard care based transitional probabilities for exiting any state in which no adalimumab is consumed. Abbott considers that model analyses should be conducted applying this amendment to the WMHTAC model.

1.2 Adalimumab maintenance (MNT) versus episodic (IND) therapy cost-effectiveness is a function of one parameter in the model (sc_relapse); if a valid input is used for this parameter, MNT is cost-effective versus IND

Abbott considers that the evidence around the validity of the standard care relapse parameter has not been taken into account and argues that had more realistic relapse rates been used in the model then adalimumab maintenance would be a cost-effective option vs. episodic therapy.

1.2.1 The 0.0059 relapse rate parameter for standard care is invalid

The standard care relapse (sc_relapse) parameter is the basis of the WMHTAC argument that IND is more cost-effective than MNT. The finding that episodic (IND) therapy is superior to maintenance (MNT) therapy is based on the sc_relapse parameter in the WMHTAC model. The sc_relapse parameter is the four-week transitional probability of moving from the remission state to the relapse state when being treated by standard care. IND patients do not receive therapy as often as MNT patients; therefore, this parameter largely governs how often they receive additional doses.

The ICER estimates of the newly revised WMHTAC model provided in September 2008 are very sensitive to this parameter. WMHTAC's base case model uses an sc_relapse value of 0.0059, which results in an ICER of MNT versus episodic (IND) of £4,980,000/QALY; a WMHTAC sensitivity analysis based on a systematic literature review uses a parameter of 0.82, which results in MNT strongly dominating episodic therapy (incremental costs of £-2,114 and incremental QALYs of 0.071).

WMHTAC and NICE recognise the importance of the sc_relapse parameter, stating that: "*The Committee noted that the cost effectiveness of different treatment strategies depended on the number of relapses a person is assumed to have over the course of the natural history of the disease, and therefore the number of relapses that would be prevented by maintenance treatment. It noted that the Assessment Group model assumed a very low yearly relapse rate and that the patient and clinical specialists had commented that in severe disease, a much higher relapse rate would be expected.* (ACD pg 22)"

The 0.0059 value used as the parameter estimate for sc_relapse in the WMHTAC model is based on the Silverstein et al. (1999) Markov model. Their base case estimate is far too low: if the 0.0059 relapse rate parameter were valid, the median time until a severe, refractory patient relapsed would be 468 weeks or 9.1 years. WMHTAC's calculation is incorrect on page 30 of the WMHTAC's response to consultee's comments (page 460 of the Evaluation Report). The WMHTAC states in their revised report that, "*The implication of our baseline remission figure is that the average remitted period is 764 days – a little over 2 years.*" This is mathematically incorrect. A transitional probability of 0.0059 implies a constant hazard rate of 0.00592; setting S(t)=0.5 to calculate the median time to relapse gives 117.1 four-week cycles; transforming into years gives approximately 9.1 years until the median patient relapses.

The Silverstein *et al.* model is an inappropriate basis for modelling this patient population for three reasons:

1) It uses Markov states based on practice patterns over the period 1960-1995 and not on disease activity – those practice patterns are now irrelevant;

2) It does not focus on the severe, refractory patient population indicated for biologics; and

3) Because it uses Markov methods, it necessarily assumes memorylessness and patient homogeneity – assumptions which are clearly invalid in this patient population.

Further, it is still unclear as to how WMHTAC changed the eight-state Silverstein et al. model to a four-state model; their changes seem to be ad hoc and anti-theoretical.

1.2.2 Testing the validity of the sc_relapse parameter

The validity of the 0.0059 value for the sc_relapse parameter in the WMHTAC model can be tested in at least two ways. Firstly, it can be compared versus the CHARM placebo arm, while addressing the concern that this arm is not representative of standard care; and secondly, it can be compared versus the literature.

1.2.2.1 Comparison of the sc_relapse parameter vs. the CHARM placebo arm

The CHARM placebo (IO/RI) arm provides a better proxy for episodic treatment than does the WMHTAC model episodic arm base case; as such, it should be used as a valid source for deriving a conservative transitional probability for the sc_relapse parameter. The transitional probability derived from CHARM is very conservative because sc_relapse should correspond to patients only receiving standard care, and not induction and episodic doses of adalimumab.

First, the remission-to-relapse transitional probability in the CHARM placebo arm was derived, which is also termed "induction only/reinitiation therapy" (IO/RI) in the Colombel *et al.* abstract entitled "The Effects of Adalimumab on Patients with Moderate to Severe Crohn's Disease – An Intent-To-Treat Analysis." All placebo/IO/RI patients received adalimumab doses at week 0 and 2, and then as per required after week 12.

The WMHTAC argues that CHARM placebo (IO/RI) is not a reasonable proxy for episodic therapy based on the logic that these patients were denied doses of adalimumab over a ten-week period in the trial (Page 438 of the Evaluation Report). Specifically, the WMHTAC argument against accepting CHARM data as a proxy for episodic use is that these IO/RI patients received too few doses as a result of the CHARM trial design; i.e. placebo IO/RI patients were not allowed to receive the adalimumab doses they would have consumed for clinical reasons because the trial design enforced a 2.5 month dosing hiatus.

Measuring the number of adalimumab doses actually having been consumed in CHARM by the placebo IO/RI patients demonstrates these patients consume a substantial number of adalimumab doses over the 46 weeks when they were eligible to receive doses in the trial. The time period during which the patients randomised to IO/RI were not allowed to receive ADA doses was 10 weeks, or 17.9% of the total 56-week period duration of the CHARM trial. The average number of 40mg adalimumab doses that the placebo arm (IO/RI) patients received over the 56-week period was 15.4 doses (this figure of 15.4 doses matches to 14.4 injections in the Colombel "All Comers Analysis;" the first injection is for two doses because of the 80/40 induction). Of the 15.4 doses of adalimumab, 3.0 were in the induction period, and 12.4 were in the period from week 12 to week 56. After week 12, any IO/RI patient could receive additional doses of adalimumab if they went into relapse.

The argument that the CHARM placebo (IO/RI) patients used too few doses to be a proxy for episodic care is inconsistent with other arguments and subsequent modelling put forth by the WMHTAC. In the WMHTAC model, the expected average number of adalimumab doses consumed per patient in the episodic arm is 3.15, which is calculated by identifying the total drug costs in the IND arm and dividing by the price of a 40 mg dose of adalimumab. Of the 3.15 doses of adalimumab in the IND arm of the WMHTAC model, 3.0 were in the induction period, and 0.15 were in the remainder of the 56-week period. The following table demonstrates differences in the two analyses.

Table 1.2.2.1: Average Adalimumab Doses Consumed by CHARM placebo (IO/RI) Patients and Expected to be Consumed in WMHTAC Version of Episodic Therapy

	Induction Doses	Post-induction Doses	Total Doses
CHARM placebo (IO/RI) arm, weeks 0-56	3.0	12.4	15.4
WMHTAC model Episodic arm (IND)	3.0	0.15	3.15

Thus, the difference in post-induction doses, which are a function of relapse, is 12.4 to 0.15; the CHARM placebo (IO/RI) patients receive more than 80 times the number of doses that the WMHTAC modelled patients do. Despite using 12.4 doses per patient, there is still a high relapse rate in the CHARM patients. WMHTAC argues on the one hand that relapse rates are extremely low, as is the case in their own model, and on the other hand that a ten week period of not receiving doses invalidates the CHARM placebo arm as a comparator because many patients would have required doses during this period.

The low figure for post-induction doses in the WMHTAC model is driven by the 0.0059 transitional probability from remission into relapse. The low number of doses after the induction period is due to the very low sc_relapse parameter, which governs the timing by which patients exit remission and need to receive additional episodic therapy adalimumab doses in the WMHTAC model. When comparing the two figures, the post induction period doses in CHARM placebo IO/RI are 12.4, versus 0.15 for the WMHTAC model.

Therefore when taken altogether, this is clear evidence that:

1) CHARM placebo (IO/RI) patients use more doses than WMHTAC episodic patients; thus the argument that CHARM placebo (IO/RI) is not representative of episodic therapy because these patients had a 2.5 month dosing hiatus is not valid.

2) CHARM placebo (IO/RI) patient data could be used to calculate a transitional probability from remission to relapse. Further, such a value would also be a more reasonable input parameter than the 0.0059 transitional probability.

1.2.2.2 Sc_relapse parameter using CHARM placebo (IO/RI) data showing that MNT is more cost-effective than IND based on the primary data

Under the assumption that IO/RI could be used as a proxy for episodic therapy, a sc_relapse transition probability from the CHARM IO/RI arm was derived. This analysis has already been performed and the results reported for moderate and severe patients in Table 2.2.2.4 of Abbott's previous response document (Page 22, submitted 28 July 2008). The results are presented below in Table 1.2.2.2, to include the same analysis of the subset of patients with severe disease at baseline. Specifically, for all observations of IO/RI patients that occurred in a remission state at weeks 0, 2, 4, 6, 8, 12, 16, 20, 26, 32, 40, 48, or 56, a logistic regression model was estimated to generate the probability the patient would move into the non-remission state (y = 1) or remain in remission (y = 0). To standardise the duration of the time interval, d a time in weeks (duration) and time-squared ($duration^2$) term was included in the model. The four-week transitional probability of moving from the remission state to the relapse state was then predicted (see Appendix 1 for information regarding the logistic regression). In the base case, the sample was

limited to placebo IO/RI values only. Sensitivity analyses included: excluding data prior to week 12, and including only severe patients at baseline. The results appear in the following table:

Table 1.2.2.2: Sc_relapse parameter calculation based on four-week transitional probability from the remission state to the relapse (non-remission) state using CHARM placebo (IO/RI) data for adalimumab maintenance (MNT) vs. episodic adalimumab therapy (IND)

Episodic Proxy Analysis	PLACEBO (IO/RI) treatment group:	Median Time in Weeks to Relapse:	Probability of going from remission to relapse (moderate and severe patients):
Base Case [a] (all from week 0-56)	moderate and severe patients	5.1	0.4213
	severe patients only	4.6	0.4563
Sensitivity analysis 1 (all values from week 12-56)	moderate and severe patients	5.4	0.3992
	severe patients only	5.0	0.4279

[a] See Appendix 1 for further information

As per Table 1.2.2.2, the relapse parameter for a CHARM placebo (IO/RI) patient who begins in remission to move to non-remission four weeks later is 0.4213, as calculated using all CHARM data from week 0 to week 56. That is, the four-week probability of a relapse by the standard care-treated patient is approximately 42%. This is a high relapse rate, and reflects the volatility of the patients' disease activity.

To lessen the concern that patients' transitional probability from remission to non-remission could be biased by having a 2.5 month dosing hiatus, the calculation was also made using data for the placebo (IO/RI) arm from week 12 to week 56 in sensitivity analysis 1 in Table 1.2.2.2. The placebo transitional probability in this case is 0.3992, or approximately 40%. Of note, during this period, all patients could enter the open label trial and receive doses. For severe only patients, the figures are 0.4563 and 0.4279 respectively.

Abbott considers it is important to assess the impact of these alternative estimates for SC relapse on the cost effectiveness estimates in the WMHTAC modelling. These greater rates of SC relapse in line with the available evidence from the CHARM trial would give lower cost per QALY estimates for adalimumab maintenance therapy versus episodic therapy.

1.2.2.3 Comparison of the sc_relapse parameter vs. the literature

Using Abbott's systematic literature review and meta-regression research presented in the last two response documents, the WMHTAC found that MNT dominated both standard care and IND therapy. Table 10 on page 29 of the WMHTAC's response to the consultees comments indicates that in an incremental comparison of MNT versus IND, MNT yields incremental costs of £-2,114 and incremental QALYs of 0.071, which results in maintenance strongly dominating episodic therapy.

Abbott considers that the previously presented systematic literature review and meta-regression is valid and uses published, peer-reviewed, independent literature of clinical trials for biologics.

Moreover, it had similar findings to another similar, already published, independent analysis by Su *et al* [1].

A systematic literature review of all clinical trials of biologic agents involving Standard Care-treated (i.e., pure placebo arm) patients published after 1990 was conducted. The full description of this research can be found in the form of a manuscript first-authored by Dr. Ed Loftus of the Mayo Clinic. This analysis was submitted in February and July 2008 as an appendix. Overall, 21 clinical trials publications included valid arms with pure placebo groups. This research represents a valid source for measuring the true rate of sc_relapse in severe patients indicated for biologics. In terms of verifying the validity of the research as a source for sc_relapse, it is recognised that the manuscript has not yet been published. However, an abstract and poster presentation have been submitted to UEGW 2008 and accepted. Of note though, the data in the systematic literature are exclusively based on figures from published studies, such that all of the data in the literature review can be directly verified versus the published literature.

Importantly, another paper by Su *et al.* strongly supports Abbott's findings. WMHTAC identified the Su et al. study in its review, but mischaracterised its findings, stating: "*Varied and high rates of placebo response have previously been documented for many CD intervention trials*." The actual conclusion of Su et al. is in fact: "*Placebo remission and response rates in PC-RCTs for active CD are variable. Study duration, number of study visits, and disease severity at entry have a large influence on placebo remission rates.*" Abbott's remission rate is 11% to 14%; Su *et al*.'s rate is somewhat higher (pooled rate of 18%). However, of the Su *et al.* study patients, only 37% (262/707) were in studies evaluating biologic agents, the average or median CDAI at entry was 265, and none of the trials were published after 2001. Abbott's study included 100% biologic arm patients (who are the most severe, refractory patients): their average CDAI at entry was 296, and the major biologic trials published between 2001 to 2007 were included. In this analysis, meta-regressions estimate week 26 remission rates of 11.5% to 13.8%, depending on specification.

WMHTAC criticised Abbott's systematic literature review and meta-analysis on the following three grounds (WMHTAC August Response Document to consultees comments, page 29):

1) "*We suspect, but could not verify in the time available, that the analysis of some trials relates to continuous remission rather than health status per se, and that this would complicate matters*."

2) "*The issue of selectivity is also important here, with clinical trial populations typically less healthy than the general CD population, and Abbott has further selected its sample by removing all studies that included any patients with a baseline CDAI score below 150.*"

3) "*We find that this would require that we increase the probability of relapse by approximately 140 times*."

As such, Abbott would like to address the three points that the WMHTAC based its ultimate rejection of the analysis on:

1) The outcome variable in each study is remission and not continuous remission. Abbott used the same outcome variable as Su et al. Further, the raw data for the longest, largest pure placebo study, PRECISE 1, show that the endpoint is remission over time, and not continuous remission. In the PRECISE 1 study the remission rate from week 6 to week 26 was about 18%[2]. Of note, PRECISE 1 included moderate and severe patient at baseline (average CDAI at baseline = 297).

2) WMHTAC argues that these pure placebo patients from clinical trials are too severe and not representative of the patient population indicated for adalimumab, stating: "*clinical trial populations [are] typically less healthy than the general CD population.*" While sometimes true, Abbott is not modelling a general CD population, but one that is specifically indicated for anti-TNF therapy. Patients' baseline information was collected from all trials, which were presented in the previous submission on page 21 of Abbott's 28 July 2008 response. As can be noted, the

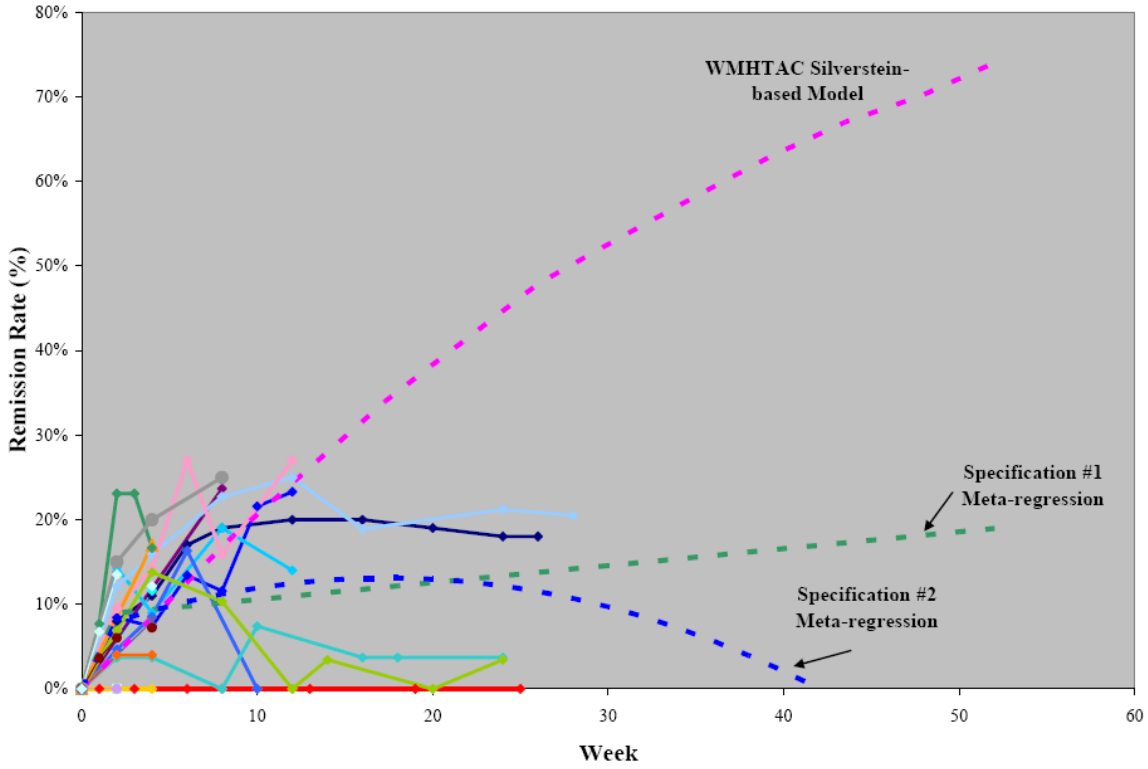
average CDAI at baseline is 296 in the clinical trials in our systematic literature review, which is below the 300 threshold for a severe patient. NICE stated on page 20 of the ACD: *"The Committee heard from the clinical specialists that the definition of 'severe' as specified in 'Guidance on the use of infliximab for Crohn's disease' (NICE technology appraisal guidance 40) was an appropriate definition of severe Crohn's disease, that is, normally corresponding to a CDAI score of 300 or more."*

Based on this criterion, the average patient across these 19 trials has less severe disease than those indicated for adalimumab based on the WMHTAC criterion used in the model.

3) WMHTAC's last comment was that the sc_relapse value derived from the systematic literature review is too high compared to its own base case value. As previously noted, Abbott considers that their base case estimate is not valid for a number of reasons: a) it is based on antiquated states not based on disease activity, b) it uses inappropriate data and methods, and c) it is composed of the entire CD population, instead of the subset who are indicated for adalimumab.

Abbott's systematic literature review and meta-regression-based remission rate of 11% to 14% is consistent with Su et al.'s estimate of 18%, and is much lower than the monotonically increasing 76% predicted by the WMHTAC model for SC-treated patients, which is a function of the very low sc_relapse parameter used in the WMHTAC model. Figure 2.2.2.3 from Abbott's previous response has again been included below to illustrate this point.

Figure 2.2.2.3. Comparison of meta-analysis results with Abbott and WMHTAC Model remission rate by week - placebo arms of biologic trials only



Abbott would welcome a sensitivity analysis for the WMHTAC model based on Su *et al*. data, if these data are considered more appropriate than the meta-regression provided by Abbott.

1.2.3 Conclusion with regard to the sc_relapse parameter and its effect on the cost-effectiveness of adalimumab MNT therapy vs. IND

Data and analyses have been provided using CHARM placebo (IO/RI) to identify the parameter in a group of patients who received therapy that was a proxy for IO/RI, or at least a more reasonable proxy than the IND arm in the WMHTAC model. Secondly, Abbott's systematic literature review and the analysis performed by WMHTAC using those data have been reviewed, and Abbott has attempted to refute WMHTAC's rationale for discarding this analysis. Together, this evidence demonstrates that the SC relapse rate should be higher than applied in the WMHTAC base case analyses and that adalimumab maintenance therapy will be more cost-effective versus episodic therapy than estimated in the WMHTAC base case analysis. Given that the sc_relapse parameter is critical to the outcome of the analysis, Abbott feels that greater consideration needs to be given to its value and impact.

1.3 Other issues with the design and structure of the model constituting relevant evidence

1.3.1 The post surgery relapse probability is too low

Abbott considers that the post surgery relapse (ps_relapse) probability is too low, which underestimates the benefits of MNT therapy. The value of the WMHTAC relapse probability is 0.0011, which indicates that the median time until relapse after surgery is 48 years.

In an abstract presented at ACG 2008 by Regueiro *et al.*[3], researchers studied the efficacy of infliximab in preventing recurrent CD after resective intestinal surgery. At the end of 1 year, 9 of 10 patients (90%) in the infliximab group were in endoscopic remission compared with 2 of 13 patients (15.4%) in the placebo group ($p = 0.0006$). The severe endoscopic recurrence was 53.8% in one year in placebo. Clinical recurrence was 38.5% for placebo in one year. This recurrence rate in placebo is much higher than the rate used in the Assessment Group's model.

1.3.2 Adalimumab use in patients undergoing surgery

In the model, adalimumab maintenance patients who undergo surgery continue adalimumab doses. This does not reflect the clinical situation, as there are no data to support the use of anti-TNF maintenance therapy post surgery. This assumption biases upwards the cost of adalimumab maintenance arm patients without providing any additional benefit. Abbott considers that the cost of adalimumab therapy should be removed from the post surgical remission state in the WMHTAC model for patients receiving adalimumab maintenance therapy.

1.3.3 Cost of infliximab

The correct cost per 100mg vial of infliximab is £419.62 rather than £419.73 as used in the WMHTAC revised model.

1.3.4 Discounting of long-term cost-effectiveness and use of probabilistic sensitivity analyses

It is unclear whether the results from the long term modelling of cost effectiveness in the WMHTAC modelling have been discounted using the reference case rates of 3.5%. Abbott therefore considers that these analyses are not appropriate for assessing the long term cost effectiveness of anti-TNF therapy.

The majority of sensitivity analyses have been conducted for the WMHTAC model applying univariate sensitivity analyses. Abbott considers it is important to also assess the impact of uncertainty in all key parameters such as the rate of sc_relapse in probabilistic sensitivity analysis (PSA). It appears that a number of these key parameters were not varied in the PSA.

1.3.5 Invalid state transitions in the model structure

A number of invalid state transitions are still included in the WMHTAC model structure. The following gives a list of invalid state transitions, which can take place in the model and their associated probability. Abbott considers that these transitions should be removed from the model:

From state	To state
SC Remission	Post Surgery Remission (p=0.0035)
SC Relapse	Post Surgery Remission (p=0.0189)
SC Surgery	Remission (p=0.0521)
SC Post Surgical Remission	Remission (p=0.0054)
MNT Remission	Post Surgery Remission (p=0.0035)
MNT Relapse	Post Surgery Remission (p=0.0189)
MNT Surgery	Remission (p=0.0521)
MNT Post Surgical Remission	Remission (p=0.0054)
MNT Relapse 2	Post Surgery Remission (p=0.0189)
IND Remission	Post Surgery Remission (p=0.0035)
IND Relapse	Post Surgery Remission (p=0.0189)
IND Surgery	Remission (p=0.0521)
IND Post Surgical Remission	Remission (p=0.0054)
IND Relapse 2	Post Surgery Remission (p=0.0189)

1.4 Consideration of new data that have arisen since the evidence submission on 30 July 2007

Abbott would like to draw attention to the fact that considerable additional evidence has been submitted since the original evidence submission on 30 July 2007. As there was a delay to this appraisal, a significant amount of time elapsed before the release of the ACD from the date when evidence was first submitted (> 1 year), in which a substantial amount of additional data from open-label extension trials have arisen. The August 2008 WMHTAC response to Abbott's comments acknowledges that sections 1.2.2, 1.2.3, 1.2.4, 1.3, 1.5 and 1.6 of the manufacturer's 28 July response provide new data which is beyond Abbott's original submission and coverage in the TAR II. These data include information on fistula healing, mucosal healing, reduction in the risk of all-cause hospitalisation, sustained long-term remission data, and long-term steroid free remission. The majority of these data can be considered additional favourable outcomes to those based on CDAI, realised later than 10-12 weeks, which was one of the caveats the WHMTAC included when discussing the likelihood that adalimumab maintenance therapy is a clinical- or cost-effective treatment option for patients with severe Crohn's disease (page 8 of the WMHTAC August response to consultees comments). Therefore, Abbott asks that due consideration be given by the Appraisal Committee to these new data demonstrating the benefits of adalimumab maintenance therapy.

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?

2.1 Adalimumab has a better cost effectiveness profile than infliximab but this is not reflected in the current ACD recommendations

The ACD recommendations do not indicate a preference for adalimumab versus infliximab, instead noting that: *"The Committee concluded that the least expensive treatment option should be chosen, taking into account dose and administration cost."* Nevertheless, independent analysis, WMHTAC modelling analysis, and the modelling of Abbott have all shown adalimumab maintenance therapy to have a better cost effectiveness profile than infliximab maintenance therapy.

Adalimumab maintenance therapy is dominant or close to dominant versus infliximab maintenance therapy in all cases considered in the WMHTAC analyses. In the WMHTAC base case, adalimumab maintenance is associated with a mean cost and QALY of £14,041 and 0.896, while infliximab maintenance is associated with a mean cost and QALY of £19,143 and 0.897, respectively.

In the Abbott model, we matched data from the CHARM trial for adalimumab to the baseline characteristics of infliximab. The costs of adalimumab therapy lower, and the expected QALYs from adalimumab therapy were also higher. As such, we demonstrated that adalimumab dominates infliximab therapy.

Bodger *et al*[4]. have presented findings from a UK cost effectiveness analysis comparing adalimumab, infliximab, and standard care. The key finding of Bodger et al. was that adalimumab maintenance therapy is very cost effective versus SC at one and two years after initiating therapy. However, based on the results of that analysis, comparing adalimumab to infliximab indicates that adalimumab maintenance therapy dominates infliximab maintenance therapy in the analysis at the two time points for which incremental results are reported.

It should be noted that the previous analyses have focused on the comparison of adalimumab maintenance therapy versus infliximab maintenance therapy. Given the current ACD recommendation for infliximab use as episodic therapy, it is important to also consider the cost effectiveness profile of adalimumab maintenance therapy versus infliximab episodic therapy.

Table 2.1.1 below summarises the results of the WMHTAC modelling analyses presented in the "Addendum" document (PDF page 465-466 of the Evaluation Report). The results presented focus on the comparison of adalimumab maintenance therapy versus infliximab episodic therapy.

Table 2.1.1 WMHTAC model analyses from "Addendum" in evaluation report. Adalimumab maintenance therapy versus infliximab episodic therapy

		Mean Costs	Mean QALYs	ICERs
Base case (sc relapse = 0.0059)	Infliximab IND	12,051	0.8943	-
	Adalimumab MNT	14,047	0.8956	£1.54m per QALY
Base case (sc relapse = 0.0590)	Infliximab IND	15,477	0.8814	-
	Adalimumab MNT	14,292	0.8938	ADA MNT dominates
Base case (sc relapse = 0.1434)	Infliximab IND	19,821	0.8623	-
	Adalimumab MNT	14,461	0.8901	ADA MNT dominates
Base case (sc relapse = 0.30)	Infliximab IND	25,386	0.8391	-
	Adalimumab MNT	15,198	0.8825	ADA MNT dominates

Aside from the base case analysis, where it is assumed that patient median time to relapse after stopping anti-TNF therapy is 9 years, these results indicate that adalimumab maintenance therapy is likely to be similar or lower cost than infliximab episodic therapy and gives a greater mean QALY gain on average. Given these results it is unclear why adalimumab maintenance therapy has been restricted whereas infliximab episodic therapy is recommended for use. Abbott considers it is inappropriate to restrict the use of adalimumab maintenance therapy using these modelling analyses whilst also using them to support the recommendation for use of infliximab episodic therapy. The available data indicate that adalimumab maintenance therapy is likely to be similar or lower cost than infliximab episodic therapy.

2.2 Factual accuracy of clinical and cost effectiveness summaries

Abbott has checked the ACD for factual accuracy and suggests the following points need to be amended:

- The following statement on page 11, section 4.1.6 of the ACD is open to misinterpretation: *"In CLASSIC I, only the result for 'response 70' (RR 1.61 95% CI 1.13 to 2.29) was statistically significant; the results for the 80-mg/40-mg regimen did not achieve statistical significance against placebo for the endpoints of remission (RR 1.97, 95% CI 0.95 to 4.11) or 'response 100' (RR 1.56, 95% CI 0.97 to 2.51)"*. The first part of this sentence before the semi-colon needs to include wording specifying the 80/40mg dosing statement, as it implies that only the result for CR-70 was significant for all doses evaluated in the trial, which is incorrect. Furthermore, the statement needs to specify "at week 4" as patients receiving adalimumab 80/40mg achieved statistical significance for the CR-100 outcome at week 2.

- Section 4.1.6 of the ACD on page 11 – Although patients in CLASSIC I who received the 80-40mg adalimumab induction dose did not achieve statistical significance for the outcome of clinical remission at week 4, these patients did achieve statistical remission vs. placebo by week 8. These data are an important consideration for adalimumab therapy in Crohn's disease and illustrate the fact that some patients require a longer period of treatment to respond to adalimumab. This is reflected in the Humira summary product of characteristics, which states that, "Some patients who have not responded by week 4 may benefit from continued maintenance therapy through week 12 after which, continued therapy should be carefully reconsidered in a patient not responding within this time period." Therefore, maybe a qualifying statement can be added stating that statistical significance was achieved by week 8 for clinical remission in patients receiving the 80/40mg loading dose.

- Section 4.1.9 of the ACD on page 13 – the CHARM trial has co-primary endpoints of remission at week 26 and 56 not the CLASSIC II trial. The CLASSIC II trial has a primary endpoint of remission measured at 56 weeks only.

3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

3.1 Not a reflection of the decision problem outlined in the scope

Abbott considers that the provisional recommendations of the Appraisal Committee are not sound. The scope for this appraisal required an anti-TNF comparison versus conventional therapies and each other where appropriate. The economic analysis performed by WHMTAC showed maintenance treatment of adalimumab to be a cost-effective use of NHS resources vs. standard care with ICERs at £7,478/QALY. The modelling submitted by Abbott also indicated that adalimumab maintenance therapy would be cost-effective vs. standard care. Abbott considers that the scope does not indicate that adalimumab maintenance therapy should be compared versus adalimumab episodic therapy. Therefore, Abbott believes that the most relevant comparators for adalimumab maintenance therapy in line with the appraisal scope are conventional non-biologic therapy or infliximab episodic therapy. Abbott considers that the ACD recommendations for adalimumab maintenance therapy are not in line with the appraisal scope by comparing versus an inappropriate comparator (adalimumab episodic therapy) rather than versus conventional non-biologic therapy (standard care) or infliximab episodic therapy.

3.2 Not representative of clinician or patient views

Abbott considers that the provisional recommendations of the Appraisal Committee are not reflective of the available evidence nor the views of clinicians and patient organisations, and thus do not constitute a suitable preparation of guidance to the NHS. The Royal College of Physicians (RCP) stated that, "*Current evidence suggests that regular therapy is more effective and has fewer side effects than 'as required' therapy. From personal experiences in managing patients with CD, it seems illogical and unfair for patients to have to wait until their symptoms are sufficiently severe before they can be eligible for a therapy* (pg. 2 of RCP response to the TAR)." The RCP recommends maintenance therapy, on the basis that 'Regular scheduled treatment' is more effective than 'as required' and importantly avoids the patient enduring relapse of disease before 'earning' further therapy (pg. 4 of RCP response to TAR)." Furthermore, the National Association for Colitis and Crohn's Disease stated that: "*it feels it is essential that approval is specifically given for maintenance treatment with TNF inhibitors to make it clear that continued treatment funded by the NHS is approved… However, it is not satisfactory for patients to have to relapse before further treatment is authorised, with all the uncertainty about future treatment and the impact on health and quality of life that such a requirement would entail*". (Section 7.5 of their response to the TAR, pg. 14)

Of significant concern is the wording that patients must relapse and experience severe symptoms before anti-TNF therapy is recommenced. Abbott considers that for patient quality of life reasons if would be preferable for patients to be allowed access to anti-TNF therapy before severe symptoms recur. In practice, the only way that this is likely to be achievable is through the use of anti-TNF maintenance therapy. A recent study by Bitton et al. suggests that stress is an important determinant of relapse rates in CD[5]. Given that fear of surgery is the greatest worry for CD patients identified in the NACC survey, it is possible that allowing only episodic therapy for CD patients could increase the relapse rate for patients worrying about their condition. It should also be noted that the impact of recurrent relapses and surgery on patient quality of life has not been captured in the health economic modelling. A study of CD patients in Norway found that patients experiencing more relapses in the preceding year had significantly lower Norwegian-IBDQ scores[6]. These data indicate that allowing patients to relapse and experience severe symptoms will reduce their quality of life. Treatments that reduce relapse frequency will give an improved quality of life that is not reflected in the current equivalent QALY gains in the WMHTAC modelling for anti-TNF maintenance and episodic therapy.

4. Are there any equality related issues that may need special consideration?

Given the ACD preliminary recommendation that patients need to experience the recurrence of severe symptoms before they are eligible for access to further anti-TNF therapy, it is important to consider the equality related issues that could result. In particular, consideration should be given to ensuring patients with communication difficulties have equal access to anti-TNF therapy.

Appendix 1

A1.1 Logistic regression information

The probability was generated as the expected value for the dependent variable, using duration of 4 weeks. The values were estimated by taking the exponentiation of the estimated model parameters generated via logistic regression, setting the duration variable constant to 4 weeks: expected value of $(p(y_{i=1})=\exp(\beta_{0+}\beta_1(4 \text{ weeks})+ \beta_2(16 \text{ weeks}))/(1+ \exp(\beta_{0+}\beta_1(4 \text{ weeks})+ \beta_2(16 \text{ weeks})))$.

A1.2 Base case analysis additional information

The specifications, coefficients, and fit statistics appear in the tables below for the analysis on the base case model's (week 0 to week 56) two samples (moderate and severe and severe only). To be included in the sample, patients had to have been in remission during at least one observation over the study period. Observations were based on remission status after having been observed in remission at the previous clinical trial visit.

Base Case: moderate & severe patients	**Coefficient**	**Std Err**	**P-value**
Intercept	-1.66	(0.50)	0.0009
Time (weeks) until next trial observation	0.59	(0.24)	0.0151
Time $(weeks)^2$	-0.06	(0.02)	0.0086
No. Observations included	549		
No. Patients included	129		
Log-likelihood	-311.99		

Base Case: severe patients only	**Coefficient**	**Std Err**	**P-value**
Intercept	-2.34	(0.89)	0.0083
Time (weeks) until next trial observation	0.91	(0.41)	0.0279
Time $(weeks)^2$	-0.09	(0.04)	0.0238
No. Observations included	213		
No. Patients included	54		
Log-likelihood	-121.56		

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