TOCILIZUMAB

FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

REPORT BY THE DECISION SUPPORT UNIT

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1. SYNOPSIS OF THE TECHNICAL ISSUE

Following the most recent Appraisal Committee meeting in February 2010, a third appraisal consultation document (ACD 3) was issued. During consultation on this document, the manufacturer of tocilizumab (Roche Products) submitted additional evidence (25th March 2010) using revised parameter assumptions and presented additional cost effectiveness analyses that require further investigation.

Both the Committee and Roche have agreed that a sequence of 3 biologics is clinically more effective than 2 biologics for rheumatoid arthritis (RA). However, a key issue that has emerged during the course of the appraisal is how the sequence of 3 biologics should be evaluated from a cost-effectiveness perspective. Roche have argued that the lifetime costs and QALYs will be approximately the same no matter when tocilizumab is given and that all treatment sequences including tocilizumab are cost effective (with updated costs, QALYs and ICERs presented in the latest submission). The Appraisal Committee have consistently argued that the mixed treatment comparison (MTC) of ACR response rates demonstrates that tocilizumab is likely to be no more effective than etanercept and, due to the route of administration, etanercept is also cheaper than tocilizumab. This is similar for rituximab. The Committee therefore do not consider that it would be sensible to recommend tocilizumab ahead of etanercept and rituximab in the pathway.

Nevertheless, the Committee did consider the manufacturer's previous cost effectiveness estimates and had a number of concerns which were outlined in ACD 3:

1. The MTC was viewed cautiously and considered that the results of this differed substantially from the direct trial results (the MTC was used to derive the probability of initial ACR response rates with each treatment).
2. Long-term HAQ modelling favoured tocilizumab (only biologic with long-term HAQ improvement) and the modelling of HAQ rebound was unclear.
3. The utility values had been mapped to HAQ, even though EQ-5D was available from 2 trials.
4. Adverse events had not been included.
5. No degradation of response to treatments given later in the pathway had been included.

Therefore, the ICERs previously presented by Roche were considered to be underestimated by the Committee and tocilizumab was not recommended. However, a 'minded no' was issued for tocilizumab given after rituximab and tocilizumab given instead of rituximab (if rituximab was unsuitable or not tolerated); these scenarios had not been modelled by the manufacturer and the Appraisal Committee heard that the clinical community considered these the appropriate positions for tocilizumab in the pathway.

Following the latest submission by Roche as part of the response to ACD 3, the NICE Decision Support Unit (DSU) was requested to undertake the following tasks:

1. To provide a conceptual view on the overall decision problem and sequencing issues and to consider the cost effectiveness of the specific sequences in this appraisal.
2. To clarify and comment on the key assumptions used by the manufacturer in their response to ACD 3, with a specific focus on the following issues:
   (i) initial response rates ('adjusted' MTC or 'unadjusted' trial effects),
   (ii) long-term HAQ improvement and rebound assumptions;
   (iii) degradation of treatment effect for different positions in sequence;
   (iv) utility mapping approach;
   (v) adverse events;
   (vi) administration costs of tocilizumab.
3. To undertake additional cost-effectiveness analyses to validate the manufacturer's response to ACD 3 and correct for any errors/inconsistencies identified.
4. To undertake fully incremental cost effectiveness analyses of alternative sequencing positions of tocilizumab. To conduct additional sensitivity analyses to address the Appraisal Committee's concerns about key assumptions underpinning the manufacturer's results.

2. IDENTIFYING THE MOST COST EFFECTIVE SEQUENCE

2.1 INTRODUCTION

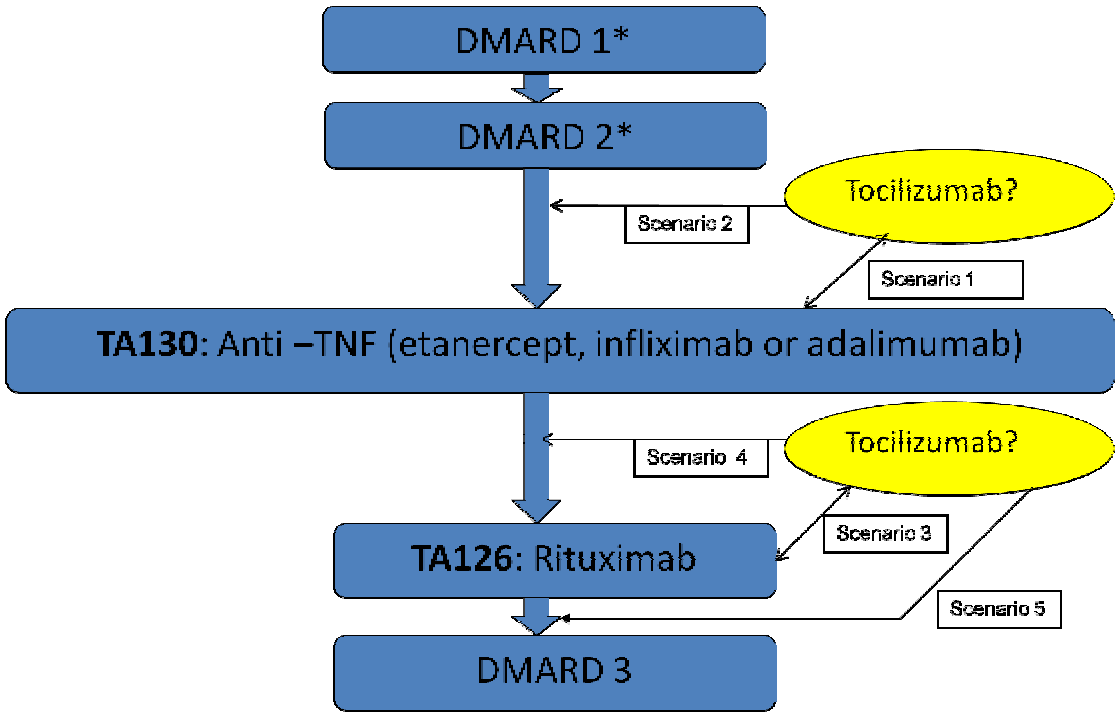
The appropriate use of new biologic therapies in RA inevitably involves a consideration of the appropriate sequence of therapies given the chronic nature of the condition, the fact that

therapies do not typically remain efficacious and tolerable on a permanent basis and the availability of a number of biologic therapies which are licensed for RA. When sequential therapy is clinical appropriate, it is important to establish which sequence is the most cost-effective – that is, the most effective with an incremental cost-effectiveness ratio (ICER) below the decision maker's threshold. A key issue with tocilizumab, therefore, is at which point in a treatment sequence is the therapy most cost-effective, where one comparative sequence would not include tocilizumab at all. A series of questions need to be addressed.

2.2 WHAT IS THE FULL LIST OF COMPARATIVE SEQUENCES?

Figure 1 below was produced by NICE and identified 5 potential sequences where tocilizumab is either added to the therapies in an existing sequence or replaces one of those therapies. A sequence without tocilizumab would be a sixth.

Figure 1. Possible sequences involving tocilizumab based on briefing note from NICE



Two of these scenarios were not considered as requiring further consideration by the Appraisal Committee from this list of comparative options. The first is Scenario 1 where tocilizumab replaces the anti-TNF, its removal being justified on the basis that etanercept is

considered of broadly similar efficacy as tocilizumab and is less costly, so replacing it with tocilizumab would make little sense. The second sequence that has been removed from further consideration is tocilizumab's replacement of rituximab (scenario 3) given than rituximab is half the cost of tocilizumab and no clinical evidence exists to compare them. Hence, four main sequences remain for consideration as shown in Table 1. For simplicity of subsequent interpretation, these scenarios have been renumbered 1-4. In addition, the term 'scenario' has also been replaced by 'strategy' since the former term could imply separate decision problems and/or populations, whereas in reality there is a single decision problem relating to the 'optimal' positioning of tocilizumab.

Table 1: Main sequencing strategies considered by the DSU

Strategies	Position in sequence	Sequence evaluated
1 (E,R)	Standard care (excluding tocilizumab)	Etanercept -> Rituximab -> DMARDs -> Palliative Care
2 (T,E,R)	Tocilizumab 1st in sequence	Tocilizumab -> Etanercept ->Rituximab- >DMARDs -> Palliative Care
3 (E,T,R)	Tocilizumab 2nd in sequence	Etanercept -> Tocilizumab -> Rituximab -> DMARDs -> Palliative Care
4 (E,R,T)	Tocilizumab 3rd in sequence	Etanercept ->Rituximab ->Tocilizumab - >DMARDs -> Palliative Care

2.3 WHAT IS THE MOST COST-EFFECTIVE SEQUENCE?

To establish the most cost-effective of the four strategies it is necessary to undertake a fully incremental analysis comparing all the sequences simultaneously. This is a central tenet of cost-effectiveness analysis and involves assessing the incremental cost of generating additional health effects when moving from one option to a more effective one, and assessing this against a relevant measure of opportunity cost (e.g. the NICE threshold).[1 2] Calculating a series of pair-wise ratios between the alternative tocilizumab-based sequences and the standard of care is not appropriate when considering the optimal position of tocilizumab and, in particular circumstances, can be misleading as demonstrated below.

Table 2 shows the results of the pair-wise cost-effectiveness ratios compared to the current standard of care from the manufacturer's latest model (dated 19/04/10) using their base-case assumptions. The pair-wise ratios for Strategies 2 to 4 are all below a £30,000 per QALY

threshold and range from £21,733 to £25,244 per QALY. However, this does not demonstrate that each of the sequences can be considered cost-effective as there are a series of mutually exclusive sequences available – only one can be selected for a given patient so the issue is which is the most cost-effective. This can only be addressed using a fully incremental analysis where the alternative sequences are ranked in ascending order of costs or effects. Options that are dominated (i.e. those which are more expensive and less effective than one or more alternatives) are removed from further consideration. So too are options which are extendedly dominated – that is, more costly and less effective than a combination of two alternatives. The ICERs of each of the remaining options are then calculated as the additional costs divided by the additional effects by comparing on option with the next least costly/effective.

Table 2: Pair-wise and incremental cost-effectiveness analysis of scenarios

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£81,010	7.914	-	-	-
2 (T,E,R)	£95,464	8.579	£21,733	£21,733	Vs Strategy 1
3 (E,T,R)	£102,469	8.836	£23,285	£27,310	Vs Strategy 2
4 (E,R,T)	£98,439	8.605	£25,244	Extendedly Dominated[1]	By Strategy 1&3

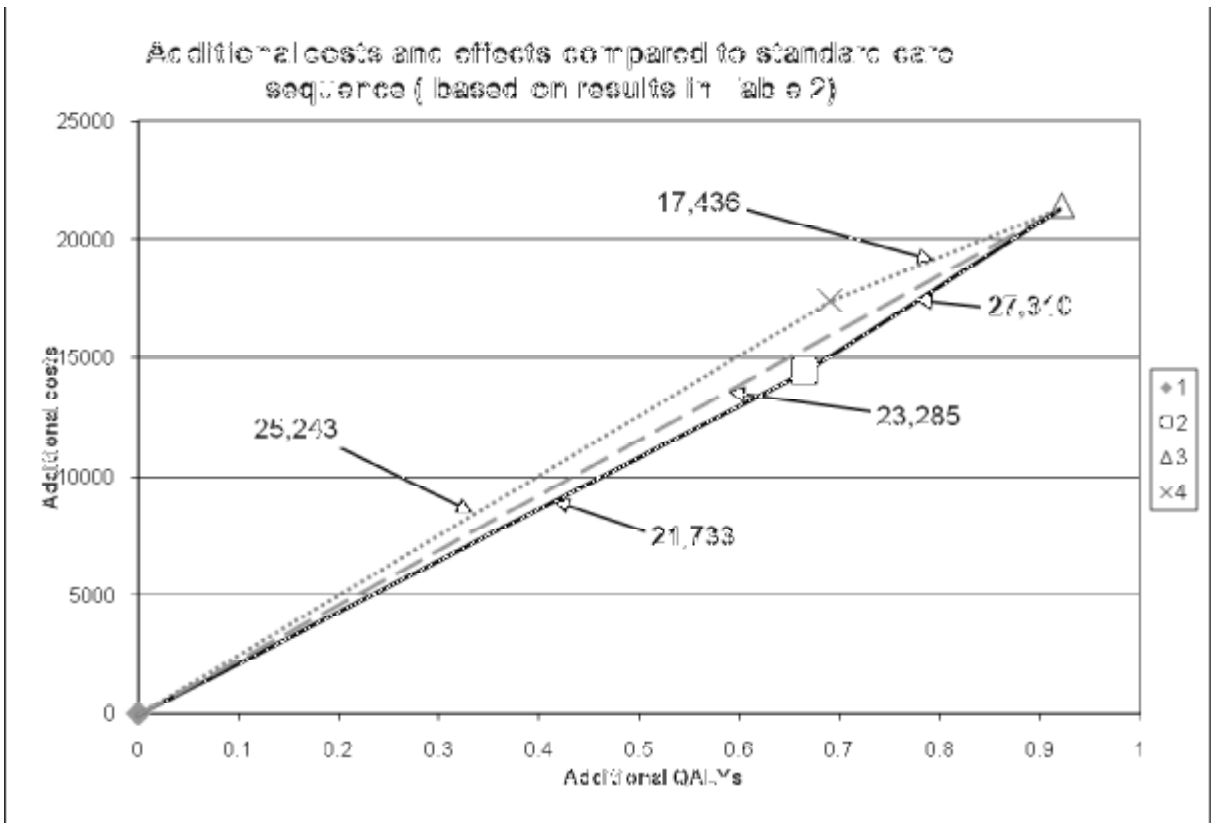
* Compared to Strategy 1 (Standard Care)
1. Extendedly dominated (ED) by combination of strategies 1&3 (ICER of 4 vs 2 = £117,366, ICER of 3 vs 4 = £17,436)
E=Etanercept, R = Rituxumab, T=Tocilizumab

Table 2 also shows this fully incremental analysis of the cost-effectiveness ratios for the tocilizumab sequences. Although none of the sequences is dominated, Strategy 4 (the use of tocilizumab 3rd line after rituximab) is subject to extended dominance, meaning that a strategy of using Strategy 2 for some patients and Strategy 3 for the remainder would be less costly and more effective than using Scenario 4 for all patients. The incremental ICER of Strategy 2 (the use of tocilizumab 1st line before etanercept) is £21,733 per QALY compared to standard care alone. The incremental ICER of the next most costly and effective (non-dominated) scenario, Strategy 3 (the use of tocilizumab 2nd line after etanercept), is £27,310 per QALY compared to Strategy 2. At a £30,000 per QALY threshold, Strategy 3 would be considered the most cost-effective sequence. However, at a threshold of £20,000 per QALY

gained, Strategy 1 (current standard of care) would be considered the most cost effective and no sequence involving tocilizumab would be considered cost effective.

The comparison of the results of the pair-wise and fully incremental analysis of the ICER can also be shown graphically as illustrated in Figure 2. Here, the additional costs and QALYs of the 3 tocilizumab strategies (Strategies 2 to 4) are presented compared to standard care alone (Strategy 1). Strategy 1 represents the origin point (i.e. 0 additional QALYs and cost) and the slope of the 3 lines directly connecting the origin to each of the 3 tocilizumab strategies are the 3 pair-wise ICERs. The slope of the additional lines connecting the tocilizumab strategies are the incremental ICERs between tocilizumab strategies. The solid black line represents the 'cost-effectiveness frontier'. Points above the line of this frontier are ruled out either by dominance or extended dominance (e.g. Strategy 4 represented by the symbol 'X' is ruled out by extended dominance).

Figure 2: Graphical comparison of pair-wise and incremental ICERs



The comparison of the ICERs demonstrates the importance of undertaking fully incremental analyses when comparing more than 2 mutually exclusive interventions. In these instances

the comparative assessment of incremental costs and outcomes being considered should be made against the successively more costly and effective treatments from the ranking of alternative sequences in order of costs or effects. Hence, the incremental ICER of Strategy 3 requires a comparison with Strategy 2 (£27,310) rather than Strategy 1 (£23,285).

Roche argues in its note of 25th March that comparing the cost-effectiveness of different tocilizumab-based sequences 'lies outside the remit of the NICE STA process' (page 4). NICE will need to consider issues of process in this regard. However, from a methodological viewpoint it would be inappropriate to conclude that all the tocilizumab-based sequences are equally cost-effective and it seems potentially perverse for NICE to ignore this finding. Even if all therapies were considered to have broadly the same clinical effectiveness, it is clear that they do not have the same cost. When this is alone is considered, leaving aside the impact of discounting, it is simply not plausible for all sequences to be equally cost-effective. Furthermore, Section 5.9.3 of the Methods guide states: "Standard decision rules should be followed when combining costs and QALYs. These should reflect any situation in which dominance or extended dominance exists. ICERs reported must be the ratio of expected additional total cost to expected additional QALYs compared with alternative treatment(s)." We would argue that what we are suggesting is the correct interpretation of "standard decision rules" as opposed to the presentation of separate pair-wise ICERs.

The Committee commonly 'optimises' guidance based on STAs in a number of respects, most notably with regard to identifying the most cost effective sub-group(s) of patients from a broader population and starting and stopping rules for therapies. The identification of the most cost-effective place of a new drug in a sequence is entirely consistent with this approach to 'optimisation'.

3. CLARIFICATION OF MANUFACTURER ASSUMPTIONS AND ALTERNATIVE APPROACHES CONSIDERED BY THE DSU

The following sections outline the assumptions used in the manufacturer's latest submission and the extent to which these reflect the 'Consideration of evidence' section reported in ACD 3. The additional analyses which have been undertaken by the DSU to reflect the key considerations are also summarised.

3.1 COMPARISON OF MANUFACTURER ASSUMPTIONS AND 'CONSIDERATION OF EVIDENCE' SECTION REPORTED IN ACD3

Table 3 provides a summary of the Appraisal Committee's concerns and their conclusions on key parameters reported in Sections 4.7 to 4.14 of ACD 3.

Table 3: Summary of Committee concerns, additional scenarios requested and the approach used by the manufacturer

Committee concern in ACD 3	Additional scenarios requested by Committee in ACD 3	Approach used by manufacturer in response to ACD 3
Initial HAQ improvement derived from ACR response rates in the MTC	DMARD-IR and TNF-IR: 'Unadjusted' trial data.	MTC in the base-case. Separate scenario presented using 'unadjusted' trial data.
HAQ progression while on treatment	Average zero HAQ progression for all biological treatments (including tocilizumab)	Continued long term HAQ improvement for tocilizumab for DMARD-IR and TNF-IR populations (3 years) and zero HAQ progression for all other biological treatments.
Rebound to baseline HAQ on withdrawal	Equal to initial improvement (i.e. back to baseline HAQ).	Equal to initial improvement (i.e. back to baseline HAQ)
Mapping of utility values	No specific scenarios requested but preference stated for use of directly observed EQ-5D data.	Continued use of HAQ mapping based on LITHE trial data.
Lack of modelling of adverse events	Utility decrement of adverse events associated with tocilizumab should be incorporated.	No utility decrement applied.
Cost of administering tocilizumab	At least £154.	£154.30.
Possibility of treatments being less effective later in the sequence	No specific scenarios requested but request to assume reduced response rate for treatments if used later in sequence.	'Degraded' response rates modelled for tocilizumab after 2 biologics, etanercept after 1 biologic and rituximab after 2 biologics.

The revised Roche submission following ACD 3 made several changes within the revised base-case analysis, most notably to model 'degraded' response rate for treatments used later in a sequence. The submission also presented additional cost-effectiveness results for patients that are intolerant or unsuitable for treatment with rituximab as requested by the Appraisal Committee. However, Table 3 also demonstrates that in several key areas the latest set of

results presented by Roche do not concur with the Appraisal Committee conclusions on several key parameter assumptions. Most notably, the revised base-case results:

- Are still based on the MTC, although a separate scenario has been conducted by Roche using the 'unadjusted' trial results which is reported to have only a minor effect on the ICER results (reported on pages 19 and 20 of the manufacturer's response).
- Assume continued long term HAQ improvement for 3 years with tocilizumab compared to other biologic treatments. No alternative scenarios are presented and Roche continue to assert in the latest submission that the existing evidence base demonstrates a unique positive effect associated with tocilizumab (discussed on pages 20 and 21 of the manufacturer's response).
- Use HAQ mapping based on the LITHE trial data. No additional scenarios are presented, although the manufacturer submits additional evidence in support of the mapping approach employed (page 5 and pages 22-23 of the manufacturer's response).
- Do not incorporate adverse events. The latest submission states that the manufacturer was unclear how the Committee's conclusions were reached, stating that a transparent assumption and justification had not been stated. Further discussion is also provided by Roche on whether it is appropriate to assume to treat palliative care differently from other biologics and DMARDs and reference to the fact that treatment related AE will have been captured in the EQ-5D utility data.

3.2 ACR RESPONSE RATES AND MODELLED OF DEGRADATION OF TREATMENT EFFECT

Table 4 summarises the ACR response rates used in the latest submission by Roche. As previously noted the base-case results presented by the manufacturer were based on the 'adjusted' MTC results although a separate scenario was presented using the 'unadjusted' trial results. Both analyses took into account the Committee's recommendations related to a 'degradation' of efficacy for treatments used at later points in a sequence. The sources and assumptions are reported in the manufacturer's latest response (Table 6, p12).

Table 4: Summary of ACR response rates used in 'adjusted' and 'unadjusted' analyses

	'Unadjusted' trial			'Adjusted' MTC		
	ACR20	**ACR50**	**ACR70**	**ACR20**	**ACR50**	**ACR70**
DMARD-IR						
Tocilizumab	0.59	0.37	0.19	0.63	0.41	0.26
Etanercept	0.71	0.39	0.15	0.62	0.38	0.16
TNF/BIO-IR						
Tocilizumab	0.50	0.29	0.12	0.62	0.31	0.12
Etanercept[1]	0.49	0.26	0.07	0.49	0.26	0.07
Rituximab	0.51	0.27	0.12	0.46	0.23	0.14
2*BIO-IR						
Tocilizumab[1]	0.50	0.31	0.15	0.5	0.31	0.15
Rituximab[1]	0.42	0.22	0.1	0.42	0.22	0.1

1. Results used in the 'adjusted' analyses are actually derived from 'unadjusted' results based on the 'degradation' of response rates

It is worth noting that the 'adjusted' MTC results estimate higher ACR response rates for tocilizumab compared to etanercept, while the opposite result is estimated based on the 'unadjusted' trial results (with the exception of the ACR70 response rate which remains marginally higher for tocilizumab based on the 'unadjusted' results). The difference in the results from these approaches has been a source of concern for the Committee and led to the request for separate comparisons based on the results of the 'adjusted' and 'unadjusted' trial results.

With respect to the etanercept response rates applied in the alternative approaches, there are several further considerations that should be noted:

1. For the DMARD-IR population, the response rates for etanercept in the 'adjusted' MTC analysis are derived from a pooled analysis of anti-TNFs, which excludes the Klareskog and Moreland trials, and only includes a subgroup from the Furst trial. The included trials in the 'adjusted' analysis for etanercept are: Weinblatt et al, 2003 - Adalimumab; Furst et al, 2003 – Adalimumab; Keystone et al, 2004 – Adalimumab; Weinblatt et al, 1999 – Etanercept; Combe et al, 2006 – Etanercept; Maini et al, 1999 – Infliximab and Westhovens et al, 2006 – Infliximab).
2. For the DMARD-IR population, the response rates reported for etanercept using the 'unadjusted' trial results are actually derived from a single etanercept trial (Weinblatt et al, 1999). It is unclear why this single study was chosen and why other potentially relevant etanercept trials were excluded (e.g. Combe et al 2006).

3. The ‘unadjusted’ ACR 70 response rate reported by the manufacturer for Weinblatt et al, 1999 does not appear to be correct. The ACR 20, 50 and 70 response rates applied by the manufacturer in the model are: 71%, 39% and 15% respectively. However, the actual ACR 20, 50 and 70 response rates reported in Weinblatt et al, 1999 appear to be: 71%, 39% and 17%. Hence, the estimates applied in the manufacturer’s ‘adjusted’ analysis appear to under-estimate the ACR70 response rate for etanercept.
4. The DSU has also undertaken a fixed-effect meta-analysis to pool ‘unadjusted’ ACR response rates for etanercept using both the Weinblatt and Combe studies. The pooled estimate of the ACR 20, 50 and 70 response rates are: 73%, 47% and 22%, respectively. The impact of using the pooled estimate on the cost-effectiveness results are considered in later sections of this report.

The ‘degradation’ of treatment effect assumed for tocilizumab (used after 2 biologics), etanercept (used after 1 biologic) and rituximab (used after 2 biologics) were derived from 3 separate sources. Response rates for tocilizumab were based on the subgroup of patients that had an inadequate response to more than 1 aTNF from the RADIATE trial. Estimates for etanercept were based on treatment response to a second or third aTNF in RA reported from the South Swedish Arthritis Treatment Group Register (Karlsson, 2008). The ‘degraded’ response rates for rituxumab were taken from a subgroup of patients that has shown an inadequate response to more than one aTNF in the REFLEX trial. Each of these sources provided separate ‘unadjusted’ estimates for each biologic. That is, none of the effects used to model the ‘degradation’ of response rates was derived from the ‘adjusted’ MTC. The revised base-case analysis presented by the manufacturer thus combined ‘adjusted’ results from the MTC with ‘unadjusted’ results for tocilizumab, etanercept and rituximab when used in later points in a sequence. When considering the robustness of final estimates used in the model, the DSU notes that:

- The justification for using these specific sources was not stated and there was no discussion of whether alternative estimates were available from other sources.
- The effects for etanercept were based on the reported ACR response rates for the aTNFs as a group and hence may not be generalisable to etanercept.
- The ‘degraded’ effects of tocilizumab used after 2 biologics were marginally better than when used after a single biologic which appears counter-intuitive.

3.3 ALTERNATIVE ANALYSES UNDERTAKEN BY THE DSU

Given the disparity between the results of the 'adjusted' MTC and 'unadjusted' trial results and the concerns expressed by the Committee, the DSU has undertaken 4 separate analyses using alternative approaches to informing the ACR response rates.

Approach 1: Using 'adjusted' MTC results from the manufacturer combined with the 'unadjusted' degraded effects. This is the same as the manufacturer's revised base-case analysis.

Approach 2: Using the 'unadjusted' trial results for etanercept when used 1st in sequence rather than the 'adjusted' MTC results. All other estimates the same as applied in Approach 1.

Approach 3: Using 'unadjusted' trial results for all treatments (biologics and non-biologics). This is similar to the scenario undertaken by the manufacturer (reported on page 20 of the manufacturer's response). However, the DSU have replaced the 'degraded' effect assumed by the manufacturer for tocilizumab when used after 2 biologic with the same effect assumed after a single aTNF, due to the counter-intuitive finding noted for the 'degraded' effect (i.e. it would seem implausible for tocilizumab to be more effective at later points in the sequence).

Approach 4: Using 'unadjusted' trial results for all treatment (biologics and non-biologics). This is similar to Approach 3. However, the DSU have also replaced the 'unadjusted' effect assumed by the manufacturer for etanercept used and replaced it with the pooled results from the 2 etanercept trials (Weinblatt and Combe studies).

For each of these approaches to modelling ACR response rates, 4 separate sets of sensitivity analyses were undertaken to assess the robustness of the ICER results to other key parameters and assumptions.

(i) Employing the same set of parameter assumptions employed by manufacturer in their base-case.

(ii) Altering long-term HAQ progression assumptions for tocilizumab.

(iii) Altering long-term HAQ progression assumptions for tocilizumab and excluding negative utilities from the HAQ EQ-5D mapping.

(iv) Altering HAQ progression assumptions for tocilizumab and doubling administration costs for tocilizumab.

These analyses are summarised in Table 5 below.

Table 5: Sensitivity analyses undertaken by DSU to reflect Committee concerns

Committee concern in ACD3				
	(i)	**(ii)**	**(iii)**	**(iv)**
HAQ progression while on treatment	As per manufacturer base-case	Average zero HAQ progression for all biological treatments - <u>including tocilizumab</u>	Average zero HAQ progression for all biological treatments - <u>including tocilizumab</u>	Average zero HAQ progression for all biological treatments - <u>including tocilizumab</u>
Rebound to baseline HAQ on withdrawal	As per manufacturer base-case	Equal to initial improvement	Equal to initial improvement	Equal to initial improvement
Mapping of utility values	As per manufacturer base-case	As per manufacturer base-case	As per manufacturer base-case but <u>negative utilities not allowed</u>	As per manufacturer base-case
Lack of modelling of adverse events	As per manufacturer base-case	As per manufacturer base-case	As per manufacturer base-case	As per manufacturer base-case
Cost of administering tocilizumab	As per manufacturer base-case	As per manufacturer base-case	As per manufacturer base-case.	Doubled (£308.60)
Possibility of treatments being less effective later in the sequence	As per manufacturer base-case	As per manufacturer base-case	As per manufacturer base-case	As per manufacturer base-case

4. RESULTS FROM DSU ANALYSES

4.1 ANALYTIC APPROACH

The cost-efffectiveness results from the 4 separate approaches to informing ACR response rate (and the 4 different sets of parameter assumptions) are reported in detail in sections 4.2.1

to 4.2.4. In each case the results from both the pair-wise cost-effectiveness ratios and the fully incremental analysis are reported. The pair-wise ICER column reports the cost-effectiveness ratio for a particular strategy versus the current standard of care. The incremental analysis (Incremental ICER column) follows the correct approach outlined previously by ranking the alternatives and excluding any strategies which are ruled out by either dominance or extended dominance. When a strategy is ruled out on these grounds, the strategy which dominates it is reported (or the combination of strategies which extendedly dominate it are reported alongside the ICER estimates demonstrating this). Finally, the ICERs of any non-dominated strategies are reported together with the comparator which is used as the basis for each calculation.

Where 2 or more ICERs are reported, the optimal sequence from a cost-effectiveness perspective is determined by whether one or more of these ICERs are below a particular cost-effectiveness threshold. When only one ICER is below the threshold, this is the strategy considered to be most cost-effective. When more than one ICER is below the threshold, the strategy with the value closest to the threshold is considered the most cost-effective. A hypothetical example is provided below to illustrate this concept.

Example

- Assume that strategies 1, 2 and 3 are successively more costly and more effective and none of these strategies are ruled out by dominance or extended dominance.
- Assume that the ICER of 2 vs 1 = £19,000 per QALY and the ICER of 3 vs 2 = £29,000 per QALY.
- At a £20,000 threshold, strategy 2 would be considered the most cost-effective strategy.
- At a £30,000 threshold, strategy 3 would be considered the most cost-effective strategy.

These decision rules are applied to the detailed results reported in sections 4.2.1-4.2.3 (Tables 6 – 21) and the most cost-effective sequences at thresholds of £20,000 and £30,000 per QALY are then summarised and discussed in section 4.3.

4.2.1 RESULTS FROM APPROACH 1 - USING 'ADJUSTED' MTC RESULTS FROM MANUFACTURER

Tables 6 – 9 report the detailed cost-effectiveness results using Approach 1 with the 4 different sets of parameter assumptions.

Table 6: Cost-Effectiveness results from Approach 1(i)

Scenario	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£81,010	7.914	-	-	-
2 (T,E,R)	£95,464	8.579	£21,733	£21,733	By Strategy 1&3
3 (E,T,R)	£102,469	8.836	£23,285	£27,310	Vs Strategy 1
4 (E,R,T)	£98,439	8.605	£25,244	ED[1]	By Strategy 1&3

* Compared to standard care
1. Extendedly dominated by combination of strategy 1&3 (ICER of 4 vs 2 = £117,366, ICER of 3 vs 4 = £17,436)

Table 7: Cost-Effectiveness results from Approach 1(ii)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£81,010	7.914	-	-	
2 (T,E,R)	£95,415	8.430	£27,946	ED[1]	By Strategy 4
3 (E,T,R)	£102,423	8.670	£28,324	£60,771	Vs Strategy 4
4 (E,R,T)	£98,439	8.605	£25,244	£25,244	Vs Strategy 1

* Compared to standard care
1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £27,946, ICER of 4 vs 2 = £17,284)

Table 8: Cost-Effectiveness results from Approach 1(iii)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£81,010	7.950	-	-	-
2 (T,E,R)	£95,415	8.453	£28,608	ED[1]	By Strategy 4
3 (E,T,R)	£102,423	8.690	£28,914	£62,385	Vs Strategy 4
4 (E,R,T)	£98,439	8.627	£25,755	£25,755	Vs Strategy 1

* Compared to standard care
1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £28,608, ICER of 4 vs 2 = £17,461)

Table 9: Cost-Effectiveness results from Approach 1(iv)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£81,010	7.914	-		
2 (T,E,R)	£101,594	8.430	£39,935	ED[1]	By Strategy 4
3 (E,T,R)	£107,216	8.670	£34,665	£78,264	Vs Strategy 4
4 (E,R,T)	£102,086	8.605	£30,526	£30,526	Vs Strategy 1

* Compared to standard care

1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £39,935, ICER of 4 vs 2 = £2,808)

4.2.2 RESULTS FROM APPROACH 2 - USING 'ADJUSTED' MTC RESULTS FROM MANUFACTURER BUT USING 'UNADJUSTED' TRIAL RESULTS FOR ETANERCEPT WHEN USED 1ST IN SEQUENCE

Tables 10-13 report the detailed cost-effectiveness results using Approach 2 with the 4 different sets of parameter assumptions.

Table 10: Cost-Effectiveness results from Approach 2(i)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£85,259	8.066	-	-	-
2 (T,E,R)	£95,464	8.579	£19,879	£19,879	Vs Strategy 1
3 (E,T,R)	£106,247	8.948	£23,788	£29,227	Vs Strategy 2
4 (E,R,T)	£102,331	8.734	£25,568	ED[1]	By Strategy 3

* Compared to standard care

1. Extendedly dominated by strategy 2&3 (ICER of 4 vs 2 = £44,490, ICER of 3 vs 4 = £18,455)

Table 11: Cost-Effectiveness results from Approach 2(ii)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£85,259	8.066	-	-	-
2 (T,E,R)	£95,415	8.430	£27,922	ED[1]	By Strategy 4
3 (E,T,R)	£106,203	8.789	£28,960	£69,748	Vs Strategy 4
4 (E,R,T)	£102,331	8.734	£25,568	£25,568	Vs Strategy 1

* Compared to standard care

1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £27,992, ICER of 4 vs 2 = £22,753)

Table 12: Cost-Effectiveness results from Approach 2(iii)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£85,259	8.097	-	-	-
2 (T,E,R)	£95,415	8.453	£28,533	ED[1]	By Strategy 4
3 (E,T,R)	£106,203	8.807	£29,511	£71,532	Vs Strategy 4
4 (E,R,T)	£102,331	8.753	£26,041	£26,041	Vs Strategy 1

* Compared to standard care
1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £28,533, ICER of 4 vs 2 = £23,081)

Table 13: Cost-Effectiveness results from Approach 2(iv)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£85,259	8.066	-	-	-
2 (T,E,R)	£101,594	8.430	£44,912	ED	By Strategy 4
3 (E,T,R)	£110,914	8.789	£35,474	£90,279	Vs Strategy 4
4 (E,R,T)	£105,902	8.734	£30,917	£30,917	Vs Strategy 1

* Compared to standard care
1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £44,912, ICER of 4 vs 2 = £14,171)

4.2.3 RESULTS FROM APPROACH 3: USING 'UNADJUSTED' ACR RESPONSE RATES FOR ALL INTERVENTIONS

Tables 14-17 report the detailed cost-effectiveness results using Approach 3 with the 4 different sets of parameter assumptions.

Table 14: Cost-Effectiveness results from Approach 3(i)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£87,372	8.397	-	-	-
2 (T,E,R)	£95,475	8.760	£22,307	£22,307	Vs Strategy 1
3 (E,T,R)	£103,783	9.041	£25,457	£29,522	Vs Strategy 2
4 (E,R,T)	£104,023	8.999	£27,621	D[1]	By Strategy 3

* Compared to standard care
1. Dominated by strategy 3

Table 15: Cost-Effectiveness results from Approach 3(ii)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£87,372	8.397	-	-	-
2 (T,E,R)	£95,407	8.618	£36,328	ED[1]	By Strategy 1&4
3 (E,T,R)	£103,742	8.915	£31,594	ED[2]	Vs Strategy 1&4
4 (E,R,T)	£104,023	8.999	£27,621	£27,621	Vs Strategy 1

* Compared to standard care
1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £36,328, ICER of 4 vs 2 = £28,068)
2. Extendedly dominated by strategy 1&4 (ICER of 3 vs 1 = £31,594, ICER of 4 vs 3 = £3,309)

Table 16: Cost-Effectiveness results from Approach 3(iii)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£87,372	8.423	-	-	-
2 (T,E,R)	£95,407	8.639	£37,182	ED[1]	By Strategy 1&4
3 (E,T,R)	£103,742	8.932	£32,140	ED[2]	Vs Strategy 1&4
4 (E,R,T)	£104,023	9.015	£28,090	£28,090	Vs Strategy 1

* Compared to standard care
1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £37,182, ICER of 4 vs 2 = £28,425)
2. Extendedly dominated by strategy 1&4 (ICER of 3 vs 1 = £32,140, ICER of 4 vs 3 = £3,359)

Table 17: Cost-Effectiveness results from Approach 3(iv)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£87372	8.397	-	-	-
2 (T,E,R)	£101,241	8.618	£62,703	ED	By Strategy 4
3 (E,T,R)	£107,606	8.915	£39,051	D	By Strategy 4
4 (E,R,T)	£107,546	8.999	£33,465	£33,465	Vs Strategy 1

* Compared to standard care
1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £62,703, ICER of 4 vs 2 = £16,521)

4.2.4 RESULTS FROM APPROACH 4: USING 'UNADJUSTED' ACR RESPONSE RATES FOR ALL INTERVENTIONS

Tables 18-21 report the detailed cost-effectiveness results using Approach 4 with the 4 different sets of parameter assumptions.

Table 18: Cost-Effectiveness results from Approach 4(i)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£88,244	8.466	-	-	-
2 (T,E,R)	£95,475	8.760	£24,608	£24,608	Vs Strategy 1
3 (E,T,R)	£108,357	9.249	£25,692	£26,344	Vs Strategy 2
4 (E,R,T)	£104,808	9.077	£27,121	ED[1]	By Strategy 3

* Compared to standard care
1. Extendedly dominated by strategy 2&3 (ICER of 4 vs 2 = £29,549, ICER of 3 vs 4 = £20,621)

Table 19: Cost-Effectiveness results from Approach 4(ii)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£88,244	8.466	-	-	-
2 (T,E,R)	£95,407	8.618	£47,193	ED[1]	By Strategy 4
3 (E,T,R)	£108,311	9.094	£31,964	£205,448	Vs Strategy 4
4 (E,R,T)	£104,808	9.077	£27,121	£27,121	Vs Strategy 1

* Compared to standard care
1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £47,193, ICER of 4 vs 2 = £20,483)

Table 20: Cost-Effectiveness results from Approach 4(iii)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£88,244	8.491	-	-	-
2 (T,E,R)	£95,407	8.639	£48,671	ED[1]	By Strategy 4
3 (E,T,R)	£108,311	9.109	£32,510	£213,177	Vs Strategy 4
4 (E,R,T)	£104,808	9.092	£27,569	£27,569	Vs Strategy 1

* Compared to standard care
1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £48,671, ICER of 4 vs 2 = £27,569)

Table 21: Cost-Effectiveness results from Approach 4(iv)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER*	Incremental ICER	Comparison for Incremental ICER
1 (E,R)	£88,244	8.466	-	-	-
2 (T,E,R)	£101,241	8.618	£85,622	ED[1]	By Strategy 4
3 (E,T,R)	£112,987	9.094	£39,413	£274,146	Vs Strategy 4
4 (E,R,T)	£108,313	9.077	£32,860	£32,860	Vs Strategy 1

* Compared to standard care
1. Extendedly dominated by strategy 1&4 (ICER of 2 vs 1 = £85,622, ICER of 4 vs 2 = £15,409)

4.3 SUMMARY OF MOST COST-EFFECTIVE SEQUENCE IN ALTERNATIVE ANALYSES UNDERTAKEN BY THE DSU

Tables 22 and 23 summarise the most cost-effective sequence at a £20k and £30k per QALY threshold respectively.

Table 22: Summary of most cost-effective sequence at a £20k per QALY threshold

SENSITIVITY ANALYSIS: Alternative parameter sets		**ACR EFFECTIVENESS ESTIMATES**			
		APPROACH 1	**APPROACH 2**	**APPROACH 3**	**APPROACH 4**
(i)	LT HAQ gain with tocilizumab, negative utilities allowed, admin costs = £154.30.	Strategy 1 (E,R)	Strategy 2 (T,E,R)	Strategy 1 (E,R)	Strategy 1 (E,R)
(ii)	No LT HAQ gain with tocilizumab, negative utility allowed, admin costs = £154.30	Strategy 1 (E,R)	Strategy 1 (E,R)	Strategy 1 (E,R)	Strategy 1 (E,R)
(iii)	No LT HAQ gain with tocilizumab, negative utility not allowed, admin costs = £154.30	Strategy 1 (E,R)	Strategy 1 (E,R)	Strategy 1 (E,R)	Strategy 1 (E,R)
(iv)	No LT HAQ gain with tocilizumab, negative utility allowed, admin costs doubled (£308.60)	Strategy 1 (E,R)	Strategy 1 (E,R)	Strategy 1 (E,R)	Strategy 1 (E,R)

Combining the 4 alternative approaches used by the DSU to inform the ACR response rates with the 4 alternative sets of parameter assumptions defines a total of 16 separate scenarios that have been considered. Table 22 demonstrates that, at a £20k threshold, Strategy 1 (i.e. standard care) is considered the most cost-effective sequence in 15 of these 16 scenarios. Hence, only in 1 of the 16 scenarios is a sequence incorporating tocilizumab considered more cost-effective than standard care. This scenario employs the 'adjusted' MTC results for

tocilizumab and rituximab with the 'unadjusted' trial results for etanercept 1st line and assumes: a long-term continued HAQ gain (up to 3 years) for tocilizumab; negative utilities are allowed from the HAQ/EQ-5D mapping exercise; and administration costs of £154.30 for tocilizumab. Within this specific scenario the most cost-effective strategy is using tocilizumab 1st in the sequence (tocilizuimab->etanercept->rituximab->DMARDs->Palliative care). However, altering any of the parameter assumptions (and correcting the error in the ACR70 response rates used for etanercept in the unadjusted analyses) means that standard care reverts back to the most cost-effective of the strategies considered.

At first glance the results from the single scenario in which a tocilizumab sequence is considered most cost-effective may initially appear potentially counter-intuitive. That is, it may not be immediately obvious why a scenario which uses a higher 1st line ACR response rate for etanercept as part of standard care from the 'unadjusted' analyses (Approach 2 vs Approach 1) subsequently appears to improve the cost-effectiveness of a strategy when tocilizumab is used before etanercept. The reasoning appears to relate to the differential impact that using a higher etanercept 1st line response rate has on mean total costs and QALYs for Strategy 1. This impact appears to increase the mean costs of this strategy proportionately more than the increase in mean QALYs. The impact of this is then to reduce the additional costs and QALYs in the ICER calculation of the next most costly and effective strategy (namely Strategy 2). Correspondingly, this then reduces the ICER estimate of Strategy 2 relative to Strategy 1.

Table 23: Summary of most cost-effective sequence at a £30k per QALY threshold

SENSITIVITY ANALYSIS: Alternative parameter sets		**ACR EFFECTIVENESS ESTIMATES**			
		APPROACH 1	**APPROACH 2**	**APPROACH 3**	**APPROACH 4**
(i)	LT HAQ gain with tocilizumab, negative utilities allowed, admin costs = £154.30.	Strategy 3 (E,T,R)	Strategy 3 (E,T,R)	Strategy 3 (E,T,R)	Strategy 3 (E,T,R)
(ii)	No LT HAQ gain with tocilizumab, negative utility allowed, admin costs	Strategy 4 (E,R,T)	Strategy 4 (E,R,T)	Strategy 4 (E,R,T)	Strategy 4 (E,R,T)

	= £154.30				
(iii)	No LT HAQ gain with tocilizumab, negative utility not allowed, admin costs = £154.30	Strategy 4 (E,R,T)	Strategy 4 (E,R,T)	Strategy 4 (E,R,T)	Strategy 4 (E,R,T)
(iv)	No LT HAQ gain with tocilizumab, negative utility allowed, admin costs doubled (£308.60)	Strategy 1 (E,R)	Strategy 1 (E,R)	Strategy 1 (E,R)	Strategy 1 (E,R)

The results from Table 23, based on a higher £30k per QALY threshold, demonstrate that a sequence including tocilizumab appears the most cost-effective strategy in 12 of the 16 scenarios considered. The results also demonstrate an important consistency in the findings. That is, although the most cost-effective strategy appears to vary depending upon the particular set of parameter estimates employed in the 4 different sensitivity analyses, this does not vary between the 4 alternative approaches used to inform the ACR response rates. Hence, the conclusions do not appear to depend on the approach to informing ACR response rates but do appear to depend upon the assumptions for the different parameter estimates.

Applying the same set of parameter estimates (sensitivity analysis [i]) as employed in the manufacturer's base-case analysis, this results in Strategy 3 (tocilizumab 2nd in sequence: etanercept->tocilizumab->rituximab->DMARDs->Palliative care) being the most cost-effective strategy. However, if tocilizumab is assumed not to confer additional long-term HAQ gains compared to the other biologic treatments, then the most cost-effective strategy appears to be Strategy 4 (tocilizumab 3rd in sequence: etanercept->rituximab->tocilizumab->DMARDs->Palliative care) regardless of whether negative utilities derived from the HAQ/EQ-5D mapping are allowed or not. The final set of parameter estimates employed (sensitivity analysis [iv]) demonstrate the Strategy 1 is always the most cost-effective sequence when the administration costs of tocilizumab are doubled and no additional long-term HAQ gain is assumed for tocilizumab.

4.4 TREATMENT SEQUENCES FOR PATIENTS THAT ARE INTOLERANT OR UNSUITABLE FOR TREATMENT WITH RITUXIMAB

All the analyses undertaken in the previous sections have assumed that patients are suitable for treatment with rituximab. However, as reported in section 4.22 of ACD 3, the Committee noted that there may be a group of patients with moderate to severe rheumatoid arthritis who are intolerant to, or unsuitable for, rituximab. Therefore, as part of ACD 3, the Committee requested further clarification from the manufacturer together with estimates of the cost-effectiveness of tocilizumab in this position in the treatment pathway.

As part of Roche's response to ACD 3 the results of additional analyses to evaluate the cost-effectiveness of tocilizumab within this setting were provided (see Table 5, page 11 of the manufacturer's response). The manufacturer modelled two separate strategies after failure of an aTNF:

Strategy 1: Current standard of care for patients intolerant to, or unsuitable for, rituximab (DMARDs [Leflunomide->Gold->Cyclosporine]->Palliative care)
Strategy 2: Adding toclizumab (Tocilizumab->DMARDs [Leflunomide->Gold->Cyclosporine]->Palliative care)

The DSU have also considered this setting and undertaken additional analyses exploring the same alternative approaches to estimating ACR response rates and the 4 different sets of parameter estimates to maintain consistency with the analyses presented previously. In addition, to facilitate comparisons with the previous analyses and to aid transparency, the DSU has modelled the cost-effectiveness from an earlier point in the treatment sequence than the manufacturer. In other words, the same strategies are being considered as earlier in the DSU report but without rituximab in them. However, based on the previous series of results, which demonstrated that using tocilizumab before etanercept was only cost-effective in 1 out of 16 scenarios at a £20k threshold (and this finding was not sustained when the correct ACR70 response rates were used), only a strategy of adding tocilizumab after etanercept is modelled in comparison to the current standard of care. Thus the 2 strategies under consideration in the DSU analyses are:

Strategy 1: Current standard of care (Etanercept->DMARDs[Leflunomide->Gold->Cyclosporine]->Palliative care)
Strategy 2: Adding tocilizumab (Etanercept->Tocilizumab-> DMARDs[Leflunomide->Gold->Cyclosporine]->Palliative care)

Although etanercept is common to both strategies and hence cancels out these effects in an incremental analysis, discounting will have an impact compared to the approach used by the manufacturer of modelling at a later point in the treatment sequence.

Tables 24-26 report the ICERs comparing these 2 strategies for the different approaches to estimating ACR response rates and for the separate sensitivity analyses using alternative parameter assumptions. Only approaches 1 (Table 24), 3 (Table 25) and 4 (Table 26) are reported for the ACR response rates.

Table 24: Results from Approach 1 'adjusted' MTC estimates

Approach 1(i)			
Strategy	**Mean Cost**	**Mean QALY**	**ICER**
1 (E)	£75,158	7.429	-
2 (E,T)	£97,936	8.504	£21,196
Approach 1(ii)			
Strategy	**Mean Cost**	**Mean QALY**	**ICER**
1 (E)	£75,158	7.429	-
2 (E,T)	£97,928	8.336	£25,105
Approach 1(iii)			
Strategy	**Mean Cost**	**Mean QALY**	**ICER**
1 (E)	£75,158	7.472	-
2 (E,T)	£97,928	8.361	£25,619
Approach 1(iv)			
Strategy	**Mean Cost**	**Mean QALY**	**ICER**
1 (E)	£75,158	7.429	-
2 (E,T)	£102,721	8.336	£30,390

Table 25: Results from Approach 3 'unadjusted' trial estimates

Approach 3(i)			
Strategy	**Mean Cost**	**Mean QALY**	**ICER**
1 (E)	£81,180	8.012	-
2 (E,T)	£99,327	8.788	£23,370
Approach 3(ii)			
Strategy	**Mean Cost**	**Mean QALY**	**ICER**
1 (E)	£81,180	8.012	-
2 (E,T)	£99,320	8.661	£27,950
Approach 3(iii)			
Strategy	**Mean Cost**	**Mean QALY**	**ICER**
1 (E)	£81,180	8.042	-
2 (E,T)	£99,320	8.680	£28,428
Approach 3(iv)			

Strategy	Mean Cost	Mean QALY	ICER
1 (E)	£81,180	8.012	-
2 (E,T)	£103,183	8.661	£33,903

Table 26: Results from Approach 4 'unadjusted' trial estimates

Approach 4 – Sensitivity analysis (i)			
Strategy	**Mean Cost**	**Mean QALY**	**ICER**
1 (E)	£82,117	8.086	-
2 (E,T)	£100,089	8.855	£23,342
Approach 4 – Sensitivity analysis (ii)			
Strategy	**Mean Cost**	**Mean QALY**	**ICER**
1 (E)	£82,117	8.086	-
2 (E,T)	£100,079	8.729	£27,917
Approach 4 – Sensitivity analysis (iii)			
Strategy	**Mean Cost**	**Mean QALY**	**ICER**
1 (E)	£82,117	8.115	-
2 (E,T)	£100,079	8.748	£28,392
Approach 4 – Sensitivity analysis (iv)			
Strategy	**Mean Cost**	**Mean QALY**	**ICER**
1 (E)	£82,117	8.086	-
2 (E,T)	£103,908	8.729	£33,868

Tables 27 and 28 summarise the most cost-effective sequence at a £20k and £30k per QALY threshold, respectively. Table 27 demonstrates that, at a £20k threshold, Strategy 1 (i.e. standard care) is considered the most cost-effective sequence in all 12 scenarios. At a higher threshold of £30k, adding tocilizumab (after etanercept) to the current standard of care is cost-effective in 9 of the 12 scenarios. Only when the administration costs of tocilizumab are doubled does adding tocilizumab not appear cost-effective.

Table 27: Summary of most cost-effective sequence at a £20k per QALY threshold

		ACR EFFECTIVENESS ESTIMATES		
SENSITIVITY ANAYSIS		***APPROACH 1***	***APPROACH 2***	***APPROACH 3***
(i)	LT HAQ gain with tocilizumab, negative utilities allowed, admin costs = £154.30.	Strategy 1 (E)	Strategy 1 (E)	Strategy 1 (E)
(ii)	No LT HAQ gain with tocilizumab, negative utility allowed, admin costs =	Strategy 1 (E)	Strategy 1 (E)	Strategy 1 (E)

	£154.30			
(iii)	No LT HAQ gain with tocilizumab, negative utility not allowed, admin costs = £154.30	Strategy 1 (E)	Strategy 1 (E)	Strategy 1 (E)
(iv)	No LT HAQ gain with tocilizumab, negative utility allowed, admin costs doubled (£308.60)	Strategy 1 (E)	Strategy 1 (E)	Strategy 1 (E)

Table 28: Summary of most cost-effective sequence at a £30k per QALY threshold

SENSITIVITY ANAYSIS		**ACR EFFECTIVENESS ESTIMATES**		
		APPROACH 1	***APPROACH 2***	***APPROACH 3***
(i)	LT HAQ gain with tocilizumab, negative utilities allowed, admin costs = £154.30.	Strategy 2 (E,T)	Strategy 2 (E,T)	Strategy 2 (E,T)
(ii)	No LT HAQ gain with tocilizumab, negative utility allowed, admin costs = £154.30	Strategy 2 (E,T)	Strategy 2 (E,T)	Strategy 2 (E,T)
(iii)	No LT HAQ gain with tocilizumab, negative utility not allowed, admin costs = £154.30	Strategy 2 (E,T)	Strategy 2 (E,T)	Strategy 2 (E,T)
(iv)	No LT HAQ gain with tocilizumab, negative utility allowed, admin costs doubled (£308.60)	Strategy 1 (E)	Strategy 1 (E)	Strategy 1 (E)

5. SUMMARY OF FINDINGS

The results of the fully incremental analysis undertaken by the DSU indicate the following based on assuming a £20k threshold:

- Using tocilizumab at any point (i.e. 1st, 2nd or 3rd) in a biologic treatment sequence does not appear cost-effective in 15 of the 16 scenarios considered.
- The single scenario in which a tocilizumab sequence appeared cost-effective was based on using the 'unadjusted' trial estimates for etanercept and assumed a continued

long-term HAQ gain (up to 3 years) for tocilizumab. However, this finding no longer held when the corrected ACR70 response rates were used for etanercept and/or when other parameter assumptions were altered.

For patients intolerant to, or unsuitable for rituximab:

- Adding tocilizumab to the current standard of care does not appear cost-effective in any scenario considered.

The results of the fully incremental analysis undertaken by the DSU indicate the following based on assuming a £30k threshold:

- Using tocilizumab 1st line (before etanercept) is never cost-effective in any scenario.
- Using tocilizumab 2nd line (before rituximab) is only cost-effective if you assume tocilizumab has better long term HAQ improvement compared to other biologics.
- However, if tocilizumab does not have a differential effect on long-term HAQ compared to other biologics (i.e. zero HAQ change in long term) then tocilizumab is only cost-effective used 3rd line (after rituximab).
- If tocilizumab does not have a differential effect on long-term HAQ compared to other biologics and the administration costs of tocilizumab are doubled then tocilizumab is not cost-effective even used 3rd line (after rituximab) (i.e. standard of care is the most cost effective sequence).
- These general findings appear consistent whether you use the manufacturer's MTC or the unadjusted results (i.e the trial results rather than MTC) and whether you allow negative utilities or not.

For patients intolerant to, or unsuitable for rituximab:

- Adding tocilizumab to the current standard of care appears cost-effective
- However, if tocizumab does not have a different effect on long-term HAQ and the administration costs of tocilizumab are doubled then the current standard of care appears more cost-effective.

6. REFERENCES

1. Johannesson M, Weinstein S. On the decision rules of cost-effectiveness analysis. *Journal of Health Economics* 1993;12:459-467.

2. Drummond MF, Sculpher MJ, Torrance GW, O'Brien B, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes.* 3rd ed. Oxford: Oxford University Press, 2005.