TOCILIZUMAB

FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

REPORT BY THE DECISION SUPPORT UNIT

2nd September 2011

Jon Minton, Paul Tappenden, Jonathan Tosh

School of Health and Related Research, University of Sheffield

Decision Support Unit, ScHARR, University of Sheffield, Regent Court, 30 Regent Street
Sheffield, S1 4DA;

Tel (+44) (0)114 222 0734
E-mail dsuadmin@sheffield.ac.uk

GLOSSARY

Acronym	Term
DMARD-IR	Disease-modifying anti rheumatoid drug - inadequate responders
DSU	Decision Support Unit
E	etanercept
ED	Extended dominance
ERG	Evidence Review Group
ICER	Incremental cost-effectiveness ratio
PAS	Patient Access Scheme
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
R	rituximab
sJIA	systemic Juvenile Idiopathic Arthritis
T	tocilizumab
TA	Technology Appraisal
TNF-IR	Tumour Necrosis Factor - inadequate responders

EXECUTIVE SUMMARY

The purpose of this DSU report is to assess whether Roche's proposed Patient Access Scheme (PAS) for tocilizumab has been implemented within Roche's tocilizumab cost-effectiveness model as detailed in the Roche PAS template. This report addresses this issue by answering the following three questions:

1. Have the committee-agreed assumptions for all rheumatoid arthritis patient populations from TA198 final guidance (including DMARD-IR and TNF alpha-IR subgroups) been used as the starting point by Roche in their economic model?
2. Have the only changes to the economic modelling been to the costs of tocilizumab (as associated with the agreed PAS)?
3. Has the PAS been implemented in accordance with the details of the scheme agreed by the Department of Health and detailed in the PAS template submitted by Roche?

The DSU were able to replicate the results presented in both the PAS proposal and the additional supplement sent by Roche on the 24th August 2011. Across the PAS proposal and the supplement provided later, Roche have reported cost-effectiveness results within the DMARD-IR subgroup and the TNF-IR subgroup. No results were presented for those patients who are intolerant or unsuitable for treatment with rituximab. Within the TNF-IR analysis presented by Roche, the (R, T) sequence was not evaluated; this missing treatment sequence has an important impact on the cost-effectiveness of the options that Roche did evaluate. Importantly, the incremental cost-effectiveness ratios (ICERs) contained within the PAS proposal and the additional supplement were incorrect as they did not exclude treatment sequences which are subject to extended dominance. The appropriate adoption of these economic decision rules changes the interpretation of the results of Roche's economic analysis. The Committee should consider only those ICERs produced by the DSU. The following results should be considered by the Committee.

DMARD-IR subgroup results

Within the DMARD-IR subgroup, the (E, R, T) sequence was expected to be the most effective option. Without the PAS, the ICER for (E, R, T) versus (E, R) was £27,582 per QALY gained. The sequences (T, E, R) and (E, T, R) were both ruled out due to extended dominance. When the PAS was applied, (T, E, R) compared against E, R had an ICER of £5,716 per QALY gained. (E, R, T) versus (T, E, R) had an ICER of £26,549 per QALY gained. The (E, T, R) sequence was ruled out due to extended dominance.

Rituximab-intolerant subgroup results

Within the rituximab-intolerant DMARD-IR subgroup, the most effective sequence was (E, T). Without the PAS, (E, T) versus (E) had an ICER of £27,917 per QALY gained. The (T, E) sequence was ruled out due to extended dominance. When the PAS was included, (T, E) versus (E) had an ICER of £8,648 per QALY gained. The (E, T) sequence had an ICER of £30,121 per QALY gained compared against (T, E).

TNF-IR subgroup results

Within the TNF-IR subgroup, the (R, T) sequence was estimated to be the most effective. Without the PAS, (R, T) versus (R) had an ICER of £24,099 per QALY gained and (T, R) was ruled out due to simple dominance. With the PAS applied (R, T) versus (R) had an ICER of £18,527 per QALY gained, and (T, R) was again ruled out due to simple dominance.

Replacement of etanercept with tocilizumab within the DMARD-IR subgroup

An analysis in which tocilizumab is used as a replacement for etanercept was also considered. Within this analysis, (E, R) no longer lies on the cost-effectiveness frontier and the baseline is replaced by the (T, R) sequence. When the PAS is applied, the ICER for (E, R, T) versus (T, R) was £28,380 per QALY gained. The sequences (T, E, R) and (E, T, R) were both ruled out due to extended dominance. This reflects the current NICE recommendation for tocilizumab. A similar result was found when (T) was considered as an option within the rituximab-IR subgroup.

CONTENTS

TABLES AND FIGURES

1. BACKGROUND

1.1. PURPOSE OF THIS REPORT

The purpose of this DSU report is to assess whether Roche's proposed Patient Access Scheme (PAS) for tocilizumab has been implemented within Roche's tocilizumab cost-effectiveness model as detailed in the Roche PAS template. This report addresses three specific questions:

1. Have the committee-agreed assumptions for all rheumatoid arthritis patient populations from TA198 final guidance (including DMARD-IR and TNF alpha-IR subgroups) been used as the starting point by Roche in their economic model?
2. Have the only changes to the economic modelling been to the costs of tocilizumab (as associated with the agreed PAS)?
3. Has the PAS been implemented in accordance with the details of the scheme agreed by the Department of Health and detailed in the PAS template submitted by Roche?

The proposed PAS represents a discount on the price of tocilizumab for *all* indications. This report is concerned with the implementation of the PAS in adults with rheumatoid arthritis including the broader group of DMARD-IR patients, the subgroup of DMARD-IR patients for who are intolerant or unsuitable for treatment with rituximab, and patients with an inadequate response to TNF-α inhibitors (TNF-IR). The proposed PAS will also impact upon the ongoing appraisal of tocilizumab for the treatment of systemic juvenile idiopathic arthritis; the impact of the PAS within this patient group is not considered within this report.

This report is set out as follows. Section 2 outlines the current NICE recommended indications for tocilizumab for the treatment of patients with rheumatoid arthritis. Sections 3 and 4 outline previous work undertaken by the DSU concerning the cost-effectiveness of tocilizumab over the course of this appraisal, including the correction of a minor error identified within this previous work. Section 5 sets out the scope and implementation of the proposed PAS for tocilizumab within Roche's cost-effectiveness model. Section 6 presents an evaluation of the impact of the proposed PAS on the cost-effectiveness of various treatment sequences including tocilizumab within the DMARD-IR, rituximab-intolerant and TNF alpha-IR subgroups. Section 7 compares the results produced by the DSU and Roche and highlights the importance of considering extended dominance on the conclusions of the economic analysis. Section 8 presents the overall conclusions of this analysis.

2. CURRENT NICE RECOMMENDED INDICATIONS

In August 2010, NICE appraised tocilizumab (Actemra/RoActemra) and produced the following guidance recommendation:

Tocilizumab, in combination with methotrexate, is recommended for the treatment of moderate to severe active rheumatoid arthritis in people whose rheumatoid arthritis has responded inadequately to one or more tumour necrosis factor alpha (TNF-α) inhibitors and:

- *whose rheumatoid arthritis has responded inadequately to rituximab; or*
- *in whom rituximab is contraindicated or when rituximab is withdrawn because of an adverse effect.*[1]

3. PREVIOUS DSU REPORT

In May 2010, the NICE Decision Support Unit (DSU) produced a report (hereafter referred to as the 2010 DSU Report[2]) during the appraisal, which provided:

- a view on the overall decision problem, and the issues regarding potential treatment sequences relevant to the appraisal;
- a critique of particular assumptions used in the manufacturer's model;
- additional cost-effectiveness analyses to validate the manufacturer's response to the Appraisal Committee's request for extra analysis;
- a fully incremental analysis of results for alternative treatment sequences, including sensitivity analyses addressing key assumptions.

The manufacturer's model is explained in detail in Section 7.2 of the Manufacturer's Submission[3] (p.131) and is critiqued by the Evidence Review Group (ERG) within their report.[4] An overview of the model is provided on page 51 (Table 6) of the ERG report.

3.1. RECOMMENDED ASSUMPTIONS BASED ON 2010 DSU REPORT[2]

In light of the manufacturer's submission and the DSU Report, the Appraisal Committee considered a range of cost-effectiveness estimates, and concluded that the DSU's "Approach 4" for the synthesis of clinical evidence was the most appropriate for consideration.

Specifically, the DSU's Approach 4 uses the unadjusted trial results for all treatments, and replaced the manufacturer's estimate of the unadjusted effect for etanercept with pooled estimates from the two etanercept trials (Weinblatt (1999) and Combe (2006) studies). The approach also corrects a counter-intuitive ACR70 estimate for tocilizumab when used after two biologics. Originally the manufacturer provided an estimate of 12% ACR70 rate after 1 biologic, and 15% ACR70 rate after 2 biologics. This improved response rate after a subsequent treatment failure was assumed to be counter-intuitive, and instead the estimate of 12% was used at both sequence positions.

For each of the four approaches evaluated, the DSU provided four sets of sensitivity analyses:

(i) Base case manufacturer assumptions

(ii) Assume no long-term HAQ improvement with tocilizumab

(iii) Assume no long-term HAQ improvements with tocilizumab and exclude negative utilities

(iv) Assume no long-term HAQ improvements with tocilizumab and double the administration cost for tocilizumab to £308.60 per infusion.

The Appraisal Committee concluded that Scenario (ii) was the most appropriate, the results of which were presented in Table 19 of the 2010 DSU Report.[2] This stated that, at a threshold of £20,000 per QALY gained, the standard care sequence (Strategy 1 [E, R]) is expected to be the most cost-effective. At a threshold of £30,000 per QALY gained, Strategy 4 (E, R, T) is expected to be the most cost-effective. Therefore tocilizumab is cost-effective in rituximab inadequate responders (rituximab-IR) at a threshold of £30,000 per QALY gained. This led to the Committee producing guidance that recommends tocilizumab for patients who have had an inadequate response to rituximab, or who are contraindicated to rituximab or who have been withdrawn from rituximab due to an adverse event.

4. CORRECTIONS TO PREVIOUS DSU REPORT

During the present analyses we identified two erroneous parameters values within the version of the model used in the 2010 DSU report.[2] These discrepancies relate to the unadjusted ACR rates listed in the Input worksheet within the economic model. Table 1 shows the incorrect values on the left and correct values on the right. These errors and the subsequent correction were confirmed with the 2010 DSU report authors.

Table 1 Previous and corrected ACR values

	Unadjusted trial ACR rates					
	DSU analysis 2010			**Corrected analysis 2011**		
	ACR20	***ACR50***	***ACR70***	***ACR20***	***ACR50***	***ACR70***
Tocilizumab (2 previous biologics)	0.50	0.31	0.15	0.50	0.29	0.12

4.1. IMPACT OF CORRECTIONS ON THE COST-EFFECTIVENESS OF TOCILIZUMAB WITHIN THE DMARD-IR POPULATION

Correcting the ACR values to those shown in Table 1 changes the estimates of the mean costs and QALY values for the sequences considered within the DMARD-IR population. Table 2 shows the

original uncorrected estimates and Table 3 shows the corrected estimates (the impact of the error is shown in bold). Both sets of values are presented graphically in Figure 1. It should be noted that these results, and all subsequent results are based on point estimates of parameter values rather than mean estimates derived using probabilistic sensitivity analysis.

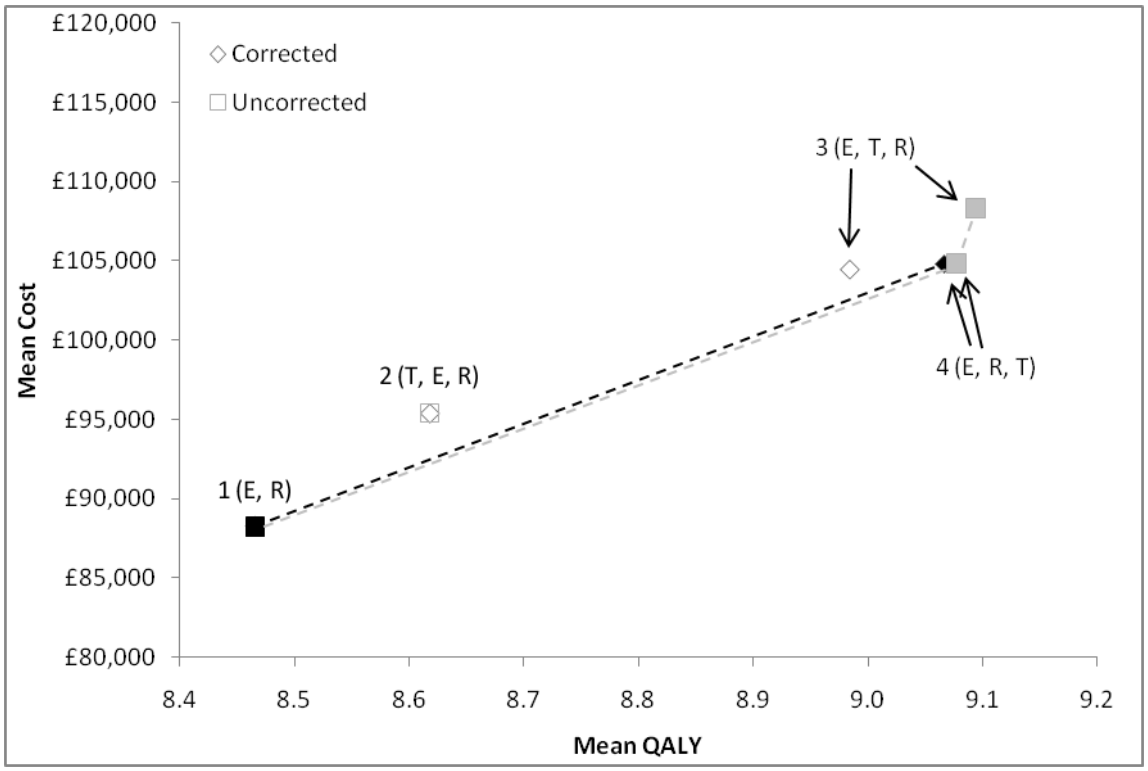
Table 2 Uncorrected DMARD-IR population results (Table 19 of 2010 DSU Report)

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs ER)	ICER	Comparison for ICER
1 (E, R)	£88,244	8.466	.	.	.
2 (T, E, R)	£95,407	8.618	£47,125	ED	By Strategy 4
4 (E, R, T)	£104,808	9.077	£27,110	£27,110	Vs Strategy 1
3 (E, T, R)	£108,311	9.094	£31,954	£206,059	Vs Strategy 4

Table 3 Corrected DMARD-IR population results

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs ER)	ICER	Comparison for ICER
1 (E, R)	£88,244	8.466	.	.	.
2 (T, E, R)	£95,407	8.618	£47,125	ED	By Strategy 4
3 (E, T, R)	**£104,486**	**8.984**	**£31,355**	**ED**	**By Strategy 4**
4 (E, R, T)	**£104,803**	**9.066**	**£27,597**	**£27,598**	**Vs Strategy 1**

Figure 1 Differences between corrected and uncorrected cost and effectiveness values for DMARD-IR population.



Filled symbols are on the cost-effectiveness frontier, empty symbols are not. The grey line shows the frontier prior to the correction. The black line shows the corrected frontier.

As shown in Figure 1, these corrections have no impact upon the costs and outcomes associated with Sequence 2 (T, E, R), which remains extendedly dominated, and only a minor impact upon Sequence 4 (E, R, T), which remains on the cost-effectiveness frontier with a very similar ICER compared with Sequence 1 (E, R) (£27,597 rather than £27,110). The effect of this correction is more pronounced for Sequence 3 (E, T, R). When the corrected ACR rates are included in the analysis, Sequence 3 moves from an ICER of £206,059 per QALY gained to being ruled out due to extended dominance. Whilst the error shifts the QALY rank between the (T, E, R) and (E, R, T) sequences, conclusions regarding the cost-effectiveness of the modelled sequences remain robust.

The results for the DMARD-IR (rituximab-intolerant) population presented within Table 26 of the 2010 DSU report[2] remain unaffected by this error.

All subsequent analyses presented within this report relate to the corrected version of the model.

5. THE PROPOSED PATIENT ACCESS SCHEME

The proposed PAS template document states that:

> *"In the FAD [Final Appraisal Determination] for TA198, etanercept was used as the main comparator to tocilizumab in the DMARD-IR population. Tocilizumab and etanercept have equivalent annual drug acquisition costs, but tocilizumab is associated with additional drug administration costs due to a monthly intravenous (IV) infusion. Etanercept, by contrast, is administered by a once weekly subcutaneous (SC) self-injection."*

The FAD noted that the cost of etanercept was similar to tocilizumab, although etanercept is given as a subcutaneous injection and therefore incurs lower administration and monitoring costs than tocilizumab. [redacted] Roche have requested that the level of discount should remain confidential.

5.1. SUPPLEMENT TO PAS PROPOSAL

On the 24th August 2011, Roche submitted a supplement to their PAS proposal, suggesting that the impact of the PAS on an additional treatment sequence should be considered by the DSU. This additional sequence applies to the two DMARD-IR populations and involves using tocilizumab as a replacement for TNF-α inhibitors (represented by etanercept in the economic model) rather than as an additional stage in the treatment sequence.

5.2. IMPLEMENTATION OF REBATE WITHIN THE ECONOMIC MODEL

Within the economic model, the effect of the patient access scheme is implemented by changing the contents of cell D10 (Drugs cost for tocilizimab + MTX) within the 'Cost_Parameters' worksheet of the model from [redacted] The DSU can confirm that this change to the model has been implemented appropriately.

5.3. SCOPE OF THE PROPOSED PAS

The Roche proposal document states that the PAS applies to the whole license for tocilizumab, including adult RA and systemic juvenile idiopathic arthritis (sJIA). Although the cost-effectiveness of drugs and drug sequences differs between patient groups, the Roche proposal only provides estimates for the DMARD-IR subgroup and the TNF-IR subgroup for adult rheumatoid arthritis. An economic analysis of the PAS within the subgroup of patients who are intolerant or unsuitable for

rituximab treatment was not provided by Roche; this analysis has instead been produced by the DSU. The DSU analyses therefore consider three distinct patient subgroups.

1. **DMARD-IR** (*Disease-modifying anti rheumatoid drugs - inadequate responders*): Patients with moderate to severe rheumatoid arthritis who have had an inadequate response to one or more DMARDs. The standard treatment sequence within the model is:
    1. Etanercept (E)
    2. Rituximab (R)
    3. Leflunomide
    4. Gold
    5. Ciclisporine
    6. Palliative Care
2. **DMARD-IR (Rituximab intolerant)** As above, but also intolerant to or unsuitable for rituximab treatment. The standard treatment sequence within the model is:
    1. Etanercept (E)
    2. Leflunomide
    3. Gold
    4. Ciclisporine
    5. Palliative Care
3. **TNF-IR** (*Tumour Necrosis Factor inhibitors inadequate responders*): Patients with moderate to severe rheumatoid arthritis who have had an inadequate response or intolerance to TNF inhibitors. The standard treatment sequence within the model is:
    1. Rituximab (R)
    2. Leflunomide
    3. Gold
    4. Ciclisporine
    5. Palliative care

As the last four treatments in the treatment sequence are identical in all subgroups and comparators, they will not be explicitly referred to in this report, and only the parts of the sequence that differ will be referred to in abbreviated form - for example, (E, R) refers to etanercept then rituximab, followed by the four final treatments leflunomide, gold, ciclisporine and palliative care.

The economic comparisons considered for each of these subgroups are:

DMARD-IR population

1. (E, R) [Baseline]
2. (T, E, R)
3. (E, T, R)
4. (E, R, T)

DMARD-IR (rituximab intolerant) population

1. (E) [Baseline]
2. (T, E)
3. (E, T)

TNF-IR population

1. (R) [Baseline]
2. (T, R)
3. (R, T)

This report considers the impact of the PAS on the cost-effectiveness of tocilizumab within each of these populations.

5.3.1. Supplementary analyses: replacement strategy

On the 24th August 2011, the DSU received a supplement to the PAS proposal which introduces an additional treatment option for the DMARD-IR population, whereby etanercept is replaced by tocilizumab (i.e. (T, R) rather than (E, R)). This additional option has a lower cost and lower QALY than (E,R) hence this affects the baseline for the incremental analysis. Results incorporating this additional strategy are discussed following the results for the options originally proposed in the PAS.

6. RESULTS WITH PAS SCHEME IMPLEMENTED

The results below show the effects of applying the [redacted] discount to the economic model previously supplied by Roche ("Tocilizumab_NICE_140611.xlsx") for the three populations previously described.

6.1. IMPACT OF THE PROPOSED PAS WITHIN THE DMARD-IR POPULATION

Table 4 shows the results for the DMARD-IR population without the incorporation of the proposed PAS. Table 5 shows the results for the same population incorporating the PAS. The two sets of results are presented graphically in Figure 2.

Table 4 Results for DMARD-IR population without PAS applied

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs ER)	ICER	Comparison for ICER
1 (E, R)	£88,244	8.466	.	.	.
2 (T, E, R)	£95,407	8.618	£47,193	ED	By Sequence 4
3 (E, T, R)	£104,486	8.984	£31,380	ED	By Sequence 4
4 (E, R, T)	£104,803	9.066	£27,582	£ 27,582	Vs Sequence 1

Table 5 Results for DMARD-IR population with PAS applied

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs ER)	ICER	Comparison for ICER
1 (E, R)	£88,244	8.466	.	.	.
2 (T, E, R)	[redacted]	8.618	£5,716	£5,716	Vs Sequence 1
3 (E, T, R)	[redacted]	8.984	£23,396	ED	By Sequence 4
4 (E, R, T)	[redacted]	9.066	£21,282	£26,549	Vs Sequence 2

Figure 2 Impact of PAS, DMARD IR subgroup.

Filled symbols are on the cost-effectiveness frontier, empty symbols are not. Note that the costs and outcomes for E, R are the same with and without the PAS

The darker dashed line shows the cost-effectiveness frontier with the PAS applied. The lighter dashed line shows the cost-effectiveness frontier without the PAS applied. Sequence 3 (E, T, R) remains extendedly dominated, but with the PAS applied Sequence 2 (T, E, R) now lies on the frontier, with an ICER of £5,716 compared against Sequence 1 (E, R).

6.1.1. Impact of replacement strategy on DMARD-IR population

The impact of incorporating an additional strategy whereby tocilizumab is used as a replacement to etanercept is shown in Table 6 and Table 7. This analysis is presented graphically in Figure 3.

Table 6 Impact of including sequence 0 (T, R) without PAS applied

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs TR)	ICER	Comparison for ICER
0 (T, R)	£79,453	8.085	.	.	.
1 (E, R)	£88,244	8.466	£23,047	£23,047	Vs Sequence 0
2 (T, E, R)	£95,407	8.618	£29,921	ED	By Sequence 4
3 (E, T, R)	£104,486	8.984	£27,844	ED	By Sequence 4
4 (E, R, T)	£104,803	9.066	£25,820	£27,582	Vs Sequence 1

Table 7 Impact of including sequence 0 (T, R) with PAS applied

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs TR)	ICER	Comparison for ICER
0 (T, R)	[redacted]	8.085	.	.	.
1 (E, R)	£88,244	8.466	£39,553	ED	By Sequence 4
2 (T, E, R)	[redacted]	8.618	£29,921	ED	By Sequence 4
3 (E, T, R)	[redacted]	8.984	£30,251	ED	By Sequence 4
4 (E, R, T)	[redacted]	9.066	£28,380	£28,380	Vs Sequence 0

Figure 3 Effect of including sequence 0 (T, R) on results with and without PAS applied

As the results above indicate, Sequence 0 (T, R) is both less effective and less costly than the current (E,R) baseline strategy, hence (T, R) becomes the new baseline for the incremental analysis. With the PAS applied, Sequence 1 (E, R) becomes extendedly dominated, as do Sequences 2 (T, E, R) and 3 (E, T, R). Compared with Sequence 0 (T, R), Sequence 4 (E, R, T) remains on the cost effectiveness frontier, and has an ICER of £28,380 per QALY gained compared against Sequence 0 (T, R). This treatment option reflects the current NICE recommendation for tocilizumab.[1]

It should be noted that the results in Table 7 replicate those presented in the Roche PAS proposal supplement, however the ICERs presented in the Roche supplement are incorrect, as they have not ruled out those options which are subject to extended dominance. Therefore, the Committee should disregard the results presented by Roche and instead consider those presented within this DSU report.

6.2. IMPACT OF THE PROPOSED PAS WITHIN THE RITUXIMAB-INTOLERANT DMARD-IR POPULATION

The second population considered by the DSU relates to those patients who are intolerant to or unsuitable for rituximab. The model estimates for this population are presented with and without the PAS in Tables 8 and 9 respectively. The results of this analysis are presented graphically in Figure 4.

Table 8 Results for rituximab-intolerant DMARD-IR population, without PAS applied

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs E)	ICER	Comparison for ICER
1 (E)	£82,117	8.086	.	.	.
2 (T, E)	£90,648	8.344	£33,007	ED	By Sequence 3
3 (E, T)	£100,079	8.729	£27,917	£27,917	Vs Sequence 1

Table 9 Results for rituximab-intolerant DMARD-IR population, with PAS applied

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs E)	ICER	Comparison for ICER
1 (E)	£82,117	8.086	.	.	.
2 (T, E)	[redacted]	8.344	£8,648	£8,648	Vs Sequence 1
3 (E, T)	[redacted]	8.729	£21,495	£30,121	Vs Sequence 2

Figure 4 Effect of PAS, DMARD-IR and rituximab-intolerant subgroup

Filled symbols are on the cost-effectiveness frontier, empty symbols are not.

As indicated by the results shown in Figure 4, incorporating the PAS within the analysis places Sequence 2 (T, E) on the incremental cost-effectiveness frontier (the black dashed line) with an ICER of £8,648 per QALY gained compared with Sequence 1 (E). The ICER for sequence (E, T) versus (T, E) is approximately £30,121 per QALY gained.

6.2.1. Impact of replacement strategy within the rituximab-intolerant DMARD-IR population

The effect of replacing etanercept with tocilizumab on the cost-effectiveness of the different treatments is shown with and without the PAS in Table 10 and Table 11 respectively. The results of this analysis are shown graphically in Figure 5.

Table 10 Results for rituximab-intolerant DMARD-IR population, without PAS applied.

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs T)	ICER	Comparison for ICER
0 (T)	£66,900	7.301	.	.	.
1 (E)	£82,117	8.086	£19,402	£19,402	Vs Sequence 0
2 (T, E)	£90,648	8.344	£22,774	ED	By Sequence 3
3 (E, T)	£100,079	8.729	£23,239	£27,917	Vs Sequence 1

Table 11 Results for rituximab-intolerant DMARD-IR population, with PAS applied

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs T)	ICER	Comparison for ICER
0 (T)	[redacted]	7.301	.	.	.
1 (E)	£82,117	8.086	£11,374	ED	By sequence 2
2 (T, E)	[redacted]	8.344	£10,698	£10,698	Vs Sequence 0
3 (E, T)	[redacted]	8.729	£15,935	£30,121	Vs Sequence 2

Figure 5 Effect of PAS, DMARD-IR and rituximab-intolerant subgroup, including tocilizumab as a replacement for etanercept

Filled symbols are on the cost-effectiveness frontier, empty symbols are not.

6.3. IMPACT OF THE PROPOSED PAS ON THE TNF-IR POPULATION

The economic model includes two different ways of specifying that a TNF-IR subgroup is being used within the "UserSelection" worksheet within the economic model: (1) through a drop-down menu allowing a range of populations to be selected, and (2) through specifying within a drug sequence selection section of this worksheet that the drugs are to be applied to TNF-IR populations. Roche were able to clarify within the supplement to the PAS proposal that their estimates were produced by using the default population selection within the drop-down menu (Pooled DMARD-IR population), and selecting TNF-IR specific drug options within the sequence. Roche also stated that the drop-down population menu was an obsolete feature of the economic model and so should not be used. It should be noted however, that changing the population option within this drop-down menu does affect both the cost and QALY estimates for each of the TNF-IR sequence options. The reasons for these differences are not clear. Having said that, the DSU were able to replicate the results produced by Roche.

Table 12 and Table 13 show the cost and QALY estimates for three treatment sequences without and with the PAS applied, respectively. These differences are shown graphically in Figure 6. It should be noted that the scope of this analysis is broader than that presented by Roche as the proposal document did not include the (R, T) sequence.

Table 12 Results for TNF-IR population, without PAS Applied

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs R)	ICER	Comparison for ICER
1 (R)	£53,608	7.134	.	.	.
2 (T, R)	£74,551	7.819	£30,574	Dominated	By Sequence 3
3 (R, T)	£73,042	7.940	£24,099	£24,099	Vs Sequence 1

Table 13 Results for TNF-IR population, with PAS applied

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs R)	ICER	Comparison for ICER
1 (R)	£53,608	7.134	.	.	.
2 (T, R)	[redacted]	7.819	£22,690	Dominated	By Sequence 3
3 (R, T)	[redacted]	7.940	£18,527	£18,527	Vs Sequence 1

Figure 6 Effect of PAS, TNF-IR subgroup

Filled symbols are on the cost-effectiveness frontier, empty symbols are not.

As stated above, Sequence 3 (R, T) was not presented as an option within the PAS proposal submission. This strategy dominates Sequence 2 (T, R), and has an ICER of £18,527 per QALY gained compared with Sequence 1 (R).

7. REPLICABILITY OF THE ECONOMIC RESULTS PRESENTED BY ROCHE

7.1. DMARD-IR SUBGROUP

Although the PAS applies to the three populations described (DMARD-IR, Rituximab-Intolerant DMARD-IR, and TNF-IR), the main PAS submission only provides results for DMARD-IR population. The results reported for this population, within Table 2 of the PAS submission, are reported below. The ICERs have been recalculated based on the costs and QALYs reported, and where they differ the recalculated values have been reported.

Table 14 Results reported in 2011 PAS proposal (Table 2). ICERs recalculated

Strategy	Mean Cost	Mean QALY	Pair-wise ICER (vs ER)	ICER	Comparison for ICER
1 (E, R)	£88,244	8.466	.	.	.
2 (T, E, R)	[redacted]	8.618	**£5,704**	**£5,704**	Vs Strategy 1
3 (E, T, R)	[redacted]	8.984	**£23,376**	**ED**	By Strategy 4
4 (E, R, T)	[redacted]	9.066	**£21,293**	**£26,583**	Vs Strategy 2

Numbers in bold have been recalculated by the DSU as they were incorrect within PAS proposal.

Within the Roche analysis, Sequence 3 (E, T, R) was erroneously included within the incremental analyses even though it is extendedly dominated by Sequence 4 (E, R, T). The path followed by the incremental analysis within the PAS proposal document is indicated by the light grey line in Figure 7, rather than the correct path indicated by the dashed black line.

Figure 7 Results for DMARD-IR population, with PAS applied, using values reported in 2011 PAS proposal document.

Filled symbols are on the cost-effectiveness frontier, empty symbols are not. The grey lines show where the incremental analyses reported in PAS proposal deviate from correct incremental path.

As noted earlier, DSU was able to fully replicate the *absolute* costs and QALYs for each of the options included in the Roche PAS proposal. The incremental results produced by Roche should however be disregarded due to Roche's failure to rule out those options which are subject to extended dominance. Only the DSU estimates should be considered by the Appraisal Committee.

7.1.1. Impact of replacement strategy on DMARD-IR subgroup

Table 3 of the supplement to the PAS proposal provides mean costs and QALYs when sequence 0 (T, R) is included as an option. These values are identical to those produced by the DSU. However, as in the original PAS proposal, the ICERs have been incorrectly calculated and reported, following the incorrect incremental frontier shown by the grey line in Figure 8.

Figure 8 Results for DMARD-IR population, with PAS applied, incorporating the additional sequence (T, R) included in the supplement

Filled symbols are on the cost-effectiveness frontier, empty symbols are not. The grey lines show where the incremental analyses reported in PAS proposal deviate from the correct incremental path

7.2. RITUXIMAB-INTOLERANT DMARD-IR SUBGROUP

Neither the main PAS proposal nor the later supplement presented cost or QALY estimates for the rituximab-intolerant DMARD-IR population.

7.3. TNF-IR SUBGROUP

The PAS proposal supplement provides cost and QALY estimates for the TNF-IR population for the (R) and (T, R) sequences, both with and without PAS. These values match those produced by the DSU, as shown in Table 12 and 13. As previously stated, neither the original PAS proposal nor the supplement considered treatment sequence (R, T) within this patient population. When this option is included in the analysis, the (T, R) option is ruled out due to simple dominance, and the ICER for (R, T) versus (R) is £18,527 per QALY gained.

8. SUMMARY/CONCLUSION

The DSU were able to replicate the results presented in both the initial PAS proposal and the additional supplement sent by Roche on the 24th August 2011. Across the original PAS proposal and the supplement provided later, Roche have reported cost-effectiveness results within the DMARD-IR subgroup and the TNF-IR subgroup. No results were presented for those patients who are rituximab-

intolerant. Within the TNF-IR analysis presented by Roche, the (R, T) sequence was not evaluated; this missing treatment sequence has an important impact on the cost-effectiveness of the options that Roche did evaluate. Importantly, the incremental cost-effectiveness ratios (ICERs) contained within the PAS proposal and the additional supplement were incorrect as they did not exclude treatment sequences which are subject to extended dominance. The appropriate adoption of these economic decision rules changes the interpretation of the results of Roche's economic analysis. The Committee should consider only those ICERs produced by the DSU. The following results should be considered by the Committee.

DMARD-IR subgroup results

Within the DMARD-IR subgroup, the (E, R, T) sequence was expected to be the most effective option. Without the PAS, the ICER for (E, R, T) versus (E, R) was £27,582 per QALY gained. The sequences (T, E, R) and (E, T, R) were both ruled out due to extended dominance. When the PAS was applied, (T, E, R) compared against E, R had an ICER of £5,716 per QALY gained. (E, R, T) versus (T, E, R) had an ICER of £26,549 per QALY gained. The (E, T, R) sequence was ruled out due to extended dominance.

Rituximab-intolerant subgroup results

Within the rituximab-intolerant DMARD-IR subgroup, the most effective sequence was (E, T). Without the PAS, (E, T) versus (E) had an ICER of £27,917 per QALY gained. The (T, E) sequence was ruled out due to extended dominance. When the PAS was included, (T, E) versus (E) had an ICER of £8,648 per QALY gained. The (E, T) sequence had an ICER of £30,121 per QALY gained compared against (T, E).

TNF-IR subgroup results

Within the TNF-IR subgroup, the (R, T) sequence was estimated to be the most effective. Without the PAS, (R, T) versus (R) had an ICER of £24,099 per QALY gained and (T, R) was ruled out due to simple dominance. With the PAS applied (R, T) versus (R) had an ICER of £18,527 per QALY gained, and (T, R) was again ruled out due to simple dominance.

Replacement of etanercept with tocilizumab within the DMARD-IR subgroup

An analysis in which tocilizumab is used as a replacement for etanercept was also considered. Within this analysis, (E, R) no longer lies on the cost-effectiveness frontier and the baseline is replaced by the (T, R) sequence. When the PAS is applied, the ICER for (E, R, T) versus (T, R) was £28,380 per QALY gained. The sequences (T, E, R) and (E, T, R) were both ruled out due to extended dominance.

This reflects the current NICE recommendation for tocilizumab. A similar result was found when (T) was considered as an option within the rituximab-IR subgroup.

Question	**DSU Response**
Have the committee agreed assumptions for all rheumatoid arthritis patient populations from TA198 final guidance (including DMARD-IR and TNF alpha-IR subgroups) been used as the starting point by Roche in their economic model?	**Yes**. The Committee should note that a minor error in the original DSU estimates should be used as the starting point in considerations of the proposed PAS scheme. The Committee should also note that the economic analyses presented by Roche are incorrect.
Have the only changes to the economic modelling been to the costs of tocilizumab (as associated with the agreed patient access scheme)?	**Yes**
Has the PAS been implemented in accordance with the details of the scheme agreed by the Department of Health and detailed in the PAS template submitted by Roche?	**Yes**

9. REFERENCES

1. NICE. Tocilizumab for the treatment of rheumatoid arthritis. (Technology appraisal guidance 198), August 2010.
2. Palmer, S., Sculpher, M. Tocilizumab for the treatment of Rheumatoid Arthritis, report by the NICE Decision Support Unit, 2010, available from http://www.nicedsu.org.uk/
3. RoActemra (tocilizumab) NICE STA submission. Roche. Submission to the National Institute for Health and Clinical Excellence, 2009.
4. Meads, C., Jit, M., Tsourapas, A., Ashfaq, K., Connock, M., Fry-Smith, A., Jobanputra, P. Tocilizumab for the treatment of rheumatoid arthritis. A single technology appraisal. West Midlands Health Technology Assessment Collaboration, 2009.

APPENDIX: A NOTE ON THE INTERPRETATION OF INCREMENTAL RESULTS

One issue raised within the PAS proposal was of the appropriateness of full incremental analyses when considering the different range of treatment sequences in the full DMARD-IR population. Within these analyses both sequence 3 (E, T, R) and sequence 4 (E, R, T) have very similar mean costs and mean QALY estimates, and so exist in similar positions within the cost-effectiveness plane. Because the positions of these two sequences on the same plane are so close together, both the position and presence of either sequence on the cost-effectiveness frontier (the dashed lines shown on the previous graphs) can be strongly affected by even minor variations in the ways either sequences are estimated. One example of this is the way making the small number of corrections from the 2010 report affected the position of sequence 3 (E, T, R) on the cost-effectiveness frontier (see Figure 1), which moves from being on the frontier with a high ICER in the uncorrected model, to being extendedly dominated with the corrected model. Similar small changes to the parameter assumptions may have had other equally large but qualitatively different effects on the sequencing and ICERs of these two treatments, such as moving sequence 3 (E, T, R) to a position of having only a very small ICER relative to sequence 4 (E, R, T), or even to a position of extended dominance over sequence 4.

As the full incremental analyses use deterministic mean values, they do not explicitly take into account uncertainty surrounding the mean, and the effect of such uncertainty on choosing the optimal sequencing option. Such uncertainty can be demonstrated using probabilistic sensitivity analysis (PSA), and crudely represented by using confidence ellipses which indicate where the majority (say 95 percent) of the PSA estimates are bounded within, as shown in Figure 9. Where the confidence ellipses show a significant degree of overlap the degree of uncertainty about the optimal sequence of options is increased. However, Roche have not done this.

Figure 9 Confidence ellipses for four hypothetical treatments