in collaboration with:

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Single Technology Appraisal: Tocilizumab for the treatment of systemic juvenile idiopathic arthritis

Addendum to Evidence Review Group's Report following Roche's new evidence submission of 2nd September 2011

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1. Introduction

The Evidence Review Group (ERG) was requested by NICE to provide commentary and validity checks on the additional evidence submitted by the manufacturer.[1] It should be recognised that the work undertaken by the ERG does not constitute a full critique of the manufacturer's additional submission and does not accord with the procedures and templates applied to the original submission due to the limited time available to review the additional submission. However, a number of detailed checks were undertaken to ensure the validity of the manufacturer's revised analyses based on the new submission by the manufacturer.

2. Clinical effectiveness

Changes from original submission

In terms of clinical effectiveness data, the new submission provided no new data.

ERG commentary

The same critique applies as to the original submission. In summary:

- No data were provided in the MS for population 1 (children with sJIA with an inadequate response to NSAIDs and CS).

- In population 2 (children with sJIA with an inadequate response to NSAIDs, CS and MTX) an indirect comparison was possible between tocilizumab and anakinra, using 95% of the children in the TENDER trial (excluding MTX naïve children).

  However, there are serious limitations to this indirect comparison:

  1. The ANAJIS trial (anakinra versus placebo) had a duration of 1 month, compared to three months for the TENDER trial;
  2. ANAJIS included only 24 children (12 in each arm);
  3. An indirect comparison was possible for two outcomes only: ACR30 response and ACR30 response without fever.

- The indirect comparison of tocilizumab versus anakinra shows that ACR30 response favours tocilizumab (RR=2.27, 95% CI: 1.06, 4.85). ACR30 response without fever showed no significant difference between tocilizumab and anakinra.

- According to the MS, no trials are available for any of the other comparators (adalimumab, etanercept, infliximab, and abatacept) in the correct population. Therefore, an indirect comparison of tocilizumab versus anti-TNFs is presented in the MS using efficacy data from an infliximab trial (Ruperto et al., 2007: infliximab+MTX versus placebo) in children with Juvenile Rheumatoid Arthritis (JRA).[2]

  However, the ACR response in Ruperto et al. reflects a JRA population of which only 16% are systemic JIA patients.[2] Therefore, the indirect comparison results are adjusted

for the differences in the population subtypes, using data from an observational study by Prince et al. 2009.[3] The adjustment factor consists of the difference in the proportion of responders between the total population and the systemic JIA patients (see Table 5.9, page 60 in the original ERG report).

As reported in the MS (original MS, page 116): “Clinical experts [PC Westhovens R 02/03/2011, Wright S 16/03/2011], stressed the differences between a systemic JIA population and other subtypes and advised against comparing evidence from different populations.” Therefore, the ERG deems the results from this indirect comparison unreliable.

3. Cost-effectiveness

Changes from original submission

In terms of cost effectiveness data, the additional submission:

1. Presents a revised economic model with
    - Health states reflecting absolute health status as represented by CHAQ score
    - ACR30 response and no fever as the primary outcome
    - A starting age of 5 years in the model

2. Reports a cost-effectiveness analysis of tocilizumab compared with anakinra and infliximab, including scenario analyses that include:
    - Infliximab as first-line treatment followed by tocilizumab
    - Infliximab as first-line treatment followed by anakinra

3. Presents sensitivity analysis on the revised base case that includes:
    - Uncertainty around the "Prince" adjustment factor[3]
    - A stopping rule for tocilizumab after 2 years of treatment
    - A decreased frequency of administration of tocilizumab after 6 months to a 4-weekly regimen

4. Presents (in a separate document) revised results in case a Patient Access Scheme is applied

5. After request from the ERG, presents a separate document regarding a PSA, including for the PAS.

1. Presents a revised economic model with health states reflecting absolute health status as represented by CHAQ score, ACR30 response and no fever as the primary outcome, and n starting age of 5 years.

The manufacturer has presented a new model with health states defined according to categories of CHAQ, rather than being based on ACR response categories in which an average CHAQ/utility is applied. ACR score is used as a potential predictor of CHAQ score at 12 weeks. To that end, a regression model was fitted, see Table 1. Note that age was found to be non-significant and was therefore excluded. It is also important to note that in the electronic version of the model, the coefficients as presented in Table 1 are used but also an intercept of 0.940 (SE 0.20).

Table 1 Final week 12 CHAQ regression analysis results (excluding age)

Variable	Coefficient	Standard error	p-value	95% Confidence interval	
Baseline CHAQ	0.466	0.076	<0.001	0.315	0.617
ACR30	-0.425	0.244	0.085	-0.908	0.059
ACR50	-0.425	0.225	0.062	-0.871	0.022
ACR70	-0.889	0.193	<0.001	-1.271	-0.507
ACR90	-1.123	0.185	<0.001	-1.489	-0.756

Number of observations = 111
F(5, 105) = 18.50, p<0.001
R-squared = 0.44

F-test for ACR terms combined:
F(4, 105) = 1, p<0.001

For each possible baseline CHAQ score (ranging from 0 to 3, with steps of 0.125), the average CHAQ score at 12 weeks is estimated using the regression model presented above. All ACR coefficients are multiplied by the percentage of patients with that response. Thus, on average, patients with a baseline CHAQ of 1.5 receiving tocilizumab will have a 12 week CHAQ score of 0.89 (ACR 30, 50, 70 and 90 are 5%, 14%, 31% and 35%, respectively).

Next, each CHAQ score is classified into a health state. The CHAQ cut points were based on a suggestion made in the ERG report which forms part of the ACD consultation. The manufacturer acknowledges that the ERG specified these values purely hypothetically, but due to a lack of any evidence-based method, the manufacturer felt the cut-points suggested by ERG represented a reasonable starting point. These new base case health states are shown in Table 2.

The CHAQ score at 12 weeks differ by allocated treatment group, because tocilizumab, anakinra, and infliximab were all associated with different ACR responses. ACR values used are the same as those used in the original manufacturer's submission except that 'no fever' has been included in the indirect comparison with anakinra.

Once the CHAQ score have been classified into health states, costs and utility are assigned to these health states. The utilities are based on the mapping formula that was already used in the original manufacturer's submission (the midpoint of the range was applied to the formula). The costs for the state "controlled" and the state "severe" were based on the ACR90 and ACR no response, respectively. Based on this, a linear function was defined and at the midpoint of "mild" and "moderate" the costs were estimated using this function.

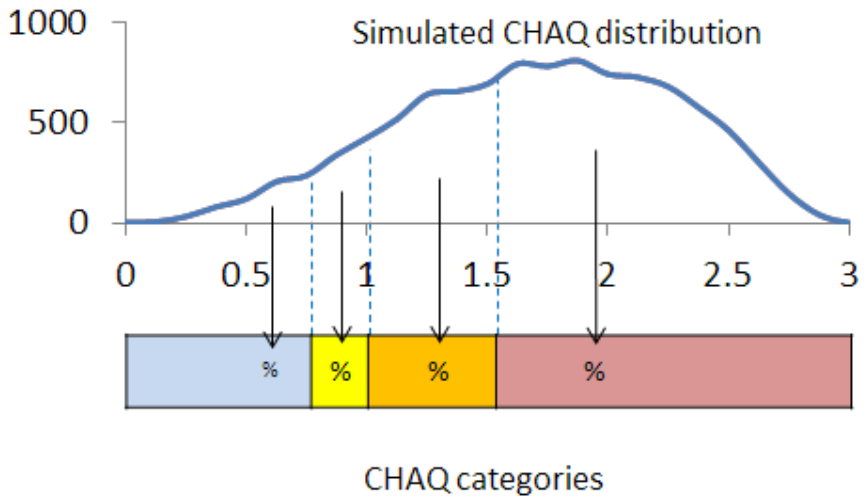
Patients stay in the health state they reach after 12 weeks until they 'drop out' and either move to the next treatment line or move to the health state 'severe' with no further treatment.

Table 2 Allocation of utility scores to CHAQ categories

Health State	CHAQ category (range)	Cost (per cycle)	Utility (per year)
'Controlled'	≥0 to ≤0.75	£345.38	0.7689
'Mild'	>0.75 to ≤1	£1,220.73	0.6554
'Moderate'	>1 to ≤1.5	£1,804.30	0.5550
'Severe'	>1.5 to ≤3.000	£3,360.47	0.1913

After average total costs and QALYs have been calculated for each different CHAQ starting point the frequency distribution of baseline CHAQ scores as observed in the Tender study is applied. This leads to a weighted average of the various total cost and total QALY estimates.

Figure 1. Simulated distribution of CHAQ scores is divided into 'CHAQ category' health states



The Appraisal Committee has requested that the revised economic model should allow "movement between categories of ACR response while on treatment". No clinical data was available to inform an estimate of the likelihood of transition between ACR categories whilst on treatment. Therefore, some explorative analyses were done with various assumptions about improvement and deterioration.

Each adjustment caused marked changes in the proportions of patients assumed to remain in each ACR category. These effects often eclipsed any effects associated with the treatments themselves. Therefore, the manufacturer considered it inappropriate to revise the base case to include any of these scenarios. The new base case maintains a zero probability of transitioning between ACR categories in any patients who have responded to, and remain on, a particular treatment.

The new model is now limited to the following comparison as a base case:

Tocilizumab → Anakinra or infliximab → Palliation

versus

Anakinra or infliximab → Palliation

For the comparison with anakinra, the outcome now used for modelling is ACR + No fever instead of ACR as in the previous model version.

For the comparison of tocilizumab versus infliximab it is important to note that the 'no fever' outcome was not captured in the infliximab trial and thus the indirect comparison of

tocilizumab with infliximab still operates on the ACR30 response parameter excluding the 'no fever' outcome.

As requested by the AC, the start age of the model is now 5 years.

2. *Reports a cost-effectiveness analysis of tocilizumab compared with anakinra and infliximab including scenario analyses with:*
    - *Infliximab as first-line treatment followed by tocilizumab*
    - *Infliximab as first-line treatment followed by anakinra*

The following table with results was presented by the manufacturer. Please note that it was necessary to use efficacy statistics excluding the 'no fever' outcome when the treatment sequence included infliximab as monotherapy or in a sequence involving tocilizumab.

Table 3. Incremental analysis results

Treatment sequence	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison	Outcome used
I	£114,593.33	2.7709					ACR-NoFever
IA	£127,802.55	3.6062					ACR+NoFever*
A	£136,871.46	3.3700	£9,068.91	-0.2361	Dominated	vs. IA	ACR+NoFever
IT	£139,674.57	3.3848	£25,081.24	0.6139	£40,855.96**	vs. I	ACR-NoFever
TI	£151,439.61	4.1262	£36,846.28	1.3553	£27,186.60	vs. I	ACR-NoFever
TA	£165,321.05	4.3310	£37,518.50	0.7248	£51,765.09	vs. IA	ACR+NoFever

NOTES: I = infliximab, A = anakinra, T = tocilizumab; *This sequence assumes that ACR response rates of I = A; **Extendedly dominated by TI

3. Presents sensitivity analysis on the revised base case that includes: Uncertainty around the "Prince" adjustment factor; a stopping rule for tocilizumab after 2 years of treatment; a decreased frequency of administration of tocilizumab after 6 months to a 4-weekly regimen

Varying adjustment factor from indirect comparison with infliximab

In the original submission, treatment effect for infliximab was taken from a trial in patients with juvenile idiopathic arthritis.[2] Of the study group, only 16% of patients had sJIA. As it was assumed that the ACR response in the sJIA group would be lower than in the whole JIA population, data from an observational study with etanercept were used to correct the ACR responses.

Tables 4 and 5 present the results when the adjustment factors are increased and decreased by 30%. As can be seen the ICERs are increased or decreased by around £3,000 per QALY as the adjustment factor is increased or decreased respectively.

Table 4. Results assuming increase of the adjustment factors by 30%

Strategy	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison	Outcome used
I	£112,068.97	2.9051					ACR-NoFever
A	£136,871.46	3.3700					ACR+NoFever
TI	£150,250.86	4.1894	£38,181.89	1.2843	£29,729.84	vs. I	ACR-NoFever
TA	£165,321.05	4.3310	£28,449.59	0.9609	£29,606.23	vs. A	ACR+NoFever

NOTES: I = infliximab, A = anakinra, T = tocilizumab

Table 5. Assume decrease of the adjustment factors by 30%

Strategy	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison	Outcome used
I	£117,031.11	2.6404					ACR-NoFever
A	£136,871.46	3.3700					ACR+NoFever
TI	£152,587.59	4.0647	£35,556.48	1.4243	£24,963.43	vs. I	ACR-NoFever
TA	£165,321.05	4.3310	£28,449.59	0.9609	£29,606.23	vs. A	ACR+NoFever

NOTES: I = infliximab, A = anakinra, T = tocilizumab

Stopping or dose-reduction scenarios

In Tables 6 and 7, the base case results are re-presented with stopping rules where tocilizumab is no longer given after either two years or where its dosing frequency is halved after six months. In both scenarios, tocilizumab sequences either dominate those without, or in the case of tocilizumab (half dose)→infliximab compared to infliximab, produced an ICER less than £1,000 per QALY gained. Total costs are lower in the tocilizumab strategies in Table 6 because:

- the shorter tocilizumab treatment duration has a strong effect on lifetime cost
- in the TI and TA strategies, infliximab and anakinra are given for a shorter duration

Table 6. Results assuming stopping rule after two years

Strategy	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison	Outcome used
I	£114,593.33	2.7709					ACR-NoFever
A	£136,871.46	3.3700					ACR+NoFever
TI	£90,314.50	4.1262	-£24,278.82	1.3553	Dominant	vs. I	ACR-NoFever
TA	£104,195.94	4.3310	-£32,675.52	0.9609	Dominant	vs. A	ACR+NoFever

Table 7. Results assuming administration every four weeks after the first six months

Strategy	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison	Outcome used
I	£114,593.33	2.7709					ACR-NoFever
A	£136,871.46	3.3700					ACR+NoFever
TI	£115,493.34	4.1262	£900.02	1.3553	£664.07	vs. I	ACR-NoFever
TA	£129,374.78	4.3310	-£7,496.68	0.9609	Dominant	vs. A	ACR+NoFever

4. Presents results after applying a Patient Access Scheme

In a separate document, the manufacturer has suggested a PAS which is a simple discount scheme [redacted] In the economic model incorporating the PAS, the individual vial prices were adjusted to reflect the discount applied to tocilizumab.

The comparisons carried out as part of this 'incremental analysis' do not match exactly the conventions set out for incremental analysis defined in this question. The manufacturer states that they match the information request posed by the Appraisal Committee in section 1.2 of the ACD.

Table 8. Base case incremental analysis results with PAS applied

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)	Comparison
I	£114,593.33	2.7709				
IA	£127,802.55	3.6062				
A	£136,871.46	3.3700	£9,068.91	-0.2361	Dominated	vs. IA
IT	[redacted]	3.3848	[redacted]	0.6139	£30629.57	vs. I
TI	[redacted]	4.1262	[redacted]	1.3553	£18,194.05	vs. I
TA	[redacted]	4.3310	[redacted]	0.7248	£34,949.43	vs. IA

[redacted]

Table 9. Fully incremental analysis with PAS applied

Treatment Strategy	Total cost (£)	Total QALYs	ICER versus baseline	Incremental Costs (£)	Incremental QALYs	ICER (incremental)
I	114,593.33	2.771				
IA	127,802.55	3.606	15,813.72	13209.22	0.84	15,813.72
A	136,871.46	3.370	37,182.74	9068.91	-0.24	Dominated
IT	[redacted]	3.385	30,629.57	[redacted]	0.01	Dominant
TI	[redacted]	4.126	18,194.05	[redacted]	0.74	7,897.39
TA	[redacted]	4.331	24,703.78	[redacted]	0.20	67,788.72

Additionally, all the sensitivity and scenario analysis presented under 3) have been rerun with the PAS included.

Table 10. Results assuming increase of the adjustment factors by 30%

Treatment Sequence	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison
I	£112.068.97	2.9051				
A	£136,871.46	3.3700				
TI	[redacted]	4.1894	[redacted]	1.2843	£20,240.04	vs. I
TA	[redacted]	4.3310	[redacted]	0.9609	£16,923.01	vs. A

Table 11. Assume decrease of the adjustment factors by 30%

Treatment Sequence	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison
I	£117,031.11	2.6404				
A	£136,871.46	3.3700				
TI	[redacted]	4.0647	[redacted]	1.4243	£16,406.71	vs. I
TA	[redacted]	4.3310	[redacted]	0.9609	£16,923.01	vs. A

Table 12. Results assuming stopping rule after two years

Treatment Sequence	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison
I	£114,593.33	2.7709				
A	£136,871.46	3.3700				
TI	[redacted]	4.1262	[redacted]	1.3553	Dominant	vs. I
TA	[redacted]	4.3310	[redacted]	0.9609	Dominant	vs. A

Table 13. Results assuming administration every four weeks after the first six months

Treatment Sequence	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison
I	£114,593.33	2.7709				
A	£136,871.46	3.3700				
TI	[redacted]	4.1262	[redacted]	1.3553	Dominant	vs. I
TA	[redacted]	4.3310	[redacted]	0.9609	Dominant	vs. A

5. After request from the ERG, presents a separate document regarding a PSA, including for the PAS.

PSA was only run on the comparison of T vs TA. The manufacturer stated that they ran the PSA with the individual simulation of starting CHAQ included. They stated that other parameters in the PSA were varied as per the original base case with no variation is applied to new parameters introduced in the revised base case, namely:

- CHAQ category cut-points (which are used to define CHAQ-based health states)
- Regression coefficients (which are used to estimate a distribution of CHAQ scores post based on treatment response and baseline CHAQ)

They did not state the number of individual samples or PSA samples, although examining the incremental scatterplots suggests that the number PSA samples were probably no more than about 200. Mean values were not provided. The results were presented in terms of scatter plots and CEACs for the base case and for the PAS. For the base case, they stated

that the percentage of samples where TA was cost effective at ICER thresholds of £20,000 and £30,000 was 23.6% and 47.8% respectively. [redacted]

ERG commentary

Ad1)
The ERG checked the revised model as presented by the manufacturer. The new modeling approach does address the important issue of mutually exclusive health states. By defining health states based on CHAQ score, and using ACR scores to define the transitions, the model now adheres to common modeling practice. The ERG is slightly weary of the use of the phrase “individual patient simulation”, as that is not really the case in this model. In a real individual patient simulation, after assigning a starting CHAQ score to a patient, the next step would have been to assign an individual response to determine the next health state. In the current set up, based on a starting CHAQ the average CHAQ score at 12 weeks is determined. This leads to the same point estimates as a true individual patient simulation, without having the ‘real’ patient variability. Given the purpose of this model, the ERG considers this an acceptable and practical approach.

The ERG furthermore considers the linear extrapolation approach to assigning costs to health states acceptable.

An important assumption made by the manufacturer is that of the cut of points to classify CHAQ scores into health states. It seems plausible that different cut of points lead to different results. However, when new cut of points are defined, the CHAQ mid points for the 4 states also change, and consequently the costs and utilities assigned to these health states. The ERG expects that this greatly reduces the influence of changing cut-of points.

While the model and its health states are as requested in the ACD (i.e. based on CHAQ score), the expert opinion described in the manufacturer’s ACD response indicate that this approach was possibly not the best possible. From the expert opinion, it may be suggested that an overall score based on the 6 ACR dimensions would be a better approach to modelling sJIA. However, further research would be required to come to a meaningful weighing of the scores on the 6 dimensions.

The ERG also notes that the sequences were reduced from four treatments to no more than two. The justification for this was presented in a footnote that stated that this was according to a view expressed at the ACM. However, no formal request was made in the ACD. Although, there are significant problems in estimating the effect of treatments after 1st line, it might have been better to have considered all options, including up to four treatments. Unfortunately, there was insufficient time for the ERG to conduct any analyses on this.

Ad 2)
The manufacturer has presented in their ACD response a table with various treatment options with pairwise comparisons. In line with the request of the AC, the ERG here presents the full incremental analysis. All treatment sequences were ordered according to QALYs. Two treatments were dominated, A and IT have both fewer QALYs and are more expensive than IA. Thus, these two options have been deleted from the table. The incremental costs, effects and ICERs are now calculated between a sequence and the next best one, leading to the following results.

Table 14. Fully incremental analysis (ERG version)

Treatment sequence	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Outcome used
I	£114,593.33	2.7709				ACR-NoFever
IA	£127,802.55	3.6062	£13,209.22	0.8353	15814	ACR+NoFever*
TI	£151,439.61	4.1262	£23,637.06	0.52	45456	ACR-NoFever
TA	£165,321.05	4.331	£13,881.44	0.2048	67780	ACR+NoFever

Using the common threshold of £20,000 per QALY gained, IA is a cost-effective strategy compared to only infliximab. Starting with tocilizumab followed by infliximab would be deemed not cost-effective, and starting with tocilizumab followed by anakinra is deemed the least favourable strategy.

Ad 3)
The manufacturer has submitted the requested sensitivity analyses. Regarding the analysis where tocilizumab is administered once every 4 weeks after the first 6 months of treatment, the manufacturer has not described what assumptions were made. From the results, the ERG concludes that it was assumed that this reduction of treatment frequency would be possible without any loss of effectiveness.

Regarding the analysis where treatment with tocilizumab is stopped after 2 years, looking at the total QALYs it is clear that here the manufacturer has also assumed that stopping treatment after 2 years, is possible without any loss of effectiveness. The ERG questions the plausibility of that assumption; a gradual weaning of treatment effect may have been a more realistic assumption.

Ad 4)
The ERG does not consider table 9 presented by the manufacturer to represent a full incremental analysis. Therefore the ERG presents below the results based on the commonly accepted approach to full incremental analysis (sorting according to costs or effects, deleting dominated or extendedly dominated strategies and calculating an ICER compared to the next best option).

Thus we find, after excluding again A and IT, the following results.

Table 15. Fully incremental analysis with PAS applied (ERG version)

Treatment Strategy	Total cost (£)	Total QALYs	Incr Costs	Incr. QALY	ICER
I	114,593.33	2.771			
IA	127,802.55	3.606	£13,209.22	0.84	£15819
TI	[redacted]	4.126	[redacted]	0.52	£22018
TA	[redacted]	4.331	[redacted]	0.21	£67714

[redacted]

Ad 5)

The ERG considers that the PSA was not performed on the correct comparators. In particular, those that in the deterministic analysis might have been cost effective, namely I, IA and TI, were excluded: a full incremental analysis i.e. with all comparators should have been used. Therefore, the results of the PSA by the company are of little value. Moreover, the PSA did not include any variation in the coefficients of the new CHAQ regression model.

However, the ERG had already noticed that no PSA was included with the original ACD response. Lack of any PSA precludes any estimate of the uncertainty in the new model: crucially, the point estimate (mean) ICER might also be different given non-linearity in the model. Such a non-linearity might have been introduced by the change in the model structure, particularly by the use of the CHAQ regression model and the correlations between coefficients. Therefore, the ERG had already considered running the PSA themselves. However, there were several problems:

1) Model only allows comparison of two sequences, precluding PSA across all options
2) The macro to run the PSA is separate to that to run individual simulation, precluding PSA 'on top of' individual simulation
3) The manufacturer did not provide the covariance matrix for the regression equation.
4) The time to run 1000 simulations for the PSA plus 10,000 for the individual simulation was estimated to be about a week, precluding delivery by the deadline of 12.30 on 7th September.

The ERG believed that it was important for the Appraisal Committee to have this information and so did the following:

1) PSA was run twice, once for IA vs. I and once for TI vs. I since these three were the only sequences that might be cost effective in the deterministic analysis, [redacted] The results for IA, TI and I (from one of the PSAs) were then used to conduct an incremental analysis, which are shown in the PAS section below.
2) A new macro was compiled to 'nest' the individual simulation within the PSA.

3) The ERG made a conservative assumption of a correlation of 0.4 between each of the coefficients in order to populate the covariance matrix.
4) The number of simulations was reduced to 200 for the PSA and 200 for the individual simulation. 200 for the individual simulation is a large reduction from 10,000, but the ERG believed that this was reasonable given the lack of variation due to use of mean values (as described above). 200 for the PSA is also low, but the results for I were checked from each of the two PSAs and found to be similar. However, the ERG considers that the results of the PSA should only be indicative.

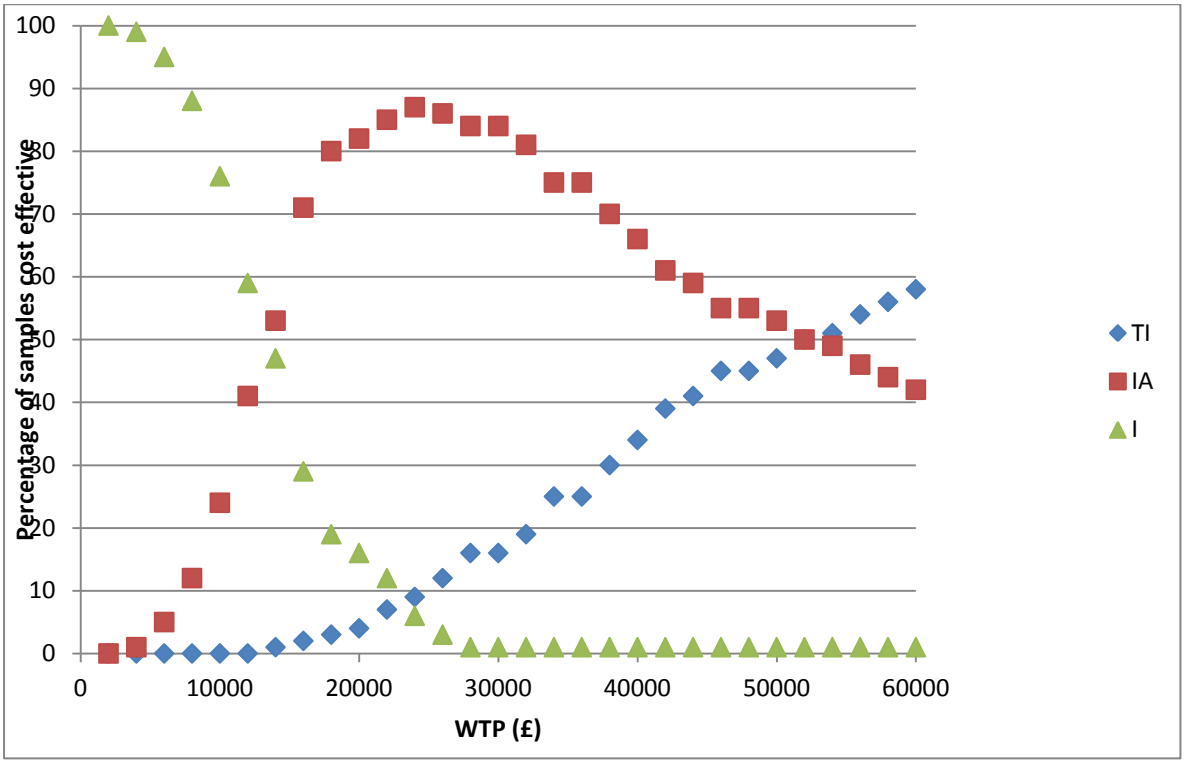
Results of PSA

Table 16. Fully incremental analysis with PAS applied, PSA results (ERG version)

Treatment Strategy	Total cost (£)	Total QALYs	Incr Costs	Incr. QALY	ICER
I	£113,914.5	2.800752			
IA	£131,654	3.594481	£17,739.47	0.793729	£22,349.53
TI	[redacted]	3.906735	[redacted]	0.312253	£32,330.52

[redacted]. As mentioned above, the difference between the means of the PSA and the deterministic analysis are not inconsistent with a non-linear model structure. The ERG does point out that there has been insufficient time to investigate this further. Figure 2 presents the CEAC.

Figure 2 CEAC (ERG analysis)



[redacted] Again the ERG would point out that there has been insufficient time to investigate this thoroughly.

4. References

1. Tocilizumab for the treatment of systemic juvenile idiopathic arthritis. Roche new evidence submission to the National Institute for Health and Clinical Excellence, submitted 2nd September 2011.

2. Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2007 Sep;56(9):3096-106.

3. Prince FH, Twilt M, ten Cate R, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. *Ann Rheum Dis* 2009;68(5):635-41.