Assessment Group report

Addendum to:

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only: systematic review and economic evaluation

Amendments to the model inputs since the first NICE appraisal committee and how these changes impact on the estimated cost per QALY gained ratios

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1. Introduction

This report is a follow-up report to the initial report presented to the NICE Appraisal Committee which can be found on the NICE website. (https://www.nice.org.uk/guidance/gid-tag313/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-assessment-report2). For clarity the report on the NICE website will be called 'August2013 report'.

Following consultation on the August 2013 report and the accompanying mathematical model (denoted as 'August 2013 model') legitimate errors and omissions were identified: this report attempts to address the identified items. Given the length of the 'August 2013' report, this report has been structured in the following manner to improve readability: a summary of the key changes made to data within the network meta-analysis; a summary of parameter changes and / or coding changes in the mathematical model; and a summary of the new cost-effectiveness results. More detail on each of these categories is then presented in Appendix 1, which contains the revised Assessment Group report.

For brevity, full definitions of components of the decision problem have not been provided in this report. Further details can be found within Appendix 1.

2. Changes to the data in the network meta-analyses.

Network meta-analyses were conducted for two broad populations: those with severe active RA (defined by a disease activity score of 28 joints (DAS28) score of ≥5.1) who were conventional disease-modifying anti-rheumatic drugs (cDMARD) naïve (Population 1 in the NICE scope) and for those who were cDMARD experienced. The cDMARD experienced patients were further divided into those with severe RA, Population 2 in the NICE scope and those with moderate-to-severe active RA (defined as a DAS28 score between 3.2 and 5.1), Population 3 in the NICE scope.

Two classifications have dominated the measurement of improvement in RA symptoms: ACR responses and EULAR responses. Evidence of the clinical effectiveness of the interventions has been considered separately for both measures. The mathematical model was based on EULAR response as this is commonly used in clinical practice in England and relied on a mapping between EULAR and ACR responses based on the Veterans Affairs Rheumatoid Arthritis registry (Table 164 of Appendix 1).

2.1 Changes for Population 1

For Population 1 two changes were made to the data set for the network meta-analyses reported in August 2013 report and used in the August 2013 model. These changes were for the ACR analyses; no changes were made for the EULAR analyses.

- Data from the COMET trial (of etanercept + methotrexate (MTX) vs. MTX) were included
- A minor amendment to the numbers in the BeST trial which compared: sequential monotherapy; step-up combination therapy; initial combination therapy with prednisone; and initial combination therapy with infliximab.

In addition, a sensitivity analysis was conducted for Population 1 in which studies with a low level of background MTX use (TEAR and TEMPO) were included

2.2 Changes for Populations 2 and 3

For Populations 2 and 3 a number of changes were made to the data set for the network meta-analyses reported in August 2013 report and used in the August 2013 model. These changes affected both the ACR and EULAR analyses. These are listed below and split by classification.

ACR data

- Data from the CERTAIN trial (of certolizumab + cDMARDs vs. cDMARDs) were now sourced from clinicaltrials.gov rather than from an abstract.
- The number of participants in RAPID1 (a trial of certolizumab + MTX vs MTX) has been slightly amended
- Data from the AMBITION trial (of tocilizumab vs MTX) have been removed as the percentage of patients who were MTX-experienced (66%) was deemed too high for inclusion in the analyses.
- Data from the SATORI trial (of tocilizumab vs MTX) are now those reported at the last observation.
- Changes were made to data from ATTRACT (a trial of a trial of infliximab + MTX vs MTX)

EULAR data

- Data from the CERTAIN trial (of certolizumab + cDMARDs vs. cDMARDs) were included
- Data from the LARA trial (of intensive cDMARDs vs etanercept + MTX) were further subdivided to include data on the division between good and moderate responders.
- Data from the SATORI trial (of tocilizumab vs MTX) were included
- Data from GO-FORTH (a trial of golimumab + MTX vs MTX) were included
- Data from START (a trial of infliximab + MTX vs MTX) were included

The complete data used within the network meta-analyses are provided in Table 19, Table 20, Table 21 and Table 22 of Appendix 1. Detailed results are provided in Section 3.3, in pages 83 to 180, of Appendix 1, with a summary of the results displayed in Figures 102 to 109. The main analyses for cDMARD-experienced patients based on EULAR response and ACR response mapped to EULAR provided are reproduced in Figure 1 and Figure 2 respectively. Figures 3 provides the results for ACR response mapped to EULAR in cDMARD-naïve, severe RA patients: there was only one trial in cDMARD-naïve, severe RA patients that reported EULAR data. It is stressed that these figures do not

reflect the considerable uncertainty in the values and reflect mean estimates only. For abbreviations refer to Appendix 1.

Figure 1: Estimated mean EULAR responses in cDMARD-experienced patients

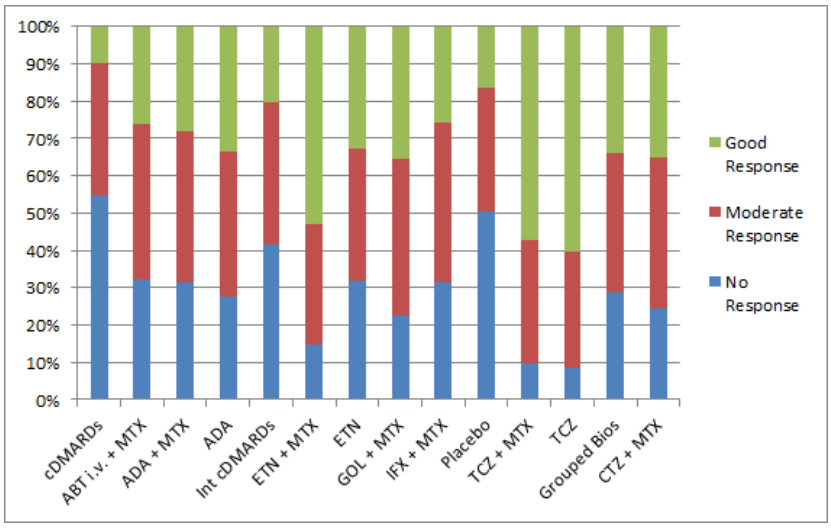


Figure 2: Estimated mean EULAR response in cDMARD-experienced patients mapped from ACR trials

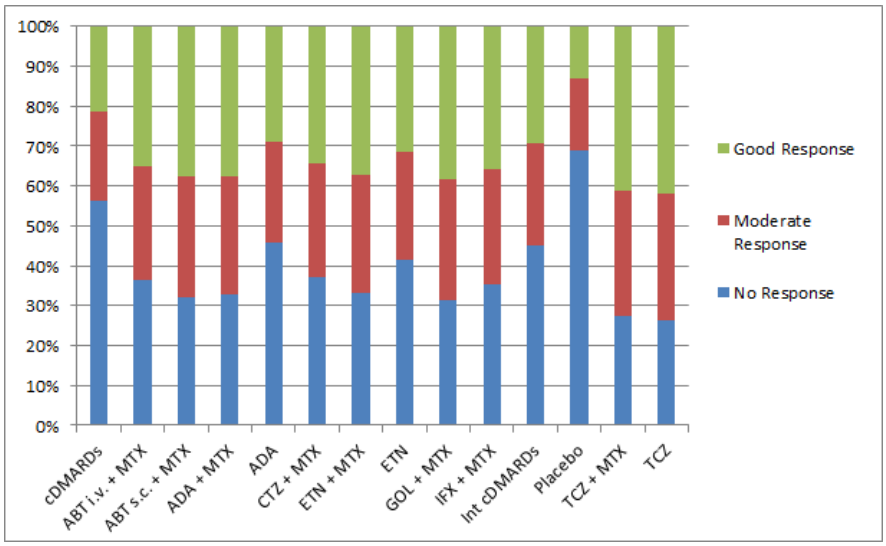
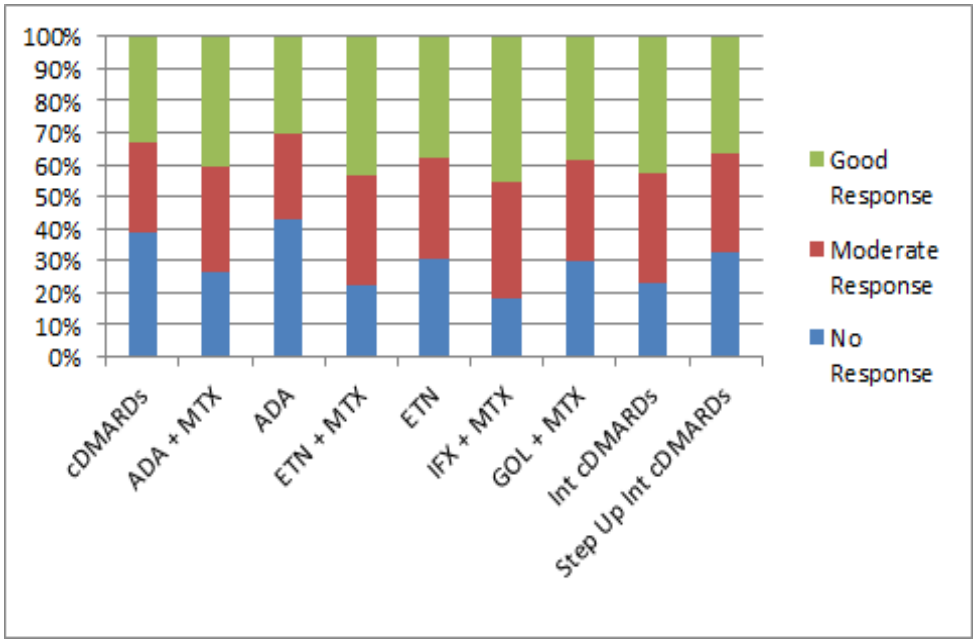


Figure 3: **Estimated mean EULAR response in cDMARD-experienced patients mapped from ACR trials in cDMARD-naïve, severe RA, patients**



3. Changes to parameters within, and corrections to, the mathematical model

This section documents changes to the coding and parameterisation of the August 2013 model in response to comments made by consultees and commentators. Nineteen amendments were made which would affect the incremental cost effectiveness ratio (ICER) in terms of cost per quality adjusted life year (QALY) presented by the Assessment Group. Errors highlighted which did not impact on the ICERs were corrected but are not detailed in this report.

The amendments made are detailed in Table 1. The impacts of the nineteen amendments on the ICER for Population 3 (severe cDMARD-experienced patients) are displayed in Figure 4 which provides a comparison with 'Amendment 0' which is the ICER from the base case using the August 2013 model.

Each change is sequential, thus the ICER for Amendment 17 will also have incorporated the changes for Amendments 1 to 16. It is commented that the ICERs in Figure 4 do not correspond to the results presented in Section 4, for the following reasons:

- Data from the revised network meta-analyses were not included as the changes to the model were completed prior to these network meta-analyses being undertaken
- The PAS for tocilizumab has not been incorporated
- The numbers of hypothetical patients sampled were 10,000 rather than 20,000 in results within Section 4. Thus there is more Monte Carlo sampling error within Figure 4 than the final results.
- Only the ICER for a strategy of etanercept + MTX → rituximab + MTX → tocilizumab + MTX → non-biologic therapy compared with MTX → non-biologic therapy was presented for each model run.

Despite these differences it is believed that Figure 4 provides a good indication of the impact of each error on the ultimate ICER.

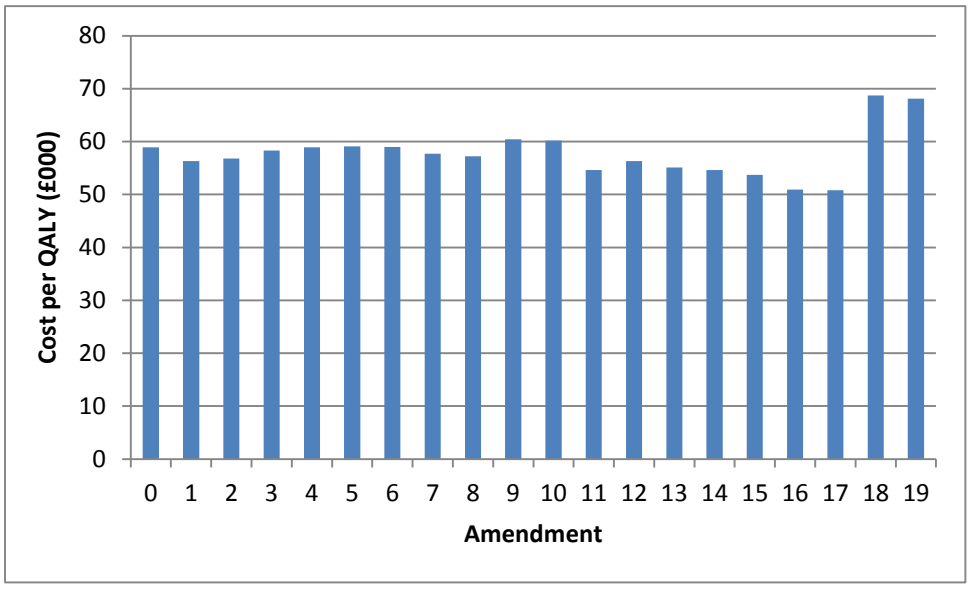
Table 1 Detailing the amendments made to the August 2013 report

Amendment	Error in the August 2013 model	Correction
0 (Submitted model)	-	-
1	Formulas within cells I25 to I108 in the 'Lifetables' worksheet had incorrectly used the male life expectancy for females.	The relevant formulae have been changed to =IF(basesex = 0, VLOOKUP(H25,$A$9:$E$109,3), VLOOKUP(H25,$A$9:$E$109,**5**))
2	Two variables (I and S) within the VBA were not defined when HAQ progression for biologics was set to zero.	Defining of I and S in the haqprog VBA module has been moved to before the tx_class IF statement
3	Cell F96 on the 'Survival' worksheet had a fixed value (0.984) rather than being set to sample from a uniform [0,1] distribution.	Cell F96 has been changed to '=rand()'
4	Discounting of the costs of abatacept + MTX was six months later than is appropriate.	The VBA code has been amended so that the discounting for abatacept (both intravenous and subcutaneous) + MTX is at the appropriate time point. This was done by changing tx_r_t to tx_s_t
5	CON_DMARD was incorrectly spelt as CON-DMARD in a line of VBA code	The typographical error has been corrected
6	Inappropriate amendment of HAQ in the first six months for moderate responders which included using a value related to the previous patient.	Line 199 of the Haqprog module has been disabled which corrects this error.
7	Inappropriate use of basesex-1 in the calc_QALY module	Code has been added to specify the value of the 'male' parameter based on 'basesex' and subsequent code now uses male rather than (basesex-1)
8	Inconsistent number of weeks per year used in the model, which took values of 52.1775, 52.25 and 52.	All references to the number of weeks per year now use 52.1775

9	Formulas within cells I25 to I108 in the 'Lifetables' worksheet had stopped at age 100 rather than age 101	The relevant formulae have been changed to =IF(basesex = 0, VLOOKUP(H25,$A$9:E**110**,3), VLOOKUP(H25,$A$9:E**110**,5))
10	The variable 'pain switch' was not defined	Code has been added to the QALY module to define pain switch. "pain_switch = Range("pain_switch").Value"
11	Minimum age of simulated individual was fixed at 50 years	This has been amended to 18 years to allow adults of any age to be simulated
12	cDMARD survival duration inappropriately sampled from Chen et al rather than that associated with bDMARDs	An 'If' statement (previously on line 515 of the toshRA module) has been removed so that the time to withdrawal is updated for both bDMARDs and cDMARDs. Furthermore the time on cDMARDs (using the linear approach) has been set until patient death
13	Hazard ratios treated as relative risks for mortality calculations, which allowed probabilities of death above 1	Probabilities have been converted to rates, the hazard ratio has been applied and then the rate has been converted back to a probability
14	The costs and disutilities associated with adverse events were not included for the bDMARDs used after first line (rituximab and tocilizumab)	This has been changed by applying the effects of AEs for all bDMARDs regardless of line of treatment. This was operationalised by moving the 'If tx_class = "Bio" clause outside of the 'If tx = 1' clause, which is line 291 of the toshRA module.
15	HAQ trajectory for cDMARDs was inappropriately using data relating to the BSRBR between months 6 and 12	The model has been amended so the use of BSRBR data has been removed. This was operationalised by disabling lines 299-313 of the haqprog module

16	The probability of class membership was not implemented correctly	This was corrected in the following manner 1) In the 'progression' worksheet, additional covariates were included (deprivation, Rheumatoid Factor positive, ACR criteria, failed 2 cDMARDs and DAS response at 6 months added) along with the mean values : Cells 'l89:t94'. These values were read into the haqprog module (line 220) 2) At the start of haqprog, an age_onset variable was defined (and if statement used to ensure this was a minimum of 1) (line 84 of the haqprog module) 3) A failed2dmards variable was defined and was 1 if basedmard value was 2 or more and 0 otherwise (line 90 of the haqprog module) 4) The disease duration was updated in the model by adding the simulation time (lines 100 and 317 of the haqprog module) 'Currentdd = basedd + t' 5) These covariates were incorporated into the progression model for cDMARDs (lines beginning p1, p2, p3…). (line 319 of the haqprog module)
17	The patient access scheme for certolizumab pegol was not incorporated	Cell G11 in the 'Costs; worksheet, which relates to the initial six months cost of certolizumab pegol has been reduced from £8295.01 to £4720.01
18	The equation linking HAQ and pain from the National Data Bank for Rheumatic Diseases (NDB) was incorrect	A third option, [NDB (updated 2014)] has been added to the model. In this option the value for pain has been divided by 10, compared with the previous NDB value, in order that the formula is correct
19	The first 13.99 weeks of cost for certolizumab was excluded rather than 14.00 weeks in alignment with the patient access scheme should a patient die or withdraw within the six month response period	This has been amended to 14.00 by changing lines 345 and 351 in the tosh RA module

Figure 4: Exploring the impact of amendments to the model on the cost-effectiveness of an etanercept + MTX → rituximab + MTX → tocilizumab + MTX → non-biologic therapy compared with MTX → non-biologic therapy in severe cDMARD-experienced patients



For details of the amendments related to each number see Table 1

4. The resulting ICERs from the revised model

Appendix 1 contains the full set of results in Tables 171 to Table 331. For brevity only the summarised results, which report the median ICER for each of the bDMARD strategies for each broad population are presented in this report. These reproduce Tables 171 to 174 in Appendix 1.

In general terms the ICER for is typically £60,000 when used in Populations 2 and 3 and is greater in individuals with moderate-to-severe RA. The incremental cost per QALY increases to £90,000 for those who receive a bDMARD without MTX and is approximately £300,000 in Population 1. The key parameter which affected the results is the assumed Health Assessment Questionnaire (HAQ) progression whilst on cDMARDs; if the values used in previous National Institute for Health and Care Excellence (NICE) appraisals were instead used the incremental cost per QALY fell to approximately £37,000 for bDMARDs compared with cDMARDs alone.

The data source used for establishing the relationship between HAQ and pain was also seen to influence the results markedly; the Assessment Group base case uses the estimate most favourable to the bDMARDs.

For full details of the base case analysis and of the changes associated with each amendment refer to Appendix 1.

Table 2: Summarised results: Median ICERs for all bDMARD strategies compared with the MTX alone strategy. Populations 2 and 3 who can receive MTX

			Base Case +								
	Response Measure	Assumed HAQ Progression	-	RCTs with small %ge of bDMARD prior use , adequate MTX-history	RCTs with small %ge of bDMARD prior use (irrespective of MTX-history)	Trials with inadequate MTX history	Malottki mapping of HAQ to utility	Discount rates (6% costs, 1.5% QALYs)	Impact of AEs assumed to be 100-fold higher	Relationship between HAQ and pain taken from ERAS	PSA
Population 2 (severe MTX – experienced)	EULAR	ERAS	£61,200	£61,400	No data	No data	£49,700	£39,500	£62,200	£73,700	£61,700
		Linear	£37,900	£36,300	No data	No data	£32,400	£22,300	£38,300	£46,300	£37,600
	ACR	ERAS	£62,200	£62,200	£62,600	£68,900	£49,700	£39,500	£62,200	£73,700	£62,700
		Linear	£35,500	£35,100	£35,700	£36,400	£30,900	£21,400	£35,600	£43,700	£35,900
Population 3 (moderate-to-severe MTX-experienced)	EULAR	ERAS	£75,000	£74,200	No data	No data	£53,400	£46,600	£78,100	£87,300	£76,800
		Linear	£37,500	£36,600	No data	No data	£31,300	£21,800	£39,300	£48,300	£35,800
	ACR	ERAS	£77,100	£77,500	£77,300	£79,200	£53,900	£48,300	£79,800	£89,300	£79,000
		Linear	£38,000	£36,700	£38,000	£39,200	£30,000	£21,800	£39,100	£46,700	£38,400

All numbers rounded to the nearest £100.

Table 3: Summary of median ICERs for all bDMARDs compared with an SSZ alone strategy. Populations 2 and 3 who are treated with monotherapy

			Base Case +								
	Response Measure	Assumed HAQ Progression	-	RCTs with small %ge of bDMARD prior use , adequate MTX-history	RCTs with small %ge of bDMARD prior use (irrespective of MTX-history)	Trials with inadequate MTX history	Malottki mapping of HAQ to utility	Discount rates (6% costs, 1.5% QALYs)	Impact of AEs assumed to be 100-fold higher	Relationship between HAQ and pain taken from ERAS	PSA
Population 2 (severe MTX – experienced)	EULAR	ERAS	£87,600	£89,000	No data	No data	£71,600	£58,200	£89,100	£107,000	£88,400
		Linear	£39,600	£38,000	No data	No data	£34,800	£24,800	£40,200	£49,200	£39,100
	ACR	ERAS	£94,800	£93,900	£99,600	£94,700	£79,000	£64,700	£97,200	£117,400	£90,000
		Linear	£38,500	£37,300	£37,200	£37,200	£34,100	£23,600	£39,300	£47,800	£38,800
Population 3 (moderate-to-severe MTX-experienced)	EULAR	ERAS	£104,800	£108,100	No data	No data	£74,400	£65,100	£108,700	£121,900	£105,400
		Linear	£41,400	£39,300	No data	No data	£32,800	£23,900	£41,600	£49,700	£41,700
	ACR	ERAS	£106,400	£107,900	£110,500	£107,900	£77,200	£70,000	£105,900	£120,300	£108,200
		Linear	£38,800	£38,500	£38,000	£37,200	£31,100	£23,800	£40,500	£47,100	£39,600

All numbers rounded to the nearest £100.

Table 4: Summarised results: Median ICERs for all bDMARD strategies compared with the MTX alone strategy. Population 1 who can receive MTX

			Base Case +						
	Response Measure	Assumed HAQ Progression	-	RCTs with small %ge of MTX prior use ,	Malottki mapping of HAQ to utility	Discount rates (6% costs, 1.5% QALYs)	Impact of AEs assumed to be 100-fold higher	Relationship between HAQ and pain taken from ERAS	PSA
Population 1 (severe MTX – naïve)	ACR mapped to EULAR	ERAS	£308,700	£571,700	£214,800	£185,000	£326,100	£344,800	£295,700
		Linear	£296,300	£432,800	£216,400	£192,900	£323,600	£344,700	£296,700

All numbers rounded to the nearest £100.

Table 5: Summary of median ICERs for all bDMARDs compared with a SSZ alone strategy. Population 1 who are treated with monotherapy

			Base Case +						
	Response Measure	Assumed HAQ Progression	-	RCTs with small %ge of MTX prior use ,	Malottki mapping of HAQ to utility	Discount rates (6% costs, 1.5% QALYs)	Impact of AEs assumed to be 100-fold higher	Relationship between HAQ and pain taken from ERAS	PSA
Population 1 (severe MTX – naïve)	ACR mapped to EULAR	ERAS	£414,700	£140,400	£340,500	£295,400	£382,000	£438,700	£404,500
		Linear	£378,000	£139,800	£357,700	£291,200	£375,300	£460,000	£408,800

All numbers rounded to the nearest £100.