National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Roche Response Version 2 (28 June 2011) to Revised ERG report (28 June 2011)

ERG report

Tocilizumab for the treatment of systemic juvenile idiopathic arthritis

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *Kleijnen Systematic Reviews Ltd* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, **5pm, Friday 24 June 2011** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

29th October 2009

ROCHE RESPONSE TO ORIGINAL ERG REPORT (RECEIVED FRIDAY, 17 JUNE 2011)

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG, under section 1.2 (p7), state the following: *"The ERG has a fundamental problem with the evidence presented in the MS as it is not in accordance with the NICE scope. It is for the Appraisal committee to decide whether it will accept the ERG approach, which means there is no evidence for any comparison in the NICE scope, or accept the MS approach, which means there is some evidence for the second population, but none for the first population….Because of the lack of information it can only be assumed that the 25% of children in the TENDER trial who stopped using MTX fit this population (population 2). The remaining 75% of children in the TENDER trial should be treated as population 1. Because no data were provided for these two populations, there is no evidence available for any of the comparisons in the NICE scope."* The above statements are factually	The ERG should reevaluate these statements, based on the 'Justification for amendment' information on the right hand column, and especially Roche's submitted evidence for Populations 1 and 2.	The TENDER study addresses Populations 1 and 2, as stated on page 39 of the manufacturer submission (MS): *"As such, by viewing only the inclusion criteria, the TENDER population matches population 1: children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s) and systemic corticosteroids.* *However, on closer analysis of patients' treatment histories on joining TENDER, the study most accurately reflects population 2: children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s), systemic corticosteroids and methotrexate.",* and was also clarified in Roche's Response to Clarification Questions (A2, p2).	**<u>NOT A FACTUAL ERROR</u>** It makes no sense to assess the effects of tocilizumab versus MTX in a population that is MTX non-responsive. Therefore, we have assumed the populations to be mutually exclusive. We were not present at the NICE decision problem meeting and cannot comment on discussions at that meeting. We have taken the scope as presented by NICE. The scope, as interpreted by the ERG, clearly describes two separate populations. One population of "children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s) and systemic corticosteroids" for which MTX is the comparator; and a second population of "children and

incorrect, based on Roche's submission and further clarified throughout this document.		**More importantly, this fundamental issue was discussed at the 'NICE Decision Problem meeting' on 8 March 2011 (11.30-1.30pm), prior to Roche's MS. At this meeting it was discussed and agreed that the Scope Populations 1 and 2 reflect the TENDER trial and that NICE has not defined any of the populations as MTX naive. At this meeting it was also agreed that this fundamental issue would be reported to the Appraisal Committee to avoid future misunderstanding. This fundamental issue was therefore subsequently reiterated throughout the MS document.** **It seems unfortunate that this fundamental issue was not taken into account in the ERG report, which could be regarded as an error of fact on behalf of the ERG.**	young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s), systemic corticosteroids and methotrexate" for which anakinra and TNF inhibitors are comparators.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer (Inadequate response to methotrexate)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the ERG report (p7), it states: "*The MS does not provide a clear definition of inadequate responders. It cannot be automatically assumed that all participants in the TENDER trial are inadequate responders to MTX. Because of the lack of information it can only be assumed that the 25% of children in the TENDER trial who stopped using MTX fit this population (population 2). The remaining 75% of children in the TENDER trial should be treated as population 1. Because no data were provided for these two populations, there is no evidence available for any of the comparisons in the NICE scope.*"	The ERG should reevaluate this statement as the MS and Roche's Response to Clarification Questions (A2, p2) stated ~95% of patients in TENDER could be classified as MTX inadequate responders (MTX-IR) and hence the ERG statement is factually inaccurate.	On page 5466-7 of the TENDER Clinical Study Report (which has been supplied to the ERG), it states the following: [redacted] As clarified in Roche's Response to Clarification Questions (A2, p2), the above inclusion criterion, coupled with patients having active disease at baseline, means that these patients are MTX inadequate responders (MTX-IR). This is how many adult RA biologic studies define their MTX-IR population – i.e. the patients do continue to take their MTX through the adult RA study but are classed as MTX-IR because they meet certain disease activity criteria at baseline, having ensured they were on a long enough course of MTX – such as 12	**NOT A FACTUAL ERROR** The manufacturer presents inclusion criteria for the TENDER trial, not a definition of inadequate response used in the MS. The TENDER trial included also 5% MTX naive children. We still think, the manufacturer should have clearly defined 'inadequate response to MTX' in their submission and then used the population fulfilling this definition for population 2. Instead, the MS provided no clear definition and used all patients from the TENDER trial for population 2, including 5% MTX naive children. Nevertheless, we have critiqued the MS following the MS approach in which 95% of children fulfil the definition of population 2.

		weeks, as in TENDER. To clarify the situation about MTX inadequate responders from the TENDER trial, we have also consulted Professor Patricia Woo, one of the investigators from the study. Her interpretation, as is Roche's view, is as follows: "*Those patients on Methotrexate (except the Methotrexate naive patients) that entered the TENDER study with active disease are de facto inadequate responders to methotrexate. Otherwise we clinicians would not have suggested the trial to the parents.*" (Professor Patricia Woo CBE, Director of University College London's centre of paediatric and adolescent rheumatology, honorary consultant and professor of paediatric rheumatology, Great Ormond Street Hospital for Children NHS Trust, June 2011).	

1.3 Summary of cost effectiveness submitted evidence by the manufacturer

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states (p9): "*The main issue was the starting age used in the model. Since the decision problem mentioned children of 2 years and older, the manufacturer used this as the starting age of the model. However, on average, patients will be 7 years before they are eligible for treatment with tocilizumab. It was found that this higher age had a significant impact on the ICER, increasing from £23,000 to £42,500*."	This is factually incorrect as, should tocilizumab be granted its licence in sJIA [redacted] Hence the statement should be reworded accordingly.	The proposed SPC for tocilizumab in sJIA states the age when eligible patients will be able to be prescribed tocilizumab. This age is also consistent with the literature and expert opinion, which follows about the onset of age of sJIA and biologic use: sJIA occurs in young children, with a peak age of onset between 18 months and 2 years in two UK series, but can occur in children of any age and, rarely, in young adults too (*Woo P, Nature Clinical Practice Rheumatology,2006, 2 (1), 28-34*). Roche has received expert opinion regarding the age of onset of sJIA and/or biologic use: "*Peak age of onset is around 2 in at least one large referral centre (Fishman et al 1998) and also quoted in many publications. Onset is in all age groups, and another small peak is around 6/7 in some series. The younger onset ones tend to be more severe (EULAR 2011- Russo et al). Biologics are used if there is poor response to a combination of steroids and methotrexate within 3-4 months in*	**<u>NOT A FACTUAL ERROR</u>** The ERG does not argue the fact that tocilizumab may be used by patients 2 years (according to the license) and older, nor does the ERG argue that the peak age of onset of sJIA is 2 years old. What the ERG does argue is that not the *peak* age of onset but the *average* age of onset is the relevant parameter to inform the health economic decision. That is, when the average age is used, the resulting costs and effects per patient can be multiplied by the total number of eligible sJIA patients, to obtain the total costs and effects associated with tocilizumab treatment. This would not be possible if the peak age of onset was used. Additionally, given that we consider tocilizumab after having failed on NSAID, CS and MTX, not the average age of *onset*, but of *start*

		the severe cases, either at onset or during a flare that persists. However, recent ACR recommendations (Beukelman, A&R 2011) are that these patients should be treated even earlier with biologics. *As for time horizon of sJIA, it can be lifelong. In the past, hips may be replaced after 10-11 years when there were no effective treatments, with the patient still having active arthritis. Systemic features can resurface in teenage and young adult years."* (Professor Patricia Woo CBE, Director of University College London's centre of paediatric and adolescent rheumatology, honorary consultant and professor of paediatric rheumatology, Great Ormond Street Hospital for Children NHS Trust, June 2011). *"Onset of sJIA can be from 1 year of age up to 16 (the paediatric cut off)."* (Dr. A. V. Ramanan, Lead Consultant in Paediatric Rheumatology, Honorary Reader, Univ. of Bristol, Bristol Royal Hospital for Children & Royal National Hospital for Rheumatic Diseases, Bath, June 2011)	*tocilizumab* should be used. Note that the average age used by the ERG was derived from the literature provided by the manufacturer.

Relative size of the TENDER study in sJIA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG, whilst recognising the high quality of the TENDER study in their report, refer to it as a small study on numerous occasions (pgs 7 and 9).	References to the TENDER study being "small" are qualified that it is one of the largest studies in the therapy area to date.	The size (number of patients) of a clinical study is often used as a quality indicator. Referring to a study as small suggests that its findings may not be of high quality. Whilst the TENDER study might seem relatively small in the wider pharmaceutical sense, it is one of the largest RCTs to have been conducted specifically in sJIA patients.	**NOT A FACTUAL ERROR** NICE takes decisions across different indications; in that sense this was a small trial.

Critique of use of the ITT population in the TENDER study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG noted as a weakness of the TENDER study that the ITT population was not used for all analyses (p10, ERG report).	The ITT population was used for all efficacy analyses in the TENDER study, apart from when specified per-protocol sensitivity analyses were performed.	The ITT population was used for **all** efficacy analyses in the TENDER study, apart from when specified per-protocol sensitivity analyses were performed. These were carried out as repeat analyses for certain endpoints, and designed to test the robustness of the respective ITT analyses and not as stand alone efficacy analyses. The Safety and PK populations were used for all Safety and PK assessments respectively - in line	**NOT A FACTUAL ERROR** See ERG report Table 4.4 and MS table 16 (labelled as ITT-population): For placebo, 17 out of 37 children were included in the analyses.

		with the study protocol. This clarification is important to avoid confusion over the robustness of the efficacy analyses in the TENDER study. If the efficacy analyses of the TENDER study were considered to be based on inappropriate methods, this might create false uncertainty around the quality of the study results.	

NICE approval for etanercept in JIA, specific to polyarticular-course

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (p12) states: *"However, it should be noted that NICE guidance on etanercept for JIA is for **all** subtypes of JIA."*	This should be removed as it is factually incorrect	The etanercept NICE TA35 is titled '*Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis*'. This would suggest the guidance covers all subtypes of JIA, including systemic. However within the document, guidance 1.1 is as follows: *"Etanercept is recommended for children aged 4 to 17 years with active polyarticular-course juvenile idiopathic arthritis whose condition has not responded adequately to, or who have proved intolerant of, methotrexate."*	Agree, sentence removed.

		This guidance in specifically polyarticular JIA is in line with the etanercept licence, and so as per the MS, there is in fact no NICE guidance currently available for sJIA. Similarly, NICE's Final Scope and experts recognise that different specific conditions fall under the term JIA.	

Current service provision analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 13 the ERG report states: *"There are several viable therapies not mentioned by the manufacturers, including: anakinra, operative treatments, and autologous stem cell transplantation"*	Removal of this sentence	**Anakinra:** The ERG suggests that the MS does not specifically mention anakinra in the context of the current clinical pathway of care. However anakinra is mentioned as follows: page 7 (Executive Summary of MS): "*..anakinra is currently used off-label and mainly uncontrolled studies support its use*…." page 22 of the MS states: *"The current clinical pathway of care for the pharmacological treatment of sJIA includes sequential NSAIDs, corticosteroids (intra-articular,*	**NOT A FACTUAL ERROR** We are discussing here the 'current service provision' section in the background section of the MS (page 20-24), with which we broadly agree (see ERG report, page 12). In this section of the MS we missed the treatments (and references) mentioned.

		intravenous or oral) and disease modifying anti-rheumatic drugs (DMARDs) – specifically methotrexate. Following failure of these treatments patients move onto biologic DMARDs including etanercept which is licensed and recommended by NICE for polyarticular JIA and other anti-TNFα therapies and immunosuppressive drugs, which are also not licensed for use in sJIA" The descriptor 'biologic DMARDs' is a standard term used to describe treatments such as anti-TNF, anakinra, tocilizumab and other therapies not mentioned here. As such anakinra is included under this broader heading. Anakinra is also mentioned in sections 5.7 (Indirect Comparison), 5.9 (Adverse events) and throughout the MS **Operative treatments, and autologous stem cell transplantation:** Since such treatments are outside of the scope of this HTA, Roche did not include them. This was done to improve clarity and ensure the MS was concise, as stipulated by NICE's	

		guidelines for submission.	

Misquoting of the Manufacturer Submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
There are some serious misquotations of our MS in the ERG report. On pages 8, 17 and 43 of the ERG report, the following remarks are made of work described on page 116 of the MS: p8: *"The manufacturer decided to broaden the inclusion criteria to include all trials in juvenile arthritis regardless of subtype, despite advice from their clinical experts to the contrary (see MS, page 116). The ERG agrees with the advice from the clinical experts; therefore, trials in children with other types of juvenile arthritis will be ignored in this report."* pgs 16-17 and 43: *"There is no direct evidence presented for these comparators and hence indirect comparisons are made…. For the comparators, the manufacturer decided to broaden the inclusion criteria (see MS, page 116):*	Roche MS, page 116: *"Due to the dearth of clinical evidence in systemic JIA, Roche augmented the dataset with evidence from a rapid review performed with objective to identify all pivotal trials in juvenile arthritis regardless of subtype.* *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.* *The broader population review was not conducted in a systematic way given that evidence from it would not fall within the scope of this submission. Furthermore, and based on clinical expert opinion, evidence from the rapid review would be used only as an alternative to*	The ERG report fails to capture that these two passages were part of the description of a process and are concurrent sentences within a wider section. Roche looked to broaden the search to "JIA regardless of subtype" *due to the dearth of clinical evidence in systemic JIA*. Clinical expert advice was sought to ensure the relevant cautions were taken with this approach. The advice received from clinicians informed how we handled the information retrieved, and it is clear that it was only used due to the extreme lack of other appropriate data.	**NOT A FACTUAL ERROR** The ERG thinks the conclusion should have been that there is insufficient evidence to make these comparisons, but that is a matter of opinion. We checked the quotes, and they are exactly the same as in the MS.

Due to the dearth of clinical evidence in systemic JIA, Roche augmented the dataset with evidence from a rapid review performed with objective to identify all pivotal trials in juvenile arthritis regardless of subtype." *Despite advise from their clinical experts to the contrary (see 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."* The entire passage from Page 116 of our MS is included in the next column for accuracy.	*data found in the systematic review in the absence of other data. The results of non-systemic JIA population trials would require adjustment for the differences in populations."*		

Consideration of clinical characteristics outside of the primary and secondary endpoints

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 18 and 43 of the ERG report state: *"Consideration of the clinical characteristics of sJIA would suggest it could be important to consider outcomes that define lymph node enlargement, hepatomegaly, splenomegaly and serositis"*	Removal of this sentence	In addition to the primary endpoint of the TENDER study, there were 22 secondary and 8 exploratory endpoints as described on pages 63-65 of the MS. Serositis was not one of these and so relevant data are not available. Characterisation of all 31 endpoints in the submission would have been excessive. Moreover, lymph node enlargement, hepatomegaly and splenomegaly were exploratory rather than secondary endpoints of the study. Additionally, Roche did not feel these would be useful outcomes to comment on, as these were not mentioned in the Final Scope and because of the following observation made in the TENDER CSR (made available to the ERG): [redacted]"	**NOT A FACTUAL ERROR** Again, this is a matter of opinion. Background reading suggested these outcomes could be important. The scope does not mention specific adverse events, but this cannot be a justification for not clearly reporting important AEs. The observation mentioned by the manufacturer was on page 241 of a 6699 page document, which was received a few weeks before our deadline, we may have missed this.

Adequate consideration of MAS within the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 18 and 43 of the ERG report state: *"MAS was mentioned within the decision problem therefore it would have been advantageous to present this more clearly within adverse events"*	Removal of this sentence	The incidence of MAS following use with tocilizumab in any trial is included numerous times in the adverse events section (5.9) of the MS. This includes pages 175, 180, 183, 184, 190, and 193. A section on page 193 specifically addresses the occurrence of MAS in patients treated with tocilizumab. Therefore MAS has been adequately and clearly included within this section.	**NOT A FACTUAL ERROR** Again, this is a matter of opinion. The MS is a 400 page document and important outcomes were not easy to find. Therefore, it could have been presented more clearly.

Clarification of clinical markers of disease as compared to adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 17-18 of the ERG report state: *"There were further tables in this section that provided information on AE including death, and macrophage inactivation syndrome (MAS) but not hepatomegaly, splenomegaly, serositis or lymph node enlargement."*	Removal of 'hepatomegaly, splenomegaly, serositis or lymph node enlargement' from this sentence	These are markers of disease activity as highlighted by the ERG on page 18. Therefore would not be characterised under the AE section as such. Please also see comment above on the same subject.	**NOT A FACTUAL ERROR** Hepatomegaly, splenomegaly, serositis and lymph node enlargement were not referred to in this paragraph as adverse events.

Clarification of availability of joint damage, mortality and HRQOL data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 18 and 43 of the ERG report state: *"There were no appropriate outcomes for joint damage, mortality and HRQOL."*	Replace with: 'Appropriate outcomes for joint damage, mortality and HRQOL were not available at this time due to lack of long-term data.'	Clarification that the joint damage, mortality and HRQOL data are not available, rather then they were not submitted as part of the MS. By the nature of these outcomes, extensive long term data are required to adequately describe results.	**NOT A FACTUAL ERROR** The statement in the ERG report is correct: *"There were no appropriate outcomes for joint damage, mortality and HRQOL."*

Datastar (specifically Embase) synonym clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23 of the ERG report states: *"All the Datastar searches would have benefitted from inclusion of more comprehensive text terms and synonyms for both the population and intervention facet; for instance the strategies could have included sJIA as an abbreviation for 'systemic juvenile idiopathic arthritis'. The search could have included several additional intervention terms, such as Roactemra, Atlizumab, Actemra, r-1569, r1569 and the CAS Registry Number (375823-41-9)."*	Modification of this sentence	Whilst we acknowledge there are certain limitations to the search strategy for clinical evidence, the ERG has not recognised the functionality of Datastar. By using EMTREE terms for the Embase searches, synonyms for disease and drug are included. For example whilst the strategy on page 335 for the Embase search uses 'tocilizumab' as a search term, by the functionality of Datastar this also includes the synonyms actemra; actemra-200; atlizumab; r-1569; r1569; roactemra.	**NOT A FACTUAL ERROR** Our statement on page 23 is still factually correct as the manufacturer did not include comprehensive text term synonyms for the intervention or the disease in Datastar strategies. The inclusion of an Emtree term only identified records indexed with that specific Emtree term; Datastar does not include a function to automatically extrapolate Emtree terms into related free-text synonyms, as suggested by the manufacturer in this

			document. The manufacturer appears to be referring to Emtree Indexing scope notes for 'Tocilizumab' which direct the searcher towards the correct term within the controlled Emtree thesaurus. The scope note alerts searchers that Tocilizumab is the correct Emtree term when searching for actemra, atlizumab, etc. Scope notes are not a substitute for free-text searching. The MS Embase search combined Tocilizumab in free-text with Tocilizumab in Emtree, restricted to focus. The ERG tested the MS terms compared to the ERG's suggested terms on 29.6.11 - Embase (1974-2011/06/29). The ERG search statement, using comprehensive text terms and synonyms, retrieved 395 more Embase records, which supports the ERG statement on page 23. Tocilizumab OR Tocilizumab.W..MJ. 714 Tocilizumab.W..DE. OR (Tocilizumab OR Roactemra OR Atlizumab OR Actemra OR 375823-41-9 OR r-1569 OR

			'r1569').AF. 1109

Clarity around non-RCT data presented

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26 of the ERG report states: *"The MS stated that the only non-RCT evidence used was the TENDER trial"*	Replace with: 'The MS stated that the only non-RCT evidence used was the extension phase of the TENDER trial'	This amendment is to allow clarity around the TENDER population and to avoid confusion around the RCT and non-RCT phases of the study.	**NOT A FACTUAL ERROR** The ERG does not think anybody will be confused by this. The TENDER trial is clearly described as an RCT.

Clarity around non-RCT data presented

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32 of the ERG report states: *"Somewhat ironically, the MRA316JP study (Yokota et al. 2008) is excluded from further discussion as the comparator is placebo and the MS states, "as such this study does not address either population in the Decision Problem."* (MS, page 40).	Amendment to sentence to include complete recall of the MS rather than a sentence taken out of the context of the whole paragraph.	This sentence is taken out of context and only partly recalled. The full reasoning on page 40 of the MS is as follows: *"The MRA316JP study (Yokota et al. 2008) has been excluded from further discussion. This is due to the study design and population. The study was initiated with a 6 week open-label led-in phase. Patients with an ACR Pedi 30 response and CRP levels below 5mg/L were then randomised in a double-blind manner to receive either placebo or tocilizumab for a further 12 weeks, with rescue therapy available if necessary. This*	**NOT A FACTUAL ERROR** The statement as such is correct and the ERG report refers to the appropriate section in the MS.

		was followed by an open-label extension period for at least 48 weeks. Methotrexate treatment was not permitted throughout the duration of the study. The comparator was placebo, and as such this study does not address either population in the Decision Problem. *Additionally the MRA316 study was carried out in Japan and so the patient population may not be reflective of a European population."* The ERG further comments (page 35): *"The Yokota trial could not be used in further analysis because it was a withdrawal trial and was therefore too dissimilar to the other trials for further synthesis."* and (page 37) *"The primary endpoint of the Yokota trial was the rate of maintained response, which was found to significantly improve with tocilizumab. JIA ACR 30 outcomes were less useful since all patients responded to tocilizumab during the open label lead in phase, therefore there was a high rate of response*	

		despite large numbers of patients dropping out of the placebo arm due to rescue medication.' Also (page 38) *"The Yokota trial had a 6 week open phase design before commencing the 12 week blinded trial, therefore those patients intolerant to the drug would have dropped out from the trial. This design will bias the results of the outcomes – particularly adverse effects, therefore caution should be used in the analysis of the results."* These comments from the ERG on the Yokota study are consistent with the rational for exclusion of this study in the MS. It is therefore unbalanced to include the sentence out of context as it currently stands.	

Error in baseline characteristics table

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 45 of the ERG report: *Table 4.11: Patient characteristics at baseline for TENDER and ANAJIS trials.*	Currently reads 28 (73.7%). Should read 63 (84%)	Error corrected as per information in the CSR	Agree, this has been corrected. This is "REVISED PAGE 44"

The 11th line which reads: 'DMARD and/or biologic agent no. patients', is incorrect for the all tocilizumab group.			

Systematic review for the cost-effectiveness studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG section 4.1.1.2 (p. 27) and 1st query (p. 28), ERG states that Emtree term 'health economics' also included the related Emtree terms: 'health care costs' 'economic evaluation' etc. and the ERG states that these terms should be redundant.	The relevant search terms were not redundant; different numbers of citations are identified if only one term is included.	The redundancy suggested by the ERG is not reflected in a keyword search (search tested on 22/06/2011 via Datastar). When combining these terms in a key word search, 474,229 citations were identified, whilst using Emtree term "health economics" identified 469,801. Hence, the ERG's suggestion of redundancy among the terms used in Roche's literature search is inaccurate.	**NOT A FACTUAL ERROR** The ERG does not believe this is a factual error. The ERG also tested these terms on Datastar Embase (1974-2011/06/29) on 29.6.11 and found the same number of references retrieved by exploding the Emtree term "Health economics" (470313), as by searching for the combined Emtree terms included in "Health Economics" (470313). This supports the ERG's statement of redundancy on page 28. Health-Economics#.DE. OR Economic-Evaluation#.DE. OR Cost-Benefit-Analysis.DE. OR Cost-Effectiveness-Analysis.DE. OR Cost-Minimization-Analysis.DE. OR Cost-Of-Illness.DE. OR Cost-Utility-Analysis.DE. OR Health-Care-Cost#.DE. OR Drug-Cost.DE. 470313 Health-Economics#.DE. 470313

ERG section 4.1.1.2 3rd query (p. 28), ERG states that MeSH term 'costs and cost analysis' has included terms such as 'cost of illness', introducing redundancy.	The relevant search terms were not redundant; different numbers of citations are identified if only one term is included.	The redundancy suggested by the ERG is not reflected in a keyword search (search tested on 22/06/2011 via Datastar). When combining these terms in a key word search, 161,149 citations were identified, whilst using MeSH term "costs and cost analysis" identified 156,280. Hence, the ERG's suggestion of redundancy among the terms used in Roche's literature search is inaccurate.	**NOT A FACTUAL ERROR** This has already been removed from the report in the latest revision.

Systematic review for the indirect comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG section 4.1.1.1 (page 24 and 1st point ERG queries on p. 25), ERG states that there is a syntax error in the search strategy 'juvenile adj arthritis adj c adj '12').ab.' in the Embase search.	Roche agrees that there is a syntax error and has performed a search with corrected syntax in Embase via Datastar on 12/04/2011.	Roche has performed a search of Embase via Datastar on 12/04/2011 with corrected search terms. The final search result remains the same. The original search strategy retrieved 68 articles and the new search retrieved the same 68 article.	**NOT A FACTUAL ERROR** Our statement on page 24 is factually correct as the manufacturer included a typographical error in the Embase search strategy, which may have impacted on the retrieval of records with 'juvenile arthritis' in abstract.
ERG section 4.1.1.1 (page 24, ERG queries about the inclusion of 'retracted article' as a synonym for randomised controlled trial in the Embase search and 'retraction of publication' and 'retracted publication' in Medline and Medline In-Process.	The RCT filter applied in the MS is derived from a filter used for BMJ clinical evidence (Embase randomised controlled trial strategy and Medline randomised controlled trial strategy). It has included search term of 'retracted article' in Embase and 'retraction of publication' and 'retracted publication' in Medline/Medline In-Process. This filter has been validated and recommended in the Centre for Reviews and Dissemination's RCT filter list, hence it is applied for the search in the MS.	Roche has applied the validated RCT filter which includes the search term for 'retracted article' in Embase, 'retraction of publication' and 'retracted publication' in Medline/Medline In-Process.	**NOT A FACTUAL ERROR** Our statement on page 24 is factually correct. Roche identified the RCT filters as BMJ Clinical Evidence strategies. The ERG contacted the BMJ Information Team for clarification regarding the role of "retracted article" in the RCT search strategies. The BMJ strategies were created to enable regular updates to the Clinical Evidence products. Therefore the inclusion of 'retracted publication' was important within this context, so that the BMJ Team could identify any erroneous references cited in their text, and correct as

			necessary. For this reason, the ERG maintains that the inclusion of 'retracted publication' in the context of the Indirect Comparisions search is not an appropriate synonym for RCT, randomisation or controlled trial. The remaining RCT synonyms are appropriate in this context. Roche appears to have misinterpreted inclusion of a filter in the ISSG Search Filter Resource (SFR) as some form of recommendation or validation by CRD. It is important to note that inclusion of a filter in the ISSG Search Filter Resource, hosted by CRD, does not in any way validate, endorse or recommend the filter. The SFR acts as a signpost to gather together potentially useful filters, however the onus is on the searcher to appraise and determine whether the filter is appropriate to their topic. The ERG contacted the ISSG SFR Editorial Team for clarification (28.6.11) and a statement of clarification will be added to the SFR in the near future.
ERG section 4.1.1.1	Roche has applied the RCT filter used	Roche also sought further information via Embase	Agree, we have amended this.

(p. 24), ERG states that 'conference paper' is not an Embase publication type, hence there is an error in the search term.	for BMJ clinical evidence, which includes 'conference paper' as an Embase publication type.	website: 'conference paper' is actually a publication type in Embase. http://www.embase.com/info/helpfiles/search-forms/advanced-search/advanced-limits/publication-types	
ERG section 4.1.1.1 (p. 24), ERG states that RCT terms in the Medline and Medline In-Process search were restricted to title, abstract and publication type, but the Embase terms were all fields.	The Embase search includes the restriction for title and abstract as well.	In MS Appendix 3 where the database search terms are presented, the RCT filters search were restricted in title, abstract and publication type in all databases.	**NOT A FACTUAL ERROR** This has already been removed from the report in the latest revision.

Comparisons of population 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 3 the ERG describes the following two comparisons for population 1: TCZ alone vs. MTX, and TCZ + MTX vs. MTX	The ERG should revise the comparisons for population 1. Additional scenario analyses as described by the ERG could be performed, however, the base case analysis should consider the treatment as per its marketing authorisation.	Section 6.2.7 of the manufacturer submission template requires the economic evaluation to consider the treatment as per its marketing authorisation. Roche considered the intervention to be used as indicated in its EU Summary of Product Characteristics (SPC). Tocilizumab is administrated by intravenous infusion (IV) as monotherapy or in combination with	**NOT A FACTUAL ERROR** As explained in the ERG report, population 1 includes children who have not been shown to have failed on MTX (the methotrexate naïve population). Otherwise the comparison with MTX makes no sense. Since only 5 children in the TENDER

		methotrexate (MTX). Additional scenario analyses can be performed with different assumptions on concomitant medication. However, the base case should reflect the marketing authorisation as presented in the MS (+/-MTX).	trial were methotrexate naïve, further analyses were not possible in population 1.

Consideration of adverse events in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 5.2.1 page 54 the ERG is inaccurately quoting the justification given by Roche for not including AE	The table should be amended to include that AE estimates were considered but not modelled given that there was not a notable difference across the comparators in population 1 and in population 2 (the latter accepted by the ERG).	The clinical trial study report under section 3.4.4 (AEs with an incidence of >5%) states that the most frequently reported AEs in the TCZ groups were upper respiratory tract infection, headache, nasopharyngitis, and diarrhoea. The most frequently reported AEs in the placebo patients were juvenile arthritis, and pyrexia and most of these events led to escape therapy. The identified adverse events are of minor severity, lasting a short duration, and it can be assumed that they do not have a considerable bearing on the HRQL of patients. With regards to the biologics, a review of comparator safety did not identify any notable differences in serious adverse events with high incidence (over 5%).	**NOT A FACTUAL ERROR** The ERG does not believe this is a factual error. In table 5.3 the ERG only states that adverse events were not modeled, without discussing the justification of the manufacturer and as such, we cannot be inaccurately quoting the MS. If instead the manufacturer refers to table 5.2 we do not see how our statement that “the manufacturer claims no differences in adverse events between treatments” is a misrepresentation of the manufaturer’s text in sections 6.4.8 and 6.5.7.

Adherence of the manufacturer model to conventions in Markov modelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 56 and page 57 the ERG suggests that the MS economic model does not adhere to the conventions of Markov modelling. According to the ERG this conclusion is based on issues related to the definition of the health states: 1. should reflect the absolute health profile of patients (vs. relative) 2. should comprise the full range of conditions 3. should be mutually exclusive The justification provided below these three points on pages 56 and 57 addresses only the first one of these points; no consideration is given to the latter two.	The ERG should revise the sections to justify why the model does not adhere to Markov modelling conventions. A justification should be given for each of the points they make. The section currently includes only a description of the reasons why the ERG would favour a different modelling approach; it does not establish objectively whether the MS model adheres to Markov modelling conventions.	We consider the three points separately: 1. On page 56 the ERG understands the process of the model as one that produces a heterogeneous cohort within a health state. On page 57 the ERG report accepts that the model assumes a homogenous cohort (after MS clarification). The ERG should explain why they state on page 56 that health states should reflect the absolute health state since the manufacturer has clarified the modelling process, and this process is described by the ERG in its report. This description is also repeated on page 80. It is not clear whether the ERG views the MS model health states as reflecting a relative or an absolute state of patients. This should be clarified. 2. The MS model assumes that the CHAQ score reflects the full range of conditions for a sJIA patient. It appears that the ERG also uses CHAQ score to reflect the full range of the patient condition in their suggestion: "*when one wants to define health states based on CHAQ*	**<u>NOT A FACTUAL ERROR</u>** The ERG does not believe a factual error has been made. 1. The ERG has explained that they consider the health states used in the MS to be relative. The manufacturer used to ACR30,50,70 and 90 health states to elicit expert opinion about resource use, and merely assigning the average CHAQ score to each 'state' does not make them absolute, as they do not relate to the real patient level CHAQ scores at 12 weeks. On page 57, the ERG mentions that patients with very different CHAQ score appear as homogeneous by assigning an average CHAQ score. This certainly does not mean that the ERG accepts the assumption of homogeneity. 2. As pointed out in the ERG report, the correct way of using the CHAQ score is to

With regards to the first point, statements made by the ERG are conflicting on pages 56 and 57 and lack justification.		*(...)"* 3. No justification is given as to why the MS health states are not mutually exclusive	define ranges of the score for example 0-0.75; 0.75-1; 1-1.5; >1.5 and to classify the individual patients to each of these 4 health states at t=0 and t=12 weeks, and derive transition probabilities from that. (Note that this is just an example of cut-off points). The purpose of this is to generate health states that are approximately homogeneous with regards to health status, QoL and costs. 3. Not mutually exclusive: Patients within each 'health state' (e.g. ACR50 and ACR90) can have a CHAQ score of e.g. 0.5 or of 2. Thus, patients with different health status can be placed in the same 'state' and patients with similar heath status can be placed in different 'states'. This is not merely a theoretical option, if we look at individual CHAQ scores and response in the clinical study report, this is actually the case.

ERG alternative modelling approach 1: acknowledging patient heterogeneity – related to the above

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 56 and 57 the ERG suggests a different modelling approach which assumes health states defined by clustering CHAQ values. The ERG also describes the health state group as only "appearing" to be homogenous because it is assigned an average value for the CHAQ score. ERG favours an analysis where patient heterogeneity is acknowledged at the start and during the modelling process. It is not clear how the current process (MS model) departs from Markov modelling conventions and how the process would be corrected by implementing the above changes.	The comment should explain how the process would improve the current MS model from one that does not adhere to Markov conventions to one that adheres to them by implementing the suggested changes. It is the manufacturer's view that the suggested improvement (if possible) would acknowledge heterogeneity in the cohort. The comment is not consistent with the principal objections of the ERG to the MS analysis, and this should be clarified.	The process described by the ERG would require a heterogeneity analysis to explore differences in patient outcomes that can be explained based on patient characteristics. Such an analysis was not deemed appropriate given the small patient group and the available evidence. To introduce variability in patient characteristics without such an analysis would produce imprecise results. If, alternatively, variability was introduced based on distributions with parameters that mirror the characteristics of the "average" from the clinical trial; if the simulation is performed correctly, that would yield to the same results as with the MS model. The model is a cohort analysis. In addition to the base-case analysis numerous sensitivity and scenario analyses are run. Some of the analyses take the form of subgroup analysis since they reflect changes to patient characteristics (starting age, starting CHAQ, CHAQ of health states etc.). Roche has the view that, on this occasion and with the available data, the decision maker is better informed on the drivers of the cost-effectiveness in this way, rather than by producing imprecise results based on a weak heterogeneity analysis.	**NOT A FACTUAL ERROR** The ERG does not believe this is a factual error. The modeling approach suggested by the ERG was meant to deal with the issue of the heterogeneity in CHAQ scores of patients with either a ACR30, 50, 70 or 90 response, not to deal with all patient heterogeneity. Thus, the ERG approach would lead to a correct set of health states that can be used for a cohort model. As mentioned earlier, in a cohort analysis, we need health states that are approximately homogeneous with regards to health status, QoL and costs. This is currently not the case, while this would be assured by an approach as suggested by the ERG.

ERG alternative modelling approach 2: ACR response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 57 the ERG does not provide sufficient detail on a suggestion for an alternative modelling method based on ACR score.	Further details should be provided along with the suggestions, if such are made, in order for NICE and the manufacturer to assess their merits and feasibility.	Without enough detail on such suggestions, the report includes comments of alternative methods which cannot be objectively assessed for their merits or their feasibility for implementation.	**NOT A FACTUAL ERROR** The ERG does not believe this is a factual error. The ERG considers it not their task to provide the manufacturer with a list of all possible (better) modeling options. The ERG has here suggested a possible alternative that would include more than just the CHAQ dimension in the description of health state. The purpose was merely to show that the model structure chosen by the manufacturer was not the only possible option. Explaining how to actually weight the different dimensions of the 6 ACR components, and which cut-off points to use for the health states, is not the ERGs obligation. Neither is the assessment whether such approach would be feasible.

Withdrawal and mortality risk

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 69 the ERG report presents as an error the use of a linear survival function and adopts an exponential function with a constant risk of 12.9%.	Roche had considered both approaches but presented the linear function as a base case analysis. Roche agreed in the clarification letter that an exponential function had a slightly better fit.	It is factually incorrect to present Roche's choice of function as an 'error' when this matter had been discussed with the ERG and clearly represents a difference in interpretation rather than an 'error'.	**NOT A FACTUAL ERROR** The ERG does not believe this is a factual error. The manufacturer's choice of function itself is not the error that the ERG discussed but the fact that the manufacturer used the linear function to *estimate a constant withdrawal risk*. This is in fact incorrect. Either a linear function is assumed, and this then leads to an increasing withdrawal risk with time (at t=1 9.5%, at t=5 15% and at t=10 65%), or, alternatively, the exponential function is used, and this leads to a constant withdrawal risk over time. Given that the electronic model uses a constant withdrawal risk, it is clear that the linear function cannot be used and that an error was made.

True N estimates in Dirichlet distributions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 84 the report discusses the Dirichlet distribution parameterisation. The manufacturer analysis is characterized by ERG as not taking into account uncertainty around the adjustments of transition probabilities (indirect comparison and adjustment factors). Moreover, the ERG considers it 'unfortunate' that the model was not made available for review.	The report should clarify how the ERG's approach departs from Roche's approach after the clarification phase. Moreover, the report should clarify what is the downward adjustment on the transition probabilities. Finally, the report should clarify the impact of all those changes to the PSA results.	Roche agreed during the clarification phase to the corrections suggested by the ERG. These corrections had no implications to the results of the PSA. By reviewing page 83 of the report, we identify that ERG performed exactly the same adjustments considering the sample size of the clinical studies. The ERG performed one additional adjustment to transition probabilities (downward adjustment) which is not clarified in the report. During the clarification phase, the ERG requested results from our re-analysis, not the model itself. Should the ERG have requested the models that produced the new results, these would have been made available.	**NOT A FACTUAL ERROR** This issue does not constitute a factual error. The ERG made chances to the parameters of the Dirichlet distribution based on the description given by the manufacturer in their response to the clarification letter. However, since the manufacturer did not provide the revised electronic model *nor* a table showing which inputs had been changed, the ERG could only make a best guess of what was changed by the manufacturer based on their written description. The ERG considers it unfortunate that the manufacturer only presented the output of the revised analysis whilst not presenting the input changes that led to this output. The exact text provided by the manufacturer states: "The model input was changed to reflect the true

			N on which the transition probabilities are based. Please note that for the input related to indirect comparison the N of the original trial of the comparator is assumed. The result of the PSA is presented below with scatterplots and CEAC for both comparisons." From this, the ERG deducted that the uncertainty due to the Prince-adjustment was not taken into account, and this was what the ERG tried to rectify in their analysis. For information, the following sample sizes were used to reflect uncertainty: Tocilizumab N=70, anakinra N=12, biologics N=25