NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultees	Comment	Response
MSD (part of Schering Plough)	The understanding at Schering-Plough Limited, which is now part of Merck Sharp & Dohme Ltd ("MSD"), is that we have been asked to: 1. Provide radiographic outcomes data supporting the recent Type II variation to the product label. 2. Re-present the economic model and results incorporating ACR70 for the DMARD-experienced population 3. Re-present the SF-36 data from GO-FORWARD and a sensitivity analysis in which SF-36 data is included in the economic model using SF-6D and/or mapping approaches to EQ-5D. 4. Present the economic model and clinical and cost-effectiveness results for the TNF inhibitor-experienced population for golimumab compared with tocilizumab with a description of methods. 5. Provide data supporting the level and frequency of dosing of golimumab. 6. Provide any additional long-term outcomes data (HAQ improvement, Maintenance of ACR response) for the DMARD-experienced population. 7. Update on Patient Access Scheme (PAS). 8. Update on recently reported longer term safety data.	The Committee considered the new evidence submitted by MSD. Golimumab is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to conventional DMARDs only if used as described for the TNF inhibitors in TA130 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD section 1.1). Golimumab is also recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, if it is used as described for the other TNF inhibitors in TA195, and the manufacturer provides the 100 mg dose at the same cost as the 50 mg dose (see FAD section 1.2).
MSD (part of Schering Plough)	**1. Radiographic outcomes data from GO-BEFORE (C0524T05) and GO-FORWARD (C0524T06) to support the recent Type II Variation to the SmPC for golimumab** A positive opinion was recently adopted, on 16 December 2010, by the Committee for Medicinal Products for Human Use (CHMP) recommending a variation to the terms of the marketing authorisation for golimumab in Rheumatoid Arthritis (RA). The CHMP adopted a new indication as follows: **"Simponi, in combination with methotrexate (MTX), is indicated for: The treatment of severe, active and progressive rheumatoid arthritis in adult patients not previously treated with MTX.** **Simponi has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with methotrexate".** The extension of the indication to include the reduction in the rate of progression of structural damage is supported by 2-year radiographic data from the GO-BEFORE clinical study and 2-year data on maintenance of improvement in signs and symptoms of disease, physical function and	Comment noted. The Committee discussed the long-term radiographic progression data provided. The Committee considered that these data had shown that golimumab reduced the rate of disease progression (see FAD section 4.10).

Consultees	Comment	Response
	health-related QoL. Comprehensive 2-year safety data supporting the continued positive benefit risk ratio of golimumab were also presented. *Information re: study and approach to measurement* Study outline The GO-BEFORE study (C0524T05) is a 256 week, multi-centre, randomised, double-blind, placebo-controlled trial of golimumab in MTX naïve patients with active RA. The primary objectives were to assess the efficacy of golimumab in MTX naïve patients with active RA as measured by: • Reduction of signs and symptoms at week 24 • Inhibition of progression of structural damage at week 52 • Long term efficacy and safety (unblinded) from week 52 through to week 256 (data up to week 104 included here) Secondary objectives included assessment of the safety of golimumab, the effect of golimumab on physical function and health related quality of life. The study schema is presented below in Figure 1. Radiographic data was collected through week 104. Figure not reproduced here. Approach to measurement of radiographic progression The van der Heijde Modified Sharp score (vdH-S) (van der Heijde et al, 1992, van der Heijde et al, 2005), was used to evaluate reduction of rate of progression of structural damage in the GO-BEFORE study. The vdH-S score is a validated radiographic measure of structural damage progression in RA widely accepted by regulatory authorities and leading academic and community rheumatologists. The vdH-S score is the sum of joint erosion score and joint-space narrowing (JSN) score and ranges from 0-448. Radiographic progression is defined as the change from baseline in total vdH-S score that is greater than the smallest detectable change (SDC). The SDC is defined as the amount of change from baseline for which any score smaller cannot be reliably distinguished from random error in measurement. (Bruynesteyn et al, 2005). In addition to standard measures of structural damage progression and RA signs and symptoms, improvement in physical function was evaluated in GO-BEFORE. This was assessed with HAQ, and phyical component summary (PCS) of SF-36, a validated self-reporting instrument used extensively in a variety of disorders including rheumatologic disorders (Bruce and Fries, 2003;	

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	Ware, 2000). Week 52 Radiographic Analyses. Efficacy was demonstrated in GO-BEFORE for golimumab + MTX compared with MTX alone in reducing the rate of progression of structural damage as measured by the change from baseline in the vdH-S score at Week 52 (golimumab 50 mg + MTX, p = 0.015; golimumab 100 mg + MTX, p = 0.025). Consistent treatment effect was observed across all sensitivity analyses performed and results were consistent across the subpopulations analysed in the study, including patients with longer duration of disease. This data is shown in table 1 below. Table not reproduced here The proportion of patients with no radiographic progression (change from baseline in vdH-S score = 0) was substantial and statistically significant in the golimumab 50 mg + MTX group as compared to the placebo + MTX group. Similar treatment effects for the golimumab + MTX groups were observed for prevention of joint damage as measured by erosion scores. At Week 52, the proportion of subjects with no newly eroded joints was statistically significantly greater in the golimumab 50 mg + MTX group (p = 0.003) than in the placebo + MTX group. The radiographic effects observed at week 52 were maintained through week 104. Two year radiographic data, as well as results from various sensitivity analyses was submitted to the CHMP. The CHMP's overall assessment was reported as "*continue to support a positive effect on progression of structural damage*". In summary, golimumab not only provided significant benefit in signs and symptoms of disease but also showed benefit in reducing the rate of progression of structural damage. The data supports the favourable benefit risk profile of golimumab 50 mg in combination with MTX for patients with moderate to severe RA. GO-FORWARD Data The effect of golimumab treatment on rate of progression of structural damage was also evaluated as a major secondary endpoint at Week 24 in GO-FORWARD (C0524T06) in patients who had active disease despite MTX therapy. There was minimal progression in structural damage in all treatment groups, including the placebo + MTX group, as indicated by the fact that most subjects had no change in vdH-S score at Week 24 and very few subjects progressed beyond the smallest detectable change threshold. There was also minimal progression in structural damage compared with the progression observed in other trials in a similar RA population treated with MTX (e.g. infliximab ATTRACT study; St Clair et al, 2002). Given the minimal radiographic progression in all treatment groups, it is difficult to evaluate the effect of golimumab + MTX on radiographic progression. A number of factors may account for the minimal progression rates in GO-FORWARD, including	

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	the trial design and subject population. The rate of progression of structural damage as measured by the change in the vdH-S score was not a primary endpoint in GO-FORWARD and, therefore, the sample size determination was not based on the expected difference in x-ray progression between groups. In GO-FORWARD had 89 subjects in MTX + golimumab and 133 in MTX. The placebo-control period was short, with placebo subjects crossing over to golimumab at Week 24. This is supported by evidence from GO-BEFORE where most benefits with respect to radiographic progression were seen from weeks 24-52. Also, for subjects who early escaped at Week 16, radiographic imaging was performed at Week 16, reducing the time for progression of structural damage. In addition, the baseline disease activity of subjects in GO-FORWARD was less severe compared with earlier infliximab trials, such as ATTRACT in MTX-experienced subjects. At baseline, the number of tender and swollen joints and the level of inflammation as measured by the median level of CRP were lower than expected. Since activity of disease, including baseline CRP levels, is an important predictor of radiologic progress, it follows that rate of progression, as measured by change in vdH-S-scores, was minimal in the trial. Golimumab has demonstrated treatment benefit on the signs and symptoms of disease in the MTX-failure RA population as demonstrated in GO-FORWARD both by the short-term control of inflammation and the long-term outcomes at Week 104. Given that control of disease activity is the best predictor of radiologic response in patients with RA, the lack of separation in treatment arms in GO-FORWARD is likely a result of the low radiographic progression rate and aspects of the trial design, rather than lack of treatment effect. These results from GO-FORWARD should not contradict the positive radiographic findings of GO-BEFORE, as the primary endpoint of GO-FORWARD was designed to demonstrate efficacy on signs and symptoms rather than radiographic benefit. Given the pathophysiology of RA and mechanism by which structural damage occurs, the GO-BEFORE data is relevant to all RA patient populations, including those for which Simponi is already approved. Based on the above, the CHMP has adopted a positive opinion recommending the granting of a type II variation to the marketing authorisation for golimumab in combination with MTX for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients when the response to disease modifying anti rheumatic drug (DMARD) therapy including MTX has been inadequate. CHMP concluded that in GO-FORWARD there was no difference in terms of progression of structural joint damage between the group originally treated with placebo + MTX, compared with the approved golimumab 50 mg + MTX group. This could be due to the fact that all placebo + MTX patients crossed over golimumab + MTX treatment by week 16 /24. However, based on the results of GO-BEFORE which demonstrated that golimumab reduced the rate of progression of joint damage as measured by X-ray when given in combination with MTX, the CHMP adopted the claim that golimumab reduced the rate of progression for the broader RA	

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	population.	
MSD (part of Schering Plough)	**2. Incorporation of ACR 70 data in the economic model.** The ERG was concerned that the submitted model was not internally consistent and therefore the ICERs provided could not be considered valid. The internal inconsistencies have now been addressed in terms of updated unit costs, anomalies in Markov sheets, and transition probabilities from the Mixed Treatment Comparison (MTC), as follows: • All analyses presented here are based on a model which incorporated the updated unit costs requested by the ERG during the clarification process. • Anomalies highlighted in the Markov sheets have now been amended, including those for etanercept (blank cells), infliximab (costs in the death state) and certolizumab (modelling of HAQ decrements). The baseline HAQ scores in the methotrexate (MTX) experienced population has also been amended and returned to 1.41. • We agree that the model should be based upon the MTC, as per the base case. We have taken into account that those patients achieving a higher response were excluded twice in the formula used to calculate transition probabilities from the MTC. This has been corrected. • The ERG commented that the rate of HAQ progression on palliative care of 0.09 per year was inconsistent with the rate of 0.06 assumed in the TA130 appraisal. We have revised the base case to account for this and all of the following results are based on a HAQ progression on palliative care of 0.06. (For completeness we have also attached the corresponding results using the original HAQ progression on palliative care of 0.09 in Appendix 1). The ERG had raised concerns around the selection of data for the MTC and the meta-analysis. For the MTC, the random effects model has been selected. The ACR70 data included in the updated modelling is derived from an MTC which includes the TEMPO trial. These results are now consistent with those which have been included for ACR20 and ACR50. (The MTC is presented in appendix 2 of this report) (The MTC submitted in response to a clarification question from the ERG earlier in the submission process was a version that excluded the TEMPO study that was not used in our submission.) These corrected results are presented in table 2 below. (Table not reproduced here) In response to the ACD, all additional analyses were inadvertently derived from a model using a meta-analysis as opposed to the MTC. For transparency and completeness, a corrected version of the base case utilising the meta-analysis has been provided in appendix 3. As well as the 52 week radiographic data, 2 year data reporting maintenance of improvement in	Comment noted. The Committee considered the revised version of the economic model and sensitivity analyses that included ACR70 response data and a rate of disease progression while on palliative treatment of 0.06 HAQ score units per year (see FAD section 4.16)

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	signs and symptoms of disease, physical function, and health-related QOL were also submitted in support of the type II variation to the SmPC for golimumab.	
MSD (part of Schering Plough)	**3. SF-36 Data** In the GO-FORWARD study health related quality of life data, as measured by the SF-36, was collected at baseline, Weeks 14, 24, 52 and 104. The results presented below, alongside the 24 week data presented to the committee in response to ACD1, provide strong supportive evidence for the long-term efficacy of golimumab 50 mg (Table 3). The improvement in the placebo + MTX arm from Week 52 onwards is consistent with the cross-over of patients to golimumab at Week 24. Table not reproduced here. **One way sensitivity analysis (OWSA) of SF-36 data** The SF-36 results have been updated and a one way sensitivity analysis provided. SF-36 data from the GO-FORWARD trial has been mapped to SF-6D using the Sheffield algorithm. SF-36 data was not collected in the GO-AFTER study and so ACR70 utilities are assumed equal to the ACR50 utility values. MTX values were estimated by applying the ratio of HAQ scores from the golimumab HAQ scores. The ERG highlighted that ACR state and utility do not move in the same direction. This is a result of the observed HAQ data from the golimumab trial, as in this trial for the golimumab arm baseline patients had higher HAQ values than the Week 24 non-responders, while in the placebo arm the Week 24 non-responders had higher HAQ values than those at baseline. When the HAQ scores were translated into SF-6D this created the differing directions of ACR response and utility observed by the ERG. However, this does not invalidate the results and the SF-6D data still acts to fulfil its role as a sensitivity analysis to provide further evidence for the efficacy and cost-effectiveness of golimumab. The ERG is also satisfied that we have provided conclusive evidence that golimumab + MTX has a significant impact on the physical component of health related quality of life for patients for a DMARD-experienced population. The ERG also commented that a normal distribution for utilities can result in probabilistic sensitivity analysis (PSA) draws of greater than 1. The model has been updated to limit PSA draws that they cannot sample above 1. A version of the model using a beta distribution has also been uploaded. By comparing the results of these two models it can be seen that the PSA is not materially affected by the choice of utility distribution. ICERs were derived from the Sheffield algorithm SF-6D mapped estimates and are shown in table 4 (as stated above, these are based on MTC): Table not reproduced here.	Comment noted. The Committee discussed the long-term SF-36 data submitted and accepted that golimumab in combination with methotrexate had been shown to have a positive benefit on health-related quality of life (see FAD section 4.8). The Committee also discussed the sensitivity analysis submitted using the SF-36 data from the GO-FORWARD study. It noted comments from the ERG about the method used to generate the SF-6D for the methotrexate group and that the ERG was unclear why this approach had been taken. The Committee considered that a more appropriate method for the analysis would have been to use the data from the placebo group directly. However, it concluded that the analysis suggested that the methodology to derive the utility in the base-case analysis had not been shown to be unreasonable (see FAD section 4.13).

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MSD (part of Schering Plough)	**4. Presentation of data for anti-TNF experienced patient population.** To provide clarity on the anti-TNF experienced patient population data, the model presented has been updated with a number of applied changes which have been included as one way sensitivity analyses. For comparison the results are presented in table 5 below with all assumptions equal to base case with the HAQ progression in palliative care updated to 0.06. Changes are applied individually in one way sensitivity analyses in subsequent tables. When adding tocilizumab into the model as a comparator it was necessary to make certain assumptions when deriving a unit cost for this drug. • The SPC states that tocilizumab should be provided intravenously (IV) at a dose of 8 mg for every kilogram the patient weighs once every four weeks. Patient weight was assumed to be 73 kg when costing infliximab in the MTX experienced population, and for consistency, the same weight of 73 kg was assumed when costing tocilizumab in this population. • A dosage of 8 mg per kg for a 73 kg patient requires 584 mg of tocilizumab, which can be provided from vials of 400 mg, 200 mg, or 80 mg. Assuming least possible wastage (although some is necessary), each 584 mg treatment with tocilizumab would require one 400 mg vial and one 200 mg vial at a total cost of £768.00. • The SPC states that tocilizumab should be administered every four weeks. This has also been accounted for, resulting in 7 doses in the first 6 month treatment period and then an average of 6.5 doses per subsequent 6 month period. Final assumptions around costing focus on the levels of monitoring required post 6 months, where the amounts required have again been kept consistent with infliximab as another IV agent. As per the comments of the ERG, abatacept has also been included as a comparator. Abatacept is also administered by intravenous infusion and as such similar assumptions to those required for tocilizumab were needed. • Patient weight and monitoring post 6 months have been kept consistent with those of tocilizumab and infliximab (as similar IV agents). This being the case, a patient weight between 60 kgs and 100 kgs (73 kgs) was assumed, meaning that, as per the SPC, the relevant dosage would be 750 mg requiring 3 vials of abatacept at a total cost of £726.51. • The SPC states that abatacept should be administered in weeks 2 and 4 and then every four weeks, this has also been incorporated, resulting in 7 doses in the first 6 month treatment period and then an average of 6.5 doses per 6 month period. Both tocilizumab and abatacept have been included with a HAQ progression equal to that of anti TNF agents so as to allow a valid comparison.	Comment noted. The Committee discussed the revised analyses submitted for the TNF inhibitor experienced population and noted that these included abatacept and tocilizumab (see FAD section 4.20).

Consultees	Comment	Response
	The following analysis of the TNF-a experienced population has been undertaken using indirect comparison as there is only 1 trial available per technology and only a small number of technologies are being evaluated. (Table not reproduced here) To compare to these base case results, the following section includes a number of OWSAs as requested by the ERG. (Tables not reproduced here)	
MSD (part of Schering Plough)	**5. Dose Selection / Frequency** The selected doses and dosage regimens for the Phase III studies in RA, PsA, and AS were golimumab 50 mg and 100 mg subcutaneously (SC) every 4 weeks. These doses were chosen based on the results of non-clinical studies, a phase II dose-ranging study of golimumab in subjects with RA, as well as clinical experience with infliximab. The phase II RA dose-finding study with golimumab demonstrated clinical efficacy in each of the 4 dose groups (fixed doses of 50 mg and 100 mg, administered SC once fortnightly or once every 4 weeks with MTX). The group receiving the lowest dosage regimen (golimumab 50 mg every 4 weeks) had ACR 20, ACR 50, and ACR 70 responses that were similar to the responses associated with the 3 higher dose regimens, and no clear dose-response relationship was shown between the four doses. Furthermore, golimumab 50 mg every 4 weeks suppressed CRP levels to a degree similar to that observed with infliximab maintenance therapy at 3 mg/kg IV infusion 8 weekly, which is both the lowest approved infliximab dose and considered the minimum effective dosage regimen of infliximab in patients with RA. Thus, these data suggest that golimumab 50 mg every 4 weeks represents the minimum effective dose shown to suppress the inflammatory effects of TNFa. Lower doses would not be expected to provide adequate suppression of CRP levels and would likely result in inferior symptomatic and radiologic outcomes. Higher doses or a shorter frequency did not demonstrate enhanced efficacy in either the Phase IIB studies or in the Phase III studies in RA or PsA therefore the recommended dose is 50 mg once monthly. In both GO-FORWARD and GO-BEFORE, golimumab 50 mg demonstrated efficacy on multiple clinical endpoints. In each study, the magnitude of treatment effect between the golimumab 50 mg or 100 mg was similar supporting that 50mg is the minimally effective dose for RA. The dosing recommendation for RA is golimumab 50 mg given as an SC injection monthly (on the same date each month) with MTX, with self-administration as an available option.	Comment noted. The Committee discussed the dosing frequency of golimumab in response to comments received during consultation. The Committee considered that the data comparing four different doses and schedules of golimumab showed that the dosing regimen of once every 4 weeks had similar ACR response rates to the fortnightly dosing regimen, and that no clear dosage–response relationship was observed. The Committee accepted that the data showed that 50 mg golimumab once every 4 weeks is the minimum effective dosage (see FAD section 4.4).
MSD (part of Schering Plough)	**6. Maintenance of ACR and HAQ Response in GO-FORWARD** The proportion of golimumab + MTX treated subjects who achieved ACR 20, ACR 50, and ACR 70 responses after Week 52 through Week 104 within each treatment group was generally	Comment noted. The Committee discussed the long-term data for ACR response and proportion of people maintaining a HAQ improvement

Consultees	Comment	Response
	maintained. (Tables not reproduced here) For subjects who achieved at least 0.25 improvement in HAQ score from baseline at Week 24, approximately 87% to 92% of subjects across all treatment groups maintained that improvement at Week 104.	equal to or greater than 0.25 in the DMARD-experienced population in the GO-FORWARD trial. The Committee noted limitations to the data, specifically that the trial had a placebo-controlled phase only up to 24 weeks, and included people in the placebo arm who had crossed over to golimumab at week 14 because their disease was inadequately controlled. Despite these limitations the Committee agreed that the data suggested that the efficacy of golimumab was maintained over the long term (see FAD section 4.8).
MSD (part of Schering Plough)	**7. Update on PAS** The PASLU committee met to discuss our PAS for golimumab on 26th January 2011. The final advice document is now being compiled by PASLU and will be sent to us for a final check on 8th February 2011.	Comment noted. The Committee recognised that the patient access scheme has been accepted by the Department of Health (see FAD section 4.14).
MSD (part of Schering Plough)	**8. Safety Data** We have provided data in appendix 5 from an integrated safety summary of all phase III studies of golimumab in patients with RA, PsA and AS. We have also provided rates of discontinuation from study drug related to AEs (appendix 6).	Comment noted. These data were discussed by the Committee but were marked as confidential and could not be reported in the FAD. Based on the evidence submitted, the Committee concluded that golimumab's adverse event profile had not been shown to be different from that of other TNF inhibitors (see FAD section 4.11).
MSD (part of Schering Plough)	Summary In summary, MSD is confident that the modelling results within this document address all of the concerns raised by the ERG and the committee. The radiographic progression data and clinical data such as ACR, HAQ and SF-36 data support the long term efficacy of golimumab in the treatment of patients with rheumatoid arthritis. The dosing recommendation within the Marketing Authorisation, for the indication of RA is golimumab 50 mg given as an SC injection monthly (on the same date each month), with MTX,	Comment noted. The Committee considered the new evidence submitted. Golimumab is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to conventional DMARDs only if used as

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	with self-administration as an available option. Evidence has been provided, based on the 24, 52 and 104-week data presented in this document, which demonstrates robust efficacy for golimumab 50 mg given once monthly for clinical, functional and radiological arthritis-related endpoints over an extended treatment period through 2 years. These data were submitted for review by EMA as part of a type II variation to the Marketing Authorisation which has received positive CHMP opinion. Significant treatment benefit was observed across all arthritis efficacy endpoints, including individual components of ACR response. Substantial treatment benefits for golimumab as related to inhibition of structural damage progression maintained through week 104. Golimumab 50 mg also resulted in significant and clinically meaningful improvements in physical function as measured by HAQ and the SF-36 PCS scores.	described for the TNF inhibitors in TA130 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD section 1.1). Golimumab is also recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, if it is used as described for the other TNF inhibitors in TA195, and the manufacturer provides the 100 mg dose at the same cost as the 50 mg dose (see FAD section 1.2).
Welsh Assembly Government	We have consulted Welsh stakeholders and the Minister would wish to pass on to NICE the views of the Welsh National Specialist Advisory Sub-committee in Rheumatological Medicine to the Welsh Medical Committee.	Comment noted. No action required.
Welsh Assembly Government	**Efficacy** The evidence provided leads me to conclude that Golimumab is as effective as other Anti TNF inhibitors in treating patients who have failed standard disease modifying anti rheumatoid drug therapy (DMARD). I note that the ACR 70 Data is lacking but in clinical practice the ACR 20 and ACR 50 responses are the relevant outcomes for patients who have not responded to first line DMARD treatments. In clinical trials it is the ACR 20 and/or ACR 50 that are used as primary outcomes. The ACR 70 is never used as a primary outcome measure and it is therefore in my view not fair or appropriate to assess the efficacy of Golimumab on ACR 70 responses.	Comment noted. The Committee considered the ACR 20, 50 and 70 response data. It concluded that there was no convincing evidence that golimumab was either more or less effective than the other TNF inhibitors (see FAD section 4.6)
Welsh Assembly Government	**Safety** There is no significant difference in the safety data comparing Golimumab to other currently available anti TNF treatments or biologic agents.	Comment noted. The Committee concluded that golimumab's adverse event profile had not been shown to be different from that of the other TNF inhibitors (see FAD section 4.11).
Welsh Assembly Government	**Clinical Use** Golimumab has some clinical advantages for patients and implications for health resource use. The current approved anti TNF subcutaneous injections require weekly or fortnightly injections. Golimumab is given as a monthly injection. This means that patients who require the injection to be provided for them will need less access to health care resources to	Comments noted. The Committee heard from the clinical specialists and the patient experts that golimumab is administered once per month and this may be an advantage for certain

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	administer the injections and the longer half life of the preparation may also improve the quality of the response to the anti TNF treatment as some patients experience end of dose worsening of their symptoms with the shorter acting weekly or fortnightly preparations. Monthly injections will also be more convenient for patients who travel with their work or going on holiday, as the current anti TNF preparations need be kept refrigerated and this can be very difficult when travelling abroad. The disadvantage of a monthly preparation is that the longer half life is undesirable in patients who stop treatment after the development of an infection, as the immunosuppressive effect of the Anti TNF treatment would persist for longer than the currently available preparations. This disadvantage could be minimised by clinicians excluding patients at high risk of infection.	groups of people. However, the Committee also heard from the clinical specialists that the length of the half-life of golimumab may be a disadvantage if a person needs to stop treatment quickly. The Committee accepted that the once-monthly administration of golimumab may be beneficial for people with rheumatoid arthritis (see FAD section 4.3)
Welsh Assembly Government	**Use after other Anti-TNF preparations** Golimumab is also the only Anti TNF treatment which has robust evidence that it is effective in patients who have had a previous Anti TNF treatment. The 'GO-AFTER' study shows response rates for Golimumab that are superior to placebo and at least equivalent to the response to Rituximab after a previous Anti TNF treatment. This data suggests that Golimumab should be recommended as a third line treatment for patients who have not tolerated or failed Rituximab after a first Anti TNF treatment. At present the other Anti TNF treatments are already recommended for this indication and they have efficacy data which is less impressive than that of Golimumab.	Comment noted. The Committee considered all the evidence submitted, including evidence from the GO-AFTER trial. The Committee considered that golimumab could be recommended as an option in the same manner as the other TNF inhibitors considered in NICE technology appraisal TA195 (See FAD sections 4.7, 4.20).
Department of Health	No comments	Comment noted. No action required
British Health Professionals in Rheumatology (BHPR)	The British Health Professionals in Rheumatology (BHPR) welcome this opportunity to respond to the ACD re Golimumab for the treatment of Rheumatoid Arthritis after failure of previous DMARD drugs. We note the ACD report and its findings and sympathise with the difficult challenges that the NICE appraisal committee constantly faces with undertaking economic modelling that only considers the short term costs and benefits of treatments. We note the following: Provisional recommendations: BHPR noted the comment in 1.4 – the 100mg dosing regime is highly unlikely to be utilised in clinical practice.	Comment noted. No action required The Committee was aware that the proportion of people who receive the

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	The monthly dosing of Golimumab is particularly important as patients generally prefer a less frequent dosing schedule as it enables them to continue working and maintain their financial independence.	100 mg dose of golimumab might be quite small (see FAD section 4.14). The Committee heard from clinical specialists and patients experts regarding the benefits of once-monthly administration of golimumab (see FAD section 4.3)
National Rheumatoid Arthritis Society (NRAS)	Thank you for the opportunity to contribute to the second ACD in respect of Golimumab for the treatment of Rheumatoid Arthritis after the failure of previous disease modifying anti-rheumatic drugs.	Comment noted. No further action.
National Rheumatoid Arthritis Society (NRAS)	We cannot comment on the trial data other than to say that golimumab appears to be as effective and as safe as other Anti-TNF treatments currently in use in the NHS. From a patient perspective, however, its administration is of interest and potential advantage over other TNFs, as a subcutaneous injection once a month as opposed to more frequently than that is likely to be preferable to patients, especially those for whom the prospect of self injecting is difficult and causing anxiety. There is a convenient injector pen and the preparation seems less likely to sting on injection than some other biologics available which may also be a factor which could be of importance to patients.	Comment noted. The Committee concluded that there was no convincing evidence that golimumab was either more or less effective than the other TNF inhibitors (see FAD section 4.6). Comment noted. The Committee heard from clinical specialists and patients experts regarding the benefits of once-monthly administration of golimumab (see FAD section 4.3).
National Rheumatoid Arthritis Society (NRAS)	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We cannot comment on the above, other than to say that golimumab appears to be comparable to other TNFs approved by NICE in terms of clinical and cost effectiveness.	Comment noted. The Committee concluded that there was no convincing evidence that golimumab was either more or less effective than the other TNF inhibitors. The Committee was persuaded that with the patient access scheme golimumab could be considered a cost-effective option for the treatment of rheumatoid arthritis if used in the same way as the other TNF inhibitors

Consultees	Comment	Response
		(see FAD sections 4.6, 4.16 and 4.20).
National Rheumatoid Arthritis Society (NRAS)	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We hope that the Appraisal Committee will reconsider their 'minded not to' recommend interim guidance. Whilst TNFs are generally considered by NICE in a 'class' way, it should be stated that they all work differently and due to the heterogeneity of RA, one cannot assume that because drug A works for one patient that it will automatically work for the next. This is why we need access to the whole range of biologic therapies but have clear starting and stopping rules. Golimumab has been shown to be effective in all its clinical trials and to improve QoL for patients who have failed standard DMARD therapy. We know from BSR Biologics Register data that approx. 30% - 50% of patients will either fail immediately or will ultimately fail on the 4 existing TNF therapies and it is vital that we have other biologic therapies available to treat these patients who, by the nature of their eligibility for TNF in the first place, demonstrates the serious and refractory nature of their disease. Golimumab has been shown to give sustained benefit over the longer term and is a welcome addition to the armamentarium of biologic therapies necessary to treat people with moderate to severe RA. This technology has the advantage of being able to be administered by the patient in their own home once every 4 weeks whereas other subcutaneous TNF options are more frequently administered. Currently for patients who are sero-negative (about 25-30% of all RA patients), Rituximab is a less attractive and less effective option for this group and therefore, golimumab would be a suitable option. It is important that we gain clinical experience with this drug which is less likely to occur unless NICE recommend it for use.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists and the manufacturer's additional analyses. The Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195 (See FAD section 4.16 and 4.20). The Committee heard from patient experts that it is not possible to predict which TNF inhibitor will produce the best effect for each person. The Committee understood that the availability of a range of treatments was valued by clinicians and patients (see FAD section 4.2). The Committee heard from clinical specialists and patient experts regarding the benefits of once-monthly administration of golimumab (see FAD section 4.3).
National Rheumatoid Arthritis Society (NRAS)	Finally we would like to say that the BSR has published a guideline on eligibility criteria to go onto and to stay on biologic therapy which we have contributed to and support. The most important element of these recommendations argues that the current eligibility criteria are set too high and the paper provides the evidence-based arguments for reducing the DAS 28 from the current 5.1 to 3.2 and that the new criteria should be applied to all appropriate first line biological therapies.	Comment noted. The Committee considered the data provided by the manufacturer for the group of patients with a DAS28 of between 3.2 and 5.1. The Committee noted that the analysis for people with moderate

Consultees	Comment	Response
	If NICE approve the use of golimumab, it will provide an important further choice for patients and the professionals who treat us.	and severe disease activity was based on only a small number of people and that it was post-hoc (see FAD section 4.9). On balance the Committee considered that golimumab had been shown to be cost effective is used as the other TNF inhibitor treatments in Technology Appraisals 130 and 195. TA130, TA186 and a part review of of this current topic (that is, the use of golimumab in after the failure of conventional DMARDs only) are due to be reviewed in 2011, the new criteria from the BSR may be considered as part of this review where such evidence is submitted.
Royal College of Nursing (RCN)	The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying antirheumatic drugs. Nurses working in this area of health reviewed the consultation documents on behalf of the RCN. The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) of the technology appraisal of Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying antirheumatic drugs. The RCN's response to the four questions on which comments were requested is set out below:	Comment noted. No action required.
Royal College of Nursing (RCN)	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate? The summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by these patients. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted. The Committee considered all the evidence submitted including that of patient experts and clinical specialists. Golimumab has been considered in the context of current UK clinical practice.
Royal College of	Are the provisional recommendations of the Appraisal Committee sound and do they constitute a	Comment noted. The Committee

Consultees	Comment	Response
Nursing (RCN)	suitable basis for the preparation of guidance to the NHS? Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and note that the committee is not recommending the use of this technology for treatment of people with rheumatoid arthritis. We also note that the Committee has asked the manufacturers for further information on the clinical and cost effectiveness of Golimumab for the treatment of rheumatoid arthritis in some populations. We are looking forward to receiving the Committee's decision after consideration at their next meeting.	considered the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. The Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195 (see FAD sections 4.16 and 4.20).
Royal College of Nursing (RCN)	Are there any equality related issues that need special consideration that are not covered in the ACD? None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	Comment noted. No equality issues were raised during this appraisal.
The Royal College of Pathologists	The Royal College of Pathologists answers to questions posed by the appraisal committee are as follows: • Has all of the relevant evidence been taken into account? Yes • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? No • Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document? No	Comments noted. No action required.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Dr Chris Deighton Clinical Advisor to the NICE RA Management Guidelines	Thank you for asking me to comment on this ACD. My answers to your questions are below. • Has all of the relevant evidence been taken into account? ***Yes*** • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? ***Yes*** • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? ***Yes*** • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? ***No*** • Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document? ***No***	Comments noted. No action required.

Comments received from commentators

Commentators	Comment	Response
Abbott	Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the appraisal of golimumab for the treatment of rheumatoid arthritis in patients who have had an inadequate response to DMARD therapy. Abbott's comments are set out under section headings containing the questions NICE asks stakeholders to comment on for the ACD. Abbott believes there is additional relevant evidence that needs to be taken into account when the Committee makes its final recommendations to the NHS regarding the use of golimumab for patients with rheumatoid arthritis (RA). Although golimumab has been shown to control the signs and symptoms of RA; it has not demonstrated that it inhibits structural joint damage in the same way the other anti-TNFs do. Therefore, Abbott asks that the Committee explores how these findings impact on the assumptions used in the economic modelling.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the Evidence Review Group's critique of the evidence, and the manufacturer's submissions, including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. See responses to

Commentators	Comment	Response
		comments below.
Abbott	**1.1 Lack of radiological progression data for golimumab** In section 3.27 of the ACD, it states that, "*The ERG noted that the manufacturer's original submission did not include any evidence of the effect of golimumab on the radiological progression of rheumatoid arthritis. This outcome measure had been specified in the scope of this appraisal. Evidence on radiological progression was subsequently provided in the form of a research abstract but was marked commercial in confidence."* This abstract was presented at the 2009 American College of Rheumatology Annual Congress in Philadelphia. Results from this abstract showed that there was no significant reduction in disease progression in patients with established RA who had an inadequate response to methotrexate receiving 50mg golimumab plus methotrexate. There was some discussion that the trial population in the GO-FORWARD study seemed to be at a lesser risk of radiographic progression as the baseline characteristics of these patients were less severe than have previously been reported for the other anti-TNF trials; however there was still no difference in the mean change from baseline in the vdH-S score between the 50mg golimumab + methotrexate group and the placebo + methotrexate group at 24 weeks, 0.55 and 0.6, respectively. Conversely, the 24 and 52 week radiographic data from the phase III trials of adalimumab, etanercept and infliximab resulted in the inclusion of specific wording in the licence to reflect this benefit. For example in the therapeutic indication section of the adalimumab SmPC it states: "*Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate"*. There is no such wording in the golimumab SmPC as the manufacturer did not include the radiographic data for golimumab in its regulatory application. Indeed, on page 69 of the EPAR the European Medicines Agency discussed the risk: benefit profile of golimumab for the treatment of RA in DMARD-IR patients and stated that, "*The lack of x-ray data are considered acceptable for a second line indication, since there is sufficient indirect evidence for no deleterious effects on the joints (e.g. data from other anti-TNFα agents, support for a relationship between CRP, tender and swollen joints and radiologic progression)*." Abbott considers that a class effect for anti-TNF agents to prevent structural joint damage cannot be assumed when the evidence for golimumab from the GO-FORWARD trial does not support this. Furthermore, golimumab was not granted a licence for use in methotrexate naïve RA patients. On page 70 of the EPAR the EMA gave the following reasoning, "*Considering the risks with anti-TNF agents, it is not considered justified to add golimumab to MTX in the treatment of treatment naïve RA without evidence of beneficial effects on structural damage. Thus, the lack of x-ray data for*	Comment noted. The data provided by the manufacturer was not the abstract submitted for the 2009 ACR congress. Following consultation on the Appraisal Consultation Document, the manufacturer submitted further long-term radiographic progression data from the GO-BEFORE and GO-FORWARD trials which were considered by the Committee (see FAD section 4.10). The Committee noted that these data had been used to support an extension to the marketing authorisation to state that golimumab in combination with methotrexate reduced the rate of progression of joint damage. At the same time, the marketing authorisation was extended to include treatment of severe, active and progressive rheumatoid arthritis in adults with rheumatoid arthritis not previously treated with methotrexate.

Commentators	Comment	Response
	golimumab is still considered a major shortcoming, particularly taking the somewhat unconvincing data for signs and symptoms with the dose applied for, both at week 24 and week 52, into account." This is in contrast to adalimumab, which has the following wording in the licence based on data from PREMIER: *Humira in combination with methotrexate, is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate* It is widely accepted that conventional DMARDs control the signs and symptoms of RA initially (i.e. tender and swollen and joints), but they do not prevent radiological progression. For example Emery *et al* showed that even ACR20 non-responders receiving adalimumab + MTX had less radiographic progression than the ACR70 responders receiving MTX alone at 26 and 104 weeks. Therefore, although it has been demonstrated that there is a relationship between CRP, tender and swollen joints and radiologic progression for adalimumab, etanercept and infliximab, this relationship hasn't been shown for conventional DMARDs or golimumab. Similarly, radiological progression data from the REFLEX study for rituximab showed no statistically significant difference in the Total Genant-modifed Sharp radiographic score between rituximab + MTX and placebo plus MTX at 24 weeks (p=0.169) Abbott presumes this is why the manufacturer of golimumab assumed a 0.045 HAQ decrement annually for rituximab in the economic model. On page 17 of the Assessment Report, the ERG notes: "*Of particular interest would be the impact of golimumab vs. comparator drugs in terms of radiological progression and the potential impact this may have on the cost-effectiveness estimates were this outcome to be incorporated in the model."* Abbott considers that the impact of radiological progression on the cost-effectiveness estimates can be incorporated in to the model to some extent. Given that physical functioning and disability (as measured by the HAQ) are highly correlated with structural joint damage (section 1.3), it can be argued that the assumption of zero HAQ progression for patients receiving 50mg golimumab + MTX doesn't hold true based on the GO-FORWARD radiological progression data. However, an assumption of zero HAQ progression for adalimumab, etanercept and infliximab is supported by radiographic progression data. Therefore, Abbott suggests it would be appropriate for the economic analyses to be re-run assuming an annual HAQ decrement for golimumab equivalent to that of conventional DMARDs or rituximab, i.e. 0.045. Given that one of the primary drivers for the cost-effectiveness of adalimumab, etanercept and infliximab is their ability to attenuate radiologic progression, resulting in substantial improvement in physical functioning and a reduction in disability in the long-term, it is highly unlikely based on the radiological progression data that golimumab will be cost-effective vs. other anti-TNFs. Furthermore, without this benefit and given its higher cost, it is also unlikely that golimumab will be cost-effective vs. conventional DMARDs.	
Abbott	**1.2 Possible rationale as to why golimumab has not been shown to prevent joint damage**	Comment noted. Golimumab has been appraised within its licensed

Commentators	Comment	Response
	The European Medicines Agency discussed the rationale for the chosen doses of golimumab in the phase III clinical trial programme, 50 mg and 100mg every 4th week. The Agency concluded that the rationale for the choice was "*not fully obvious*" (Page 63 of the EPAR). Abbott suggests that a monthly interval between doses of golimumab is probably too great to maintain tight disease control. This is evidenced by data in the EPAR discussion on serum trough levels of golimumab (outlined below) and data presented to the FDA showing variability of dosing intervals for administration of golimumab. As a consequence patients are not achieving adequate control of their underlying disease, which may explain the lack of data showing that golimumab inhibits radiographic progression in RA. The posology for golimumab states that it should be given once monthly and not once every 4 weeks. This is because although dosing was scheduled at 4-week intervals, a dose window of ± 3 to 7 days was specified in the clinical trial protocol allowing for 30 to 31 day intervals if necessary (EPAR). Data are available from the application to the FDA detailing the proportion of doses of golimumab that were administered every 4 weeks or less (0-28 days). These data indicate that 72% of doses were administered at intervals of 0-28 days, in other words, more frequently than monthly dosing. It is surprising that only 16% of doses were administered between 29-31 days which is the interval which corresponds with monthly dosing as per the licensed dosing regimen. The data are only available for the combined golimumab 50mg and 100mg doses, so it is not possible to assess whether there were any differences between the two doses. What isn't clear from the FDA application is the proportion of patients who had for example 22 or 25 day dose intervals, as this suggests there is considerable uncertainty in the 'correct' dosing interval. Even if a small proportion of patients require a 22 day dose interval before re-treatment, based on the unit price per dose, golimumab will never be a cost-effective option vs. adalimumab or etanercept. On page 19 of the EPAR it discusses the pharmacokinetic data for golimumab. In most golimumab studies, serum concentrations of golimumab were measured using the sandwich ECLIA assay. The lower limit of quantification (LLOQ) of this assay was 200 ng/ml with an MRD (minimum required dilution) of 10, however, the EPAR notes that this limit was not low enough to estimate trough concentrations in all subjects following the administration of 50 mg every 4 weeks (q4w). In other words, even with a very low level of quantification to detect serum concentrations of golimumab, following the administration of 40mg every 4 weeks it was still not possible to detect trough concentrations in some patients. Furthermore, the EPAR notes on page 20 that, "*median serum trough concentrations obtained over longer time periods indicate a tendency toward a decrease over time [up to 52 weeks], which may be related to increased formation of antibodies toward golimumab and possibly an increased risk of inefficacy."* Interestingly, as the LLOQ of the detection assay was not low enough to estimate trough	indication which specifies that it should be given once a month, on the same day each month. The Committee discussed the dosing frequency of golimumab. The Committee noted that the evidence that had been provided by the manufacturer from a phase II dose ranging study (Kay et al.) and it accepted that the data showed that 50 mg golimumab once every 4 weeks is the minimum effective dosage (see FAD section 4.4)

Commentators	Comment	Response
	concentrations in all subjects the observed median values may also be upward biased (EPAR, page 20). This coupled with a tendency toward a decrease over time suggests that serum levels of golimumab are too low when it is administered once every 4 weeks. If in some subjects serum trough levels of golimumab were not detectable following the administration of 50 mg every 4 weeks, it is a concern that an increased interval between doses will have serious implications for disease control. Therefore, if a more frequent dosing regimen was implemented for golimumab, it is possible that the underlying disease would be better controlled, which would be supported by evidence of inhibition of radiological progression. However, such a dosing regimen would have a substantial effect on the cost-effectiveness estimates.	
Abbott	**1.3 Correlation between joint damage measured by X-ray and HAQ** The prevention of radiographic progression has become an important clinical outcome for patients with rheumatoid arthritis in recent years. This is because there is an increasing amount of literature providing evidence for the links between joint damage and disability in RA. Furthermore, studies have demonstrated that inhibition of radiographic progression has a meaningful impact on patients' lives in terms of both HAQ scores and employment status. Scott *et al* conducted a systematic review to evaluate the relationship between joint damage and functional disability in patients with rheumatoid arthritis. Unsurprisingly, the authors found that joint damage and disability both increase throughout the duration of RA. Although disability (as measured by the HAQ score) was correlated with disease duration (correlation coefficients between 0.27 and 0.30), the link between X-ray damage and disability was stronger (correlation coefficients between 0.30 and 0.70). Scott *et al* concluded that joint damage progresses constantly over the first 20 years of RA, and it accounts for approximately 25% of disability in established RA. Furthermore, the link between damage and disability is strongest in established (>8 years) RA. However, avoiding or reducing joint damage in both early and established RA is likely to maintain function. Oedegard *et al* investigated the longitudinal relationship between physical disability, disease activity and radiographic damage over 10 years in patients with rheumatoid arthritis. The authors found that the HAQ score and grip strength were longitudinally associated with the momentary modified Sharp/van der Heijde score as well as with progression in this score, independent of the ESR. Using data from an RCT of etanercept + methotrexate in patients with rheumatoid arthritis, van der Heijde *et al.* found that after adjusting for age, sex and disease activity, both the absolute level of joint damage and the radiographic progression significant determinants of the HAQ score. The authors concluded that patients with greater radiographic damage, and those with recent radiographic progression, have a higher degree of disability. Although the NICE methods Guide to technology Appraisals asks that an NHS perspective is	Following consultation on the Appraisal Consultation Document, the manufacturer submitted long-term radiographic progression data and data from other outcomes which were considered by the Committee (see FAD sections 4.8, 4.10). The Committee considered that these data had shown that golimumab reduced the rate of disease progression and that the effect of golimumab was maintained over time. The Committee concluded that in line with NICE technology appraisals of other TNF inhibitors, it would be appropriate to consider the estimates of cost effectiveness that assumed no disease progression while on treatment with a TNF inhibitor. However, it considered that this assumption was uncertain and may overestimate the benefits of treatment. (see FAD section 4.15)

Commentators	Comment	Response
	adopted, work or employment status is an important and meaningful outcome which impacts on a patient's quality of life. Analysis of data from an RCT of adalimumab + methotrexate in patients with RA found that radiographic progression was significantly correlated with employment status, indicating that this measure of disease has a direct impact on the patient. Figure 1.3 from the van Vollenhoven study shows the relationship between increasing joint damage measured by the Sharp score and the percentage of decreasing odds of gaining/maintaining favourable employment. **Figure 1.3: Relationship between worsening joint damage and the odds of being in employment (not reproduced here)** Therefore, given that there is increasing evidence that radiological progression is associated with worsening physical function, disability, and other meaningful outcome measures such as employment status, Abbott concludes that the assumption of zero HAQ progression for golimumab + MTX used in the economic modelling cannot be supported by the available evidence.	
Abbott	**1.4 Exclusion of ACR70 response rates in the economic modelling** Section 3.39 of the ACD states that, "*The ERG considered that it would have been appropriate to include ACR70 response data in the model so that all the available clinical evidence is used to evaluate golimumab. The manufacturer justified the exclusion of these data by stating that there was not a statistically significant difference between golimumab and the comparators and that incorporating this outcome would only add an element of uncertainty to the model inputs. The ERG noted that this reason was not justified because there was no statistically significant difference in the ACR20 and ACR50 response data for golimumab and the comparators.*" Abbott is in complete agreement with the ERG and the Committee, and welcomes the Appraisal Committee's recommendation in section 1.4 of the ACD that the economic model be revised to include ACR70 data. Given that an ACR20, ACR50 and ACR70 response equates to a 20%, 50% or 70% improvement in the American College of Rheumatology criteria; omitting data relating to the largest improvement of the signs and symptoms of RA underestimates the benefits of the interventions. This is particularly important in the modelling because a patient achieving an ACR70 response will have a greater improvement in their quality of life, and therefore have a higher utility, than those patients achieving only a 50% improvement. The ERG recognised the implications of not including ACR70 response data in the modelling, "*Not including ACR70 responses is likely to have biased the results in favour of golimumab, as golimumab has a lower relative risk estimate than all but one comparator drug [infliximab] although the confidence intervals are wide and overlapping for all interventions*." The confidence intervals	Comment noted. The manufacturer submitted a revised version of the economic model and sensitivity analyses that included ACR70 response data. The Committee considered this evidence when making its decision (see FAD section 4.16, 4.17).

Commentators	Comment	Response
	for the ACR70 response rates are wide because the likelihood of being an ACR70 responder is relatively low compared to that for an ACR20 and ACR50 responder, and therefore there is less precision in the estimate. However, the relative treatment effect for the ACR70 response rates in the MTC for the 50mg golimumab + MTX was still one of the lowest. Furthermore, although there were no statistically significant differences in the ACR20 and ACR50 response rates between golimumab and the comparator anti-TNF agents, response rates for patients receiving 50mg golimumab + MTX were lower than they are for the other anti-TNFs. Abbott suggests that the reason there weren't any statistically significant differences between golimumab and the other interventions is because patient numbers in the golimumab trials are small. Small n numbers in the arms will obviously result in wide confidence intervals for all the golimumab estimates, which in turn will increase the likelihood of them overlapping with the other interventions resulting in non-significant differences. In total, 124 patients (89 patients receiving 50mg golimumab + MTX from GO-FORWARD and 35 receiving 50mg golimumab + MTX from Kay et al) contributed to the estimates of relative treatment effect for golimumab in the MTC. This is in comparison to the 896 RA patients who received 40mg adalimumab either as monotherapy or in combination with a DMARD(s). Therefore, as the ERG noted, excluding ACR70 data for all the interventions because there isn't a statistically significant difference between golimumab and the comparators is not a valid reason.	
Abbott	**1.5 Importance of fatigue, pain, extra-articular disease manifestations, and health related quality of life as outcome measures in RA** In section 3.24 and 3.27 of the ACD it states that, "*The ERG noted that health-related quality of life and fatigue were not adequately addressed in the clinical evidence section of the submission*" and "*The ERG also noted that SF-36 data were not provided in the manufacturer's submission or following a clarification request*", respectively. Fatigue and pain are important characteristics contributing towards the symptoms of rheumatoid arthritis. Data are widely available showing the benefits of adalimumab, etanercept and infliximab to improve all the symptoms of RA, such as pain and fatigue. Given that there is a lack of data showing that golimumab inhibits structural joint damage (discussed in section 1.1), which suggests that a class effect for the efficacy of the anti-TNFs cannot be assumed, then data ought to be provided showing the benefit of golimumab on these outcomes as they are important.	Comment noted. The manufacturer submitted long-term quality of life data following consultation on the ACD and the Committee accepted that golimumab in combination with methotrexate has been shown to have a positive benefit on health-related quality of life compared with placebo (see FAD section 4.8).
Abbott	Abbott considers that the summaries of clinical and cost-effectiveness are broadly reasonable interpretations of the evidence, however there are some issues that the Committee may want to consider when it makes its final recommendations. **2.1 Mixed Treatment Comparison (MTC)**	Comment noted. See responses below

Commentators	Comment	Response
	There are some significant differences in the study characteristics of the studies included in the MTC that may have an impact on the probability of response. The MS states that a random effects model was used to account for these differences. However, there is a misconception that applying a random effects model is all that is required to take account of notable differences in baseline patient characteristics between trials included in the MTC. Sub-sections 2.1.1 to 2.1.3 highlight the differences between the adalimumab and golimumab RA trials as an example, and provide evidence showing the impact these differences have on a given patient's ability to respond. Abbott suggests that meta-regression techniques as documented by Nixon *et al* ought to be used as standard in any evidence synthesis where there are such big differences in the trial populations of the included studies.	Comment noted. The Committee was mindful of the potential heterogeneity between the studies included in the mixed treatment comparison. However, the Committee concluded that there was no convincing evidence that golimumab was either more or less effective than the other TNF inhibitors (see FAD section 4.6).
	2.1.1 Selective inclusion of monotherapy data in the MTC The mixed treatment comparison in the manufacturer's submission (MS) included monotherapy trial data for adalimumab and etanercept; however only data from patients receiving 50mg golimumab in combination with MTX were included in the evidence synthesis, although monotherapy data are available for golimumab. The MS did discuss the inclusion of the monotherapy studies and stated that, "*To investigate the effect of the small group of monotherapy studies, and monotherapy treatment arms on the RR estimate additional fixed- and random-effects meta-analyses were performed. The RR of the monotherapy group versus the original group (all studies) was calculated*." The MS didn't quite present this, and instead presented the pooled RRs for the adalimumab and etanercept studies with and without the monotherapy studies included. Whilst not statistically significantly different, the overall RR when the monotherapy studies were included was lower than the pooled estimate when they were excluded. This is not surprising, given that it has been well documented that biologics + MTX have greater efficacy than biologics alone. The manufacturer justified the inclusion of the monotherapy trials for adalimumab and etanercept because "*there was no statistical difference for all the other anti-TNF agents vs. golimumab*". This has been discussed in section 1.4, and is probably due to the small number of patients contributing towards the relative treatment effect for golimumab. If the monotherapy data for the other anti-TNFs are included in the evidence synthesis, then so should the monotherapy data for golimumab. Furthermore, Korean and Japanese trials evaluating adalimumab in RA patients who have had an inadequate response to DMARDs were included in the MTC, but neither of the two Japanese RA trials evaluating golimumab were. It is not Abbott's intention to provide a set of different treatment effect estimates that should be used in preference to any other, but instead to highlight some inconsistencies. For example in this case, it seems that the application of inclusion criteria in the MTC has been inconsistent for golimumab vs. the other anti-TNFs.	Comment noted. The Committee noted comments received during consultation on the ACD that it was inappropriate to include the TEMPO study and the TNF inhibitor monotherapy studies in the mixed treatment comparison. However, the Committee noted the sensitivity analyses performed by the ERG, which showed that the exclusion of these studies did not significantly alter the estimates of costs effectiveness (see FAD section 4.6)

Commentators	Comment	Response
	2.1.2 Number of previous DMARDs The average number of previous DMARDs used prior to study entry in the two golimumab trials is considerably lower than reported in trials of adalimumab. In the GO-FORWARD trial, around 70-78% patients had not received another DMARD other than methotrexate, meaning that approximately 25% patients had only ever had one DMARD prior to study entry. This is compared to the adalimumab studies in which patients had received on average 2.4, 2.9 and 3.8 DMARDs prior to study entry. It could be argued that patients in the adalimumab studies have more refractory disease as they have failed more DMARDs and are therefore a more difficult to treat patient population. *2.1.3 Average disease duration and impact on magnitude of HAQ improvement* The average duration of disease differs markedly between the two golimumab RA trials and the adalimumab RCTs. Abbott considers that this difference has a considerable impact on the estimates of treatment effect for golimumab and adalimumab, particularly when comparing physical function between the interventions. In GO-FORWARD, the mean duration of RA in the 50mg golimumab + MTX arm was 4.5 (IQR = 2.1 to 9.7); whereas the mean disease duration in the 40mg adalimumab arms of the Keystone *et al*, Weinblatt *et al* and van de Putte *et al.* trials was 11.0 $\pm$ 9.4 years, 12.2 $\pm$ 11.1 years, and 10.6 $\pm$ 6.9 respectively. Therefore in the adalimumab trials, patients had RA for 6-7 years longer than patients in the golimumab trial. This is an important difference in the study populations, as patients who have had disease for longer are likely to have a greater proportion of irreversible joint destruction and therefore the magnitude of HAQ improvement is less for adalimumab than it is for golimumab. This premise is supported by data from Aletaha *et al* Aletaha analysed data from clinical trials of RA to identify reversible and irreversible components of the HAQ. The authors found that the reversibility of HAQ scores decreased with duration of RA. In a separate analysis of 42 RCTs of interventions for RA, Aletaha and colleagues also found that discrimination of functional improvement between active drug groups and placebo is reduced in patients with a longer duration of RA (p=0.02 for the change in discrimination over time). The placebo-adjusted HAQ responses decreased on average by 0.37 per year of RA duration. The authors concluded that responsiveness in HAQ scores is inversely associated with mean disease duration in RA, which impacts assessment of physical function and the ability to discriminate between active treatment and placebo. For this reason caution needs to be exercised when comparing trials with different study characteristics. Given that patients in the adalimumab trials had RA three times longer and failed considerably more DMARDs than subjects in the golimumab trials before initiating a biologic, one would expect that patients receiving golimumab would demonstrate greater HAQ improvements than have been	Comment noted. The Committee was mindful of the potential heterogeneity between the studies included in the mixed treatment comparison. (see FAD section 4.6). Comment noted. The Committee considered the evidence of comparative clinical and cost effectiveness in light of the comments received on the ACD. The Committee was mindful of the potential heterogeneity between the studies included in the mixed treatment comparison. However, the Committee concluded that there was no convincing evidence that golimumab was either more or less effective than the other TNF inhibitors (see FAD section 4.6).

Commentators	Comment	Response
	shown for adalimumab patients. However, even the absolute HAQ improvement in patients with extensive disease duration who have failed multiple DMARDs receiving adalimumab monotherapy are comparable to HAQ changes in the golimumab + MTX GO-FORWARD data. Although the MS only presents the median (IQR) absolute change from the GO-FORWARD trial, and data from the van de Putte adalimumab monotherapy study are presented in terms of the mean ± SD; the absolute HAQ improvement in patients receiving 50mg golimumab + MTX were -0.38 (-0.75—0.13) compared to -0.38 ± 0.60 in the 40mg adalimumab monotherapy group. To conclude, Abbott believes that the most appropriate method for the MTC would have been to use meta-regression techniques in an attempt to explain the differences between the studies by regressing the effect sizes from each study onto the study level characteristics in a similar way to that reported by Nixon *et al*. Abbott believes that had this methodology been used, golimumab would not be cost-effective vs. adalimumab or the other anti-TNFs.	
Abbott	**2.2 Estimation of nurse time required to teach subcutaneous administration** In the manufacturer's submission, the cost of an additional 4 hours of nurse time was added on top of the outpatient visit to train patients to self-administer an anti-TNF. This cost was applied to all the subcutaneous agents: adalimumab, etanercept and golimumab. Abbott contends that this is a gross overestimation of the time taken to train patients to self-administer. In NICE clinical guidelines and costing templates of subcutaneously administered agents, the cost of a one hour training session with a Band 6 nurse has been used routinely for the time taken to train patients to self-administer with an injectable pen. Furthermore, for patients receiving adalimumab nurse training to teach self-injection is provided free of charge as part of the home delivery package.	Comment noted. A one-off specialist nurse visit was assumed to occur at the start of treatment. As indicated in the comment this cost was applied to all of the subcutaneous agents, including golimumab. No changes made to the FAD.
Abbott	The Committee has not made any provisional recommendations for golimumab as a treatment for rheumatoid arthritis in people who have had therapy with conventional DMARDs only, as additional analyses were requested of the manufacturer. However, should the Committee make a positive recommendation for golimumab, it is important that the recommendations are made in the context of the existing NICE guidance for other anti-TNF therapies. For example, TA186 recommends certolizumab pegol only if it "is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130)" Although Abbott appreciates that the scope for this appraisal states that: "if evidence allows, the appraisal will consider subgroups of people defined by the baseline severity of their RA", the existing NICE guidance for adalimumab, etanercept, infliximab and certolizumab pegol restricts their use to patients with a DAS score >5.1. Abbott feels that issues such as expanding the population eligible for anti-TNF therapy to include patients with moderate disease activity would be	Comment noted. The Committee have made recommendations in the context of previous NICE guidance. The Committee concluded that with the patient access scheme golimumab could be considered a cost-effective option for the treatment of rheumatoid arthritis if used in the same way as the other TNF inhibitors (see FAD sections 1.1-1.3, 4.6, 4.16 and 4.20). This current topic is due to be part reviewed alongside technology appraisal guidance TA130 and TA186 in 2011. The guidance

Commentators	Comment	Response
	better dealt with as part of a multiple technology appraisal where all treatments are being assessed together. This approach seems to be particularly appropriate since NICE propose that the guidance on this technology is considered for review together with the review of NICE technology appraisal guidance 130 and 186 in 2011.	relating to the use of golimumb after the failure of another TNF inhibitor will be considered for review with guidance TA195 in June 2013.
Pfizer	Pfizer welcomes the opportunity to comment on the ACD and the evaluation report for golimumab for the treatment of Rheumatoid Arthritis after the failure of previous disease-modifying anti-rheumatic drugs. Overall we agree that the provisional recommendations for golimumab for this indication are sound and are a suitable basis for guidance to the NHS. However, we have some concerns regarding the summaries of clinical and cost effectiveness evidence for the DMARD experienced population considered in the ACD and evaluation report. In particular, our concerns are related to the scope, inclusion/exclusion criteria and the resultant trials considered within the basecase DMARD experienced population meta-analyses/MTC and sensitivity analyses, and also the failure to include ACR 70 response within the economic analyses. These concerns are summarised below: 1. The inclusion of the etanercept Tempo (Klareskog et al 2004) trial in the basecase 2. The addition of monotherapy trial data in the evidence base for comparator TNF inhibitors 3. The inconsistency of the trials included in the ACR 70 response analyses We recognise that the first two concerns have been explored **separately** in sensitivity analyses by the manufacturer. However, we believe that this is insufficient and that the manufacturers' basecase analysis should exclude **both** the TEMPO trial and monotherapy trials from the meta-analysis/MTC, as these trials are likely to be fundamentally different from the other combination therapy trials in this review. The reasons for this rationale are detailed in sections 1 and 2 below. In addition, we have identified a number of issues/errors in our review of the evaluation report and these are summarised in appendix 1, page 3 of our response.	Comment noted. See responses to comments below.
Pfizer	**1. The inclusion of the etanercept Tempo (Klareskog et al 2004) trial in the basecase** Pfizer notes in section 3.18, p.11 of the ACD, that a sensitivity analysis has been undertaken by the manufacturer in their meta-analysis/ MTC in which the TEMPO trial has been excluded. The results of the sensitivity analysis are presented below and show an increased efficacy for etanercept:	The Committee noted comments received during consultation on the ACD that it was inappropriate to include the TEMPO study and the TNF inhibitor monotherapy studies in the mixed treatment comparison. However, the Committee noted the sensitivity analyses performed by the

Commentators	Comment	Response
	'the exclusion of the TEMPO trial resulted in raised relative risks for ACR20 and ACR50, indicating increased efficacy for etanercept in comparison with golimumab. However, these results were statistically significant only in the fixed effects model for the ACR20 response. Exclusion of the TEMPO trial also altered the relative estimates for golimumab in comparison with the other treatments.' (p.11 of the ACD) Whilst we agree with this approach of removing the TEMPO study in this sensitivity analysis, we would recommend that the TEMPO trial is excluded from the basecase analysis as this trial is fundamentally different from all comparator TNF trials in this analysis since patients did not need to have demonstrated an adequate response to methotrexate at baseline. Therefore these patients were more likely to benefit from MTX and as a result the observed placebo response reported in this trial was higher than in other biological DMARD trials. Furthermore, NICE in previous published appraisals for RA treatment (tocilizumab TA198 and certolizumab pegol TA186) has noted that the TEMPO trial was different from other TNF trials because of the unusually high placebo response rate and has requested that it should be excluded from the analysis. Therefore, to be consistent this trial needs to be removed from the analysis.	ERG, which showed that the exclusion of these studies did not significantly alter the estimates of costs effectiveness (see FAD section 4.6)
Pfizer	**2. The addition of monotherapy trial data in the evidence base for comparator TNF inhibitors** From a review of the evaluation report we note that the inclusion criteria for the manufacturer's DMARD experienced population MTC allows for both combination and monotherapy trial data to be synthesised in the evidence base for the comparator TNF inhibitors. We disagree with this approach for the reason that golimumab is not licensed as a monotherapy treatment and therefore comparison of golimumab combination therapy alone versus combined monotherapy and combination therapy data for comparator TNFs leads to a bias in the data considered. Moreover, the addition of monotherapy trials will lead to increased heterogeneity in the trial population and increases the uncertainty of the results produced. Accordingly, we would recommend that the following monotherapy trials are removed from the basecase analysis: • Van der Putte et al [2004], adalimumab • CHANGE, adalimumab • Moreland et al [1999], etanercept	The Committee noted comments received during consultation on the ACD that it was inappropriate to include the TEMPO study and the TNF inhibitor monotherapy studies in the mixed treatment comparison. However, the Committee noted the sensitivity analyses performed by the ERG, which showed that the exclusion of these studies did not significantly alter the estimates of costs effectiveness (see FAD section 4.6)

Commentators	Comment	Response
	Based on this revised inclusion criteria described above we would argue that the monotherapy arm of the etanercept Combe trial can no longer be included in the analysis leaving just the placebo and etanercept plus sulfasalazine arms eligible for inclusion in the meta-analyses/MTC. Furthermore, we realise that the Combe trial meets the inclusion of the scope, but we feel it is important to note that this trial considers the use of etanercept in combination with sulfasalazine which does not reflect the UK licensed indication.	
Pfizer	**3. The inconsistency of the trials included in the ACR 70 response analyses.** Pfizer agrees with the statement section 1.4 that the ACR 70 should be included within the economic analysis. However, we would like to ensure that a consistent approach is taken to generate these estimates within the meta-analyses and MTC. Specifically, we have observed that the ACR70 response data submitted as part of the clarifying questions from the manufacture to the ERG excluded infliximab trial (Maini et al 1998) and the etanercept TEMPO trial from the analyses, which is different from the basecase ACR 20 and 50 response data. Whilst we agree that the TEMPO trial should be removed from all ACR analyses, we would like further clarification why the Maini trial has been removed.	Comment noted. The manufacturer submitted a revised version of the economic model and sensitivity analyses that included ACR70 response data. The Committee considered this evidence when making its decision (see FAD section 4.16 and 4.17).
Roche	The Final Scope for this appraisal (March 2009) listed tocilizumab as one of the comparators for this appraisal. Citing the lack of positive NICE recommendation golimumab's manufacturer has omitted the majority of data for tocilizumab. Tocilizumab has now been appraised by NICE (TA 198) and recommended in TNF-IR where rituximab and/or methotrexate is contraindicated and for patients that have responded inadequately to rituximab. Four well designed phase III RCTs provide a wealth of relevant, to this submission, data in both DMARD-IR and TNF-IR. It is therefore appropriate that any indirect comparisons of golimumab with other biologics in the DMARD-IR setting, should include tocilizumab to increase the precision of the MTC estimates. Trials that should be taken into account include LITHE, OPTION and TOWARD (summary results of which are found in the tocilizumab Summary of Product Characteristics and Full Guidance). In the TNF-IR setting the RADIATE trial should be included in the MTC that will provide an appropriate assessment of the relative effectiveness of golimumab in this setting.	Comment noted. The Committee discussed the revised analyses submitted by the manufacturer and noted that these included abatacept and tocilizumab (see FAD section 4.20).
Roche	**<u>Golimumab's licence in the treatment post aTNF treatment</u>** Roche believe that the ACD should reflect the fact that golimumab is <u>not</u> licensed for use after the failure of a TNF inhibitor, that is to say, not recommended in sequential use, in RA.	Comment noted. Following comments received during consultation regarding the marketing authorisation for golimumab, the manufacturer was asked to confirm whether the

Commentators	Comment	Response
	Roche understand that the manufacturers applied to the EMEA for the following indication for RA: "Simponi can be used in patients previously treated with one or more TNF inhibitor(s)." However, this part of the indication was rejected by the EMEA, so there is no licence for use of golimumab in TNF-experienced patients and therefore no justification for considering golimumab in this part of the RA treatment pathway.	marketing authorisation for golimumab includes people who have had previous therapy with a TNF inhibitor. The manufacturer stated that golimumab was approved on the basis of the GO-FORWARD and GO-AFTER studies and that its use in people who have had previous therapy with a TNF inhibitor is consistent with the marketing authorisation and the evidence. The Committee concluded that the two positions in the treatment pathway as included in the manufacturer's submission were appropriate to be considered in this appraisal (see FAD section 4.4)
Roche	**Rituximab efficacy in TNF-IR:** ACD section 3.35 "rituximab was dominated by golimumab because golimumab was both less costly and more effective than rituximab". However, on the contrary, and in agreement with the ERG comments in the ACD, Roche believe that rituximab is clearly more effective and less costly than golimumab in the TNF-experienced population. ACR responses at 24 weeks (the standard primary end-point in RA trials) clearly show that rituximab is more effective than golimumab in a TNF-experienced RA population. The chart and table below demonstrate the data from the REFLEX and GO-AFTER trials, showing the difference in ACR responses (active minus placebo) at 24 weeks in a TNF-experienced population. For clarity, the original ACR responses are also shown in the table below (Figure and table not reproduced here)	Comment noted. The Committee agreed that the ERG's amendments to increase the time between treatment intervals for rituximab and remove the assumption of a differential rate of underlying progression of disease were appropriate. The Committee noted that when these assumptions were changed rituximab was associated with lower costs and more QALYs than golimumab (see FAD sections 4.17, 4.18, 4.19).
Roche	**<u>Cost of rituximab</u>** The costs of rituximab quoted in the MS were also commented on in sections 3.35 and 3.36 of the ACD:	Comment noted. The Committee discussed the results of the manufacturer's base-case analysis in the original submission and the ERG's exploratory analyses for the

Commentators	Comment	Response
	ACD section 3.35: *"The results for the deterministic base-case analysis of golimumab in a TNF inhibitor-experienced population show that rituximab is dominated by golimumab because golimumab is less costly and more effective (£31 fewer costs and 0.189 additional QALYs)."* **ACD section 3.36:** *"The results from the probabilistic sensitivity analysis show that in the TNF inhibitor-experienced population, rituximab is extendedly dominated by golimumab based on the mean costs and QALYs"* Roche believe that this is an unsound conclusion, and believe that the MS has used incorrect assumptions around the time to re-treatment of rituximab in both the 1st and subsequent courses of treatment , thus increasing the cost of rituximab (section 3.40). Roche's belief is further validated by the ERG comments in the ACD (section 3.40): **ACD Section 3.40:** *"The ERG also commented that the model assumes that rituximab is re-administered every 6 months but it considered that 9 months would be more reflective of current clinical practice."* Roche has demonstrated previously (TA195) that the frequency of administration of rituximab is consistently around 9 months (Rituximab SmPC). Several sources were utilised to determine the cost of rituximab. The latest market research data suggested that rituximab was given every 8.7 months on average (GfK HealthCare, a sample of 80 rheumatology clinicians in the UK). A further analysis of extension trial re-treatment data indicated that the time between treatments may be even greater; the mean time to re-treatment, taken from an extension study was 11.6 months (Roche analysis provided in original submission for TA195). Two resource use studies also provided data in "real-life" settings, to substantiate these figures. The initial study, a single Centre study at the Norfolk and Norwich University Hospital NHS Trust, showed, in a retrospective analysis, that the mean time between the first and second rituximab cycles for patients initiated on rituximab was 10.5 months (range 4.7–17.3 months), (Somerville et al., BSR 2008). A repeat of this study in 3 centres showed a similar magnitude of response, with the time to repeat treatment being 43 weeks (range 15-84 weeks), Data on file.	group of people who have had previous treatment with both conventional DMARDs and a TNF inhibitor, which compared golimumab with rituximab. It agreed that the ERG's amendments to increase the time between treatment intervals for rituximab and remove the assumption of a differential rate of underlying progression of disease were appropriate (see FAD sections 4.17, 4.19).

Commentators	Comment	Response
	Based on all the above evidence submitted as part of the Roche submission for the MTA of treatments after the failure of one aTNF, Roche has estimated the annual cost of rituximab to be £4,817 per patients (average over 4 years).	
Roche	**Rituximab HAQ progression whilst on treatment** Roche is unclear on the evidence base used by the manufacturer of golimumab to support the long term HAQ progression of the various treatments. With respect to rituximab Roche has provided long-term data of HAQ progression while on treatment as part of the MTA (TA 195). These data (figure below) clearly demonstrate that patients show no progression while on rituximab therapy. The assumption used in the model is biasing the overall treatment efficacy comparison in favour of golimumab. (Figure not reproduced here)	Comment noted. The Committee discussed the progression of disease while on treatment. It noted that the manufacturer had assumed that the TNF inhibitors all stop progression of disease while on treatment, but that for rituximab it was assumed that the disease continues to worsen while on treatment by an increase of 0.045 per year in HAQ score (the same as the rate used for conventional DMARDs). The Committee heard from the ERG and clinical specialists that this underestimates the benefits of rituximab, and that it would have been more appropriate to assume that, for people whose disease responds to treatment, rituximab reduces the progression of disease to the same extent as the TNF inhibitors (see FAD sections 4.18, 4.19).
UCB	**Non inclusion of ACR 70 data from trials** Detail ACR 70 data has not been included in the model built by S-P and this is used as the justification for not doing the work required by the ERG. The committee has asked for this work to be done Issue ACR 70 is effective remission and as such is not a trivial outcome indicator, but central to patient response. The non inclusion of S-P GoForward data – and the data of comparators can favour the relative outcome for golimumab. The incremental QALY gain may be changed if this data is not considered UCB comment and request The response of TNFs, whilst similar, is not identical – certolizumab has a more rapid response	Comment noted. The manufacturer submitted a revised version of the economic model and sensitivity analyses that included ACR70 response data. The Committee considered this evidence when making its decision (see FAD sections 4.16 and 4.17).

Commentators	Comment	Response
	that other TNFs for example. In order that clinicians understand which TNFs can benefit which patients groups most we need a comprehensive set of comparators. Only having comparators for ACR20 and ACR50 and not ACR70 will prevent a clear understanding of which agents have the best chance of providing remission.	
UCB	**Non inclusion of SF-36 and mapping toEQ-5D** Detail SF-36 data has been collected as part of the trials and we assume, can be mapped to EQ-5D in order to assess utility in the economic model. Issue Relying on the conversion of ACR to HAQ through one algorithm and then to EQ-5D using another algorithm in the model introduces multiple uncertainties into the model. UCB comment and request The chosen utility measures in the NICE reference case are quality of life measures such as EQ-5D and SF-36. Many manufacturers have measured these outcomes (Roche and UCB both measured ED-5D as health gain measures in their trials) and where possible this should be the starting point for measuring health gain rather than a mix of HAQ, DAS, ACR, EQ-5D and SF-36 which we currently have.	Comment noted. The Committee discussed the sensitivity analysis submitted by the manufacturer following the consultation on the consultation appraisal document, using the SF-36 data from the GO-FORWARD study. The Committee concluded that the analysis suggested that the methodology to derive the utility in the base-case analysis had not been shown to be unreasonable (see FAD section 4.13).
UCB	**HAQ progression on palliative care set at 0.09** Detail Manufacturers have chosen an odd figure for the progression of patients on palliative care. Other submissions (TA130, TA126, TA186) – have used 0.06 as forward deterioration. Issue As the measures are incremental if the comparator number for palliative care is set high (i.e 0.09 rather than 0.06) it will exaggerate the treatment effect from the TNF. If the results are marginal it may make the product seem cost effective. UCB comment and request The 0.06 progression on palliative care has been a consistent level set through the previous STAs. To use a different measure now – 0.09 – is not logical or consistent and may result in the overestimation of the treatment effect gain from golimumab. We ask that the 0.06 figure for progression on palliative care is used in the model.	Comment noted. The Committee discussed the revised version of the economic model and sensitivity analyses submitted by the manufacturer that included a rate of disease progression while on palliative treatment of 0.06 HAQ score units per year (see FAD section 4.16).
UCB	**Section 3.23 - 30% of the population appear to only have received MTX – so one DMARD** Detail Section 3.23 of the ACD suggest that the population reflects that of the treatment group. However	Comments noted. The Committee considered the evidence of comparative clinical and cost effectiveness in light of the comments

Commentators	Comment	Response
	it appears that only 70% of patients in the GoForward trial have used two DMARDs in previous therapy. Issue If only 70% of the population have had two DMARDs then it is likely that the treatment effect of DMARD therapy has not been optimised. If this is the case then the benefit gained by golimumab may be over-estimated. UCB comment and request The trial populations in TNF treatments will always have an element of heterogeneity. A common challenge is finding patients who have optimised DMARD treatment. It appears that a proportion of the golimumab DMARD failure population were not optimised on two DMARDS before TNF therapy. It should be possible to sub-analyse the patients in GoForward to look at the ACR response in the group that has had two DMARDs compared to those who have only had one. We ask that a sub analysis of GoForward is carried out between the one and two DMARD group	received on the ACD. The Committee was mindful of the potential heterogeneity between the studies included in the mixed treatment comparison. However, the Committee concluded that there was no convincing evidence that golimumab was either more or less effective than the other TNF inhibitors (see FAD section 4.6).
UCB	**Section 3.26 – CZP trials "stopping at week 12"** Detail The ERG is making the case that comparing trials in biologics is complex (which it is) and uses the example of certolizumab where there is a high level of ACR response and speculates this is because failures are removed at wk12. Issue TNF response is variable. Our phase III trials for certolizumab (RAPID 1and 2) gave a very strong treatment effect, with a low placebo response. The ERG have incorrectly assumed we removed active arm non responders at week 12. This is not the case and removal was at week 16, as with the GoForward trial. UCB comment and request We need to ensure that this point is well understood. All patients remained in the trial on active, or placebo until week 16, at which point non responders entered into open label active follow up. It is possible to compare the week 14 and week 16 performance of both TNFs	Comments noted. The ERG report is an independent document, NICE does not respond to comments made on the ERG report. No further action.
UCB	**Non inclusion of bone data** Detail The has been no initial inclusion of bone data in the primary submission. It was provided as an abstract – under commercial in confidence – in follow up questions Issue One of the main treatment benefits for the TNF class is the prevention of further joint degradation – particularly as there is a much later use of TNFs here in the UK than in other developed health	Comment noted. Following consultation on the Appraisal Consultation Document, the manufacturer submitted long-term radiographic progression data which was considered by the Committee (see FAD section 4.10).

Commentators	Comment	Response
	economies. Others manufacturers have shown this outcome. In addition is seems that the bone benefits can only be gained at a higher dose level – as the published abstract only shows benefit with the higher dose. UCB comment and request Prevention of the progression of bone loss under treatment with TNF inhibitors is one of the key benefits of this class. The data redacted from the report is available in other areas and if correct does not show effectiveness in the 50mg dose which is a key issue for the cost effectiveness of golimumab particularly when compared with other treatments. We request that this information is included in the submission and that the cost structure in the model reflects a high use of 100mg dosing in the trials.	
UCB	**Injection site event risk (table 30 on page 93 ERG)** Detail The ERG report states that the injection site reactions with golimumab are significantly lower than with certolizumab Issue The injection site response for certolizumab was essentially similar to placebo. The manufacturer has compared between trials when it should be the response compared to placebo that is considered. UCB comment and request We question the analysis carried out on injection site reactions and the statement on page 96 that golimumab had significantly fewer injection site reactions that certolizumab and ask that this is reviewed. We do not believe that it is possible to compare between different trial structures and arrive at this conclusion.	Comments noted. The ERG report is an independent document, NICE does not respond to comments made on the ERG report. No further action.
UCB	**Non inclusion of Kay trial in MTC (ERG pg 121)** Detail Kay trial was not included in the MTC that provided point estimates for the economic model Issue The Kay trial was an early stage trial and provides extra patient outcome evidence for golimumab. It has not been included in the MTC that is used to inform the cost effectiveness model. It may cause increased uncertainty on the outcomes with golimumab if relevant data is not included UCB comment and request There are arms of the Kay trial that are the same as the licensed indication and regimen and an MTC that includes a meta-analysis using the Kay data in addition to the GoForward trials will provide additional certainty on the effectiveness of the treatment. We has that an MTC with the	Comments noted. The Evidence Review Group provided an exploratory sensitivity analysis that included the Kay et al study in the mixed treatment comparison. This analysis reported similar estimates of cost effectiveness to those in the manufacturer's base case (See FAD section 3.44).

Commentators	Comment	Response
	relevant Kay data is provided. This approach was taken with certolizumab where we were asked to include the outcome data from a small early phase III trial.	

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	Appraisal Committee's preliminary recommendations	NHSBA agrees with the preliminary recommendation. This technology is not affordable and were NICE to change its preliminary view we would have no option but to reduce investment elsewhere in the rheumatology spend - undoubtedly this would be in more cost effective areas of spend, thus leading to a net social loss of health. This would be neither palatable or popular.	Comment noted. The manufacturer provided additional analyses as requested by NICE. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195 (see FAD sections 4.16 and 4.20).
NHS Professional 1	The technology	There may be a problem with dose escalation. The likely weight distribution of the population to be treated should be incorporated into the model as should assumptions about dose escalation if there is no initial response to the standard dose of golimumab There were limitations to the quality of the research: Small short term RCTs of golimumab with methotrexate against placebo and methotrexate were combined in a mixed treatment analysis. Considerable uncertainties remain around the point estimates of effect and the evidence base is not considered 'sufficient' to inform these decisions. The long term adverse effects of golimumab have not been adequately studied.	Comment noted. NICE appraises technologies within their licensed indications. The marketing authorisation for golimumab specifies that the dose is increased only in those people who weigh over 100kg who do not respond to the 50mg dose. The manufacturer proposed a patient access scheme that would provide the 100 mg dose at the same cost as the 50 mg dose in people for whom the higher dose is suitable (see FAD section 4.14). The Committee concluded that golimumab's adverse event profile

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
			had not been shown to be different from that of the other TNF inhibitors (see FAD section 4.11).
NHS Professional 1	Manufacturer's submission	The committees minded not to consider for a number of the indications gives the message that the manufacturer will be invited to resubmit an economic model. It is likely this will simply skirt round, and try to obscure, the main issue - the drug is too expensive and gives too little health gain to justify a positive recommendation. Either the indication needs to be tightened considerably to those who truly do have much greater capacity to gain, or the cost needs to be reduced - substantially. on the basis of the data reviewed, this drug seems no more effective than other TNFs, and on the basis of this it would seem that RTX is the drug of choice following failure of other TNF and that there is no convincing evidence that golimumab can be recommended for funding. In the absence of head to head trials, a mixed treatment analysis was required to assess comparative effectiveness of the TNF inhibitors. outcomes, ACR responses (ACR20 etc) were measured over a relatively short term, 14 and 24 weeks. The wide credibility intervals around the estimates of effect in the mixed treatment analysis suggest that there is considerable uncertainty about the effectiveness of this drug	The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the critique by the Evidence Review Group and the manufacturer's submissions, including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no TA130 and TA195 (see FAD sections 4.16 and 4.20).
NHS Professional 1	Consideration of the evidence	We agree with the committee in the suggestion that the manufacturer's cost effectiveness model overestimated the cost of rituximab as it suggested that rituximab is re-administered every 6 months rather than every 9 months as is current practice (confirmed by clinicians). We are not in agreement with the manufacturers assumptions about rate of disease progression when on the different therapies considered. The manufacturer had suggested that disease continued to progress on rituximab but not on TNF inhibitors this is patently not the case. The clinically most preferred measure of therapeutic response was not considered. The ACR70 response is preferred by clinicians as an indication of the degree of therapeutic effect. Its omission from the model would favour golimumab. SF-36 data was available but not included in the manufacturer's model. The more indirect methods actually used by the manufacturer (deriving utilities from the ACR response, converting these to a change in HAQ score and then mapping them to EQ-5D) do not seem a sufficient basis for valuing patient utility.	Comment noted. The Committee agreed that the ERG's amendments to increase the time between treatment intervals for rituximab and remove the assumption of a differential rate of underlying progression of disease were appropriate. The Committee noted that when these assumptions were changed rituximab was associated with lower costs and more QALYs than golimumab (see FAD section 4.19).
NHS Professional 1	Implementation	Our view is that it is disingenuous for the manufacturer to seek to create a market for this drug (by giving it away for free) pre a NICE TA recommendation.	Comment noted. No further action.

Role*	Section	Comment	Response
		Commissioners may take a dim view of this strategy of "compassionate use" and seek to disagree with a recommendation that "patients currently being treated should continue till clinician feels it appropriate to stop". This is essentially putting commissioners in an impossible position and will inevitably lead to reductions in funding elsewhere in the rheumatology programme.	
NHS Professional 2	Appraisal Committee's preliminary recommendations	I fully agree with the current recommendations proposed within this ACD until such a time as the specified questions within the document are answered. As stated within this guidance it is actually rather difficult to comment on whether Golimumab is cost effective in situations under points one and three until we have the answer to the questions that NICE raised. This relates in particular to how many patients would be expected to have doses higher than 50mg due to inefficacy and being over 100kg in weight. Thus PCTs should have full opportunity to respond to the revised ACD once this information becomes available.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the critique by the evidence review group and the manufacturer's submissions, including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195 (see FAD sections 4.16 and 4.20).
NHS Professional 2	Consideration of the evidence	I agree with the proposal under indication 2 i.e. that there is insufficient evidence of superiority over Rituximab to suggest it should be used when Rituximab would otherwise be indicated in patients who did not respond to an anti-TNF. Rituximab is more cost effective.	Comment noted. No further action
NHS Professional 2	Implementation	There was no evidence within the ACD that suggested Golimumab is superior to any current treatments available. I feel it would be appropriate for NICE to produce a clinical algorithm of first, second and third line use of these drugs based on clinical efficacy and cost effectiveness rather than just adding yet another option for consultants to choose. In this way, national NHS resources would be utilised more effectively and the manufacturers may respond by adjusting prices in response to the differing market trends.	Comment noted. The Committee have made the recommendation in the context of previous NICE guidance (see FAD section 1.1). In addition, this current topic is due to be part reviewed alongside technology appraisal guidance 130 and TA186 in 2011.
NHS	The technology	For patients who weigh more than 100kg an increase to 100mg is permitted - the model should be adjusted to include the proportion of people likely to need this	Comment noted. The Committee noted that the manufacturer did not

Role*	Section	Comment	Response
Professional 3		higher dose. If the acquisition cost is included in the model the ICER for golimumab would be higher than that estimated in the base-case presented by the manufacturer.	submit any additional data regarding the 100 mg dose, but instead proposed a patient access scheme that would provide the 100 mg dose at the same cost as the 50 mg dose in people for whom the higher dose is suitable. The Committee recognised that the patient access scheme has been accepted by the Department of Health and therefore concluded that with the patient access scheme, the manufacturer's analysis including only the costs of the 50 mg dose could be used as a basis for decision making (see FAD section 4.14).
NHS Professional 3	Manufacturer's submission	This technology is not a cost effective use of NHS resources for indication 2. ERG conducted exploratory analyses for those with previous treatment with both conventional DMARDs and a TNF inhibitor. These compared golimumab with rituximab. ERG modifications to manufacturer's model appropriately remove assumption that disease progresses at a faster rate on rituximab compared with TNF inhibitors. This overturns manufacturer's first model therefore the position changes so that rituximab is associated with fewer costs and more QALYs than golimumab (ie. rituximab dominates golimumab). Rituximab, currently approved for treatment of RA after failure of a first TNF inhibitor, is therefore likely to be both a cost effective alternative to golimumab and more affordable for PCTs (lower overall cost per head).Rituximab is likely to be both a cost effective alternative to golimumab and more affordable for PCTs (lower overall cost per head). The long term adverse effects of golimumab not known.	Comment noted. The Committee agreed that the ERG's amendments to increase the time between treatment intervals for rituximab and remove the assumption of a differential rate of underlying progression of disease were appropriate. The Committee noted that when these assumptions were changed rituximab was associated with lower costs and more QALYs than golimumab. The Committee concluded that golimumab could not be considered a cost effective use of NHS resources in situations where rituximab is an appropriate treatment option (see FAD section 4.19). The Committee concluded that golimumab's adverse event profile had not been shown to be different from that of the other TNF inhibitors

Role*	Section	Comment	Response
			(see FAD section 4.11).
NHS Professional 3	Consideration of the evidence	Golimumab is no more effective than the other TNF inhibitors. The clinical trials giving the direct evidence for effectiveness of golimumab plus methotrexate versus placebo plus methotrexate were small. The wide credibility intervals around the estimates of effect in the mixed treatment analysis suggest that there is considerable uncertainty surrounding the estimates. The clarifications required could have major effects on the output from the model. Requests have been made for further information regarding the first and third indications. These are unlikely to show golimumab is more cost effective than alternatives but PCTS will need an opportunity to check this and comment again if needed. Without this data there is insufficient evidence to say whether golimumab is or is not a cost effective use of NHS resources for indication 1 and 3.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the critique by the evidence review group and the manufacturer's submissions, including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195 (see FAD sections 4.16 and 4.20).
NHS Professional 4	Appraisal Committee's preliminary recommendations	We agree with the ACD: Golimumab should not be recommended for the treatment of rheumatoid arthritis in people who have had therapy with a TNF inhibitor and for whom rituximab is appropriate. We agree that further information should be requested from the manufacturer and that these clarifications could have major effects on the output from the model for the first and third indications. Without this data there is insufficient evidence to say whether golimumab is or is not a cost effective use of NHS resources for these indications. PCTs should have the opportunity to comment when this evidence is available. As it stands we agree that golimumab should not be recommended for the first and third indications listed.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the critique by the evidence review group and the manufacturer's submissions, including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195 (see FAD sections 4.16 and 4.20).

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NHS Professional 4	The technology	Golimumab is another anti-TNF inhibitor –it has not got a markedly different mechanism of action to the 4 anti-TNFs already licensed and approved by NICE. It has similar contra indications and cautions so would not allow different patient groups to be treated e.g. patients with co-existing moderate to severe heart failure. The recommended dose is 50 mg given once a month. The SPC states that in people who weigh more than 100 kg whose rheumatoid arthritis does not show an adequate clinical response after three or four doses, the dose of golimumab may be increased to 100 mg once a month. The manufacturer's submission states that the cost of golimumab is £774.58 for a 50 mg pre-filled injection pen, and estimates an annual cost of £9294.96. People taking the 100mg dose would incur twice the annual cost and it is not clear how many would do so.	Comment noted. The Committee noted that following consultation on the appraisal consultation document, the manufacturer did not submit any additional data regarding the 100 mg dose, but instead proposed a patient access scheme what would provide the 100 mg dose at the same cost as the 50 mg dose in people for whom the higher dose is suitable. The Committee recognised that the patient access scheme has been accepted by the Department of Health (see FAD section 4.14).
NHS Professional 4	Manufacturer's submission	This technology is not a cost effective use of NHS resources for indication 1.2 The ERG conducted exploratory analyses for the group of people who had had previous treatment with both conventional DMARDs and a TNF inhibitor. These compared golimumab with rituximab. The ERG made modifications to the manufacturer's model. They increased the time between treatments for rituximab from 6 months to 9 months and removed the assumption that disease progresses at a faster rate on rituximab compared with TNF inhibitors. Rituximab now dominates golimumab. Rituximab, currently approved for treatment of RA after failure of a first TNF inhibitor, is therefore more cost effective than golimumab. Golimumab is no more effective than the other TNF inhibitors. In the absence of head to head trials, a mixed treatment analysis was required to assess comparative effectiveness of the TNF inhibitors. This was done for the "DMARD-experienced" population and the "TNF inhibitor-experienced" population. The three clinical trials giving the direct evidence for the effectiveness of golimumab plus methotrexate against placebo with methotrexate were small and the outcomes were measured over a short period	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the critique by the evidence review group and the manufacturer's submissions, including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195 (see FAD sections 4.16 and 4.20).
NHS Professional 4	Consideration of the evidence	There were limitations on the quality of the evidence. There are no head to head trials with other anti-TNFs. The trials only had a very small numbers of participants and only lasted up to 24 weeks. The Committee noted that the credibility intervals around the estimates were wide, indicating that there was a high degree of uncertainty about the effectiveness point estimates. No major differences in	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the critique by the

Role*	Section	Comment	Response
		reported adverse events were evident in the GO-AFTER study at 24 weeks. However, there are no long term data on adverse events. Further clarification is needed before decisions can be made on the cost effectiveness of golimumab for the first and third indication.	evidence review group and the manufacturer's submissions, including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195 (see FAD sections 4.16 and 4.20).
NHS Professional 4	Implementation	The exact number of people who will be switched to golimumab or start this agent in preference to alternatives is unknown. It is unlikely that golimumab, even if approved as an alternative, would completely replace the other TNF-α inhibitors. It is important that NICE considers the biological agents already approved for these indications and where exactly golimumab would sit if it where to be approved as otherwise PCTs could end up with numerous drugs for the same indication rather than a formulary of first, second and third line options taking into account cost effectiveness and safety.	Comment noted. The Committee have made the recommendation in the context of previous NICE guidance (see FAD section 1.1). In addition, this current topic is due to be part reviewed alongside technology appraisal guidance 130 and TA186 in 2011.
NHS Professional 5	Appraisal Committee's preliminary recommendations	NHS Bolton agrees with the appraisal committee's recommendations for further information. Re: 1.1: NHS Bolton agrees with NICE's preliminary recommendations for patients who have been prescribed DMARDs only not to recommend this treatment. Prescribers already have a wide choice of anti-TNFs to prescribe at this point in the pathway. If this decision were changed there would be further confusion in practice and variation in the way patients are managed as there are already several anti-TNFs to choose from. Re: 1.2: NHS Bolton agrees that patients should receive rituximab as second-line treatment following failure of an anti-TNF based on the evidence, outcomes and cost data available. NHS Bolton supports the preliminary recommendations. Re: 1.3: NHS Bolton agrees with NICE's preliminary recommendations for patients who have been prescribed DMARDs only and are unable to have rituximab due to intolerance/adverse drug reaction. There are already options for patients who fit this criteria to have treatment with tocilizumab/adalimumab/etanercept/abatacept. If this drug was found to be more effective than rituximab (from the further information asked for) in patient's who have already had anti-TNF it may have a place in practice, given the additional costs associated with rituximab (hospital admission, monitoring,	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the critique by the evidence review group and the manufacturer's submissions, including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195

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		nursing time).	(see FAD sections 4.16 and 4.20).
NHS Professional 5	The technology	2.3 Assessment to response occurs after 3-4 months, if the dose is then escalated at this point the cost per vial will double, hence the annual cost will increase. Also, if the higher dose is commenced it is not clear if the patient should have another 3-4 doses before assessing response? In addition for the 100mg dose the patient will have to inject twice – some patients will not want to do this, even if the dosing is once monthly. In practice, it is thought that not many RA patients are over 100kg. This data will hopefully be provided from the manufacturer in future. Adequate clinical response needs to be defined.	Comment noted. The Committee noted that following consultation on the appraisal consultation document, the manufacturer did not submit any additional data regarding the 100 mg dose, but instead proposed a patient access scheme what would provide the 100 mg dose at the same cost as the 50 mg dose in people for whom the higher dose is suitable. The Committee recognised that the patient access scheme has been accepted by the Department of Health (see FAD section 4.14). An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more, as is described in the guidance sections of technology appraisals no 130 and 195.
NHS Professional 5	Manufacturer's submission	The long-term effects of this drug are not known. For this TNF inhibitor to be used in practice it will need to be significantly more advantageous (either in cost, efficacy, improved outcomes) compared to other TNF inhibitors already in use in these groups of patients. Overall golimumab is not a cost-effective use of resources for the DMARD and TNF-inhibitor experienced patients, in whom rituximab would be an option for second-line treatment. Currently, within Bolton PCT, the second-line treatment for these patients would be rituximab (in-line with NICE guidance), if this is not appropriate (withdrawn due to adverse effects/loss of efficacy within first 6 months), patients have the option to be commenced on adalimumab or etanercept (monotherapy) or tocilizumab (in combination with methotrexate) in line with NICE guidance. The assumptions and subsequent amendments to the manufacturers model are appropriate to reflect current practice (i.e. increase the time between treatments for rituximab and remove the assumption that disease progresses at a faster rate on rituximab in comparison with TNF inhibitors).	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the critique by the evidence review group and the manufacturer's submissions, including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in

Role*	Section	Comment	Response
			technology appraisal no 130 and 195 (see FAD sections 4.16 and 4.20).
NHS Professional 5	Consideration of the evidence	Golimumab is no more effective than other TNF inhibitors. There are no head-to-head trials with the other TNF-inhibitors provided. The clinical trials were relatively short in timescales to assess outcomes (ACR20, ACR50, ACR70) – 14 and 24 weeks. The estimates of effect in the mixed treatment analysis with wide credibility intervals suggest there is uncertainty with the estimates. The committee has asked for further information around the indications for patients who have had DMARDs alone and those who have failed to respond to DMARDs and a TNF-inhibitor, who are not able to have rituximab. This data is required to identify if the treatment is cost-effective. NHS Bolton would need to see this newly provided data in order to review the cost-effectiveness again and determine whether this is a cost-effective use of NHS resources. 4.9 ACR70 is currently used to measure disease activity in trials but is not used practice to assess response. Response would be carried out using the DAS28 score, with a measure of response being a 1.2 reduction in practice. This terminology would be more useful when applying to real-life prescribing/patients. 4.14 The model suggests rituximab is administered every 6 months, this is not always the case in practice and patients are reviewed individually dependent on response prior to administration of subsequent doses. NHS Bolton agrees with this amendment.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the critique by the evidence review group and the manufacturer's submissions, including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195 (see FAD sections 4.16 and 4.20). The guidance in technology appraisals no. 130 and 195 use the DAS28 to measure treatment response and not ACR70. Comment noted. The Committee agreed that the ERG's amendments to increase the time between treatment intervals for rituximab and remove the assumption of a differential rate of underlying progression of disease were appropriate (see FAD section 4.19).
NHS Professional 5	Implementation	No comments	Comment noted. No further action
NHS	Related NICE	It would be useful if the new TNF-inhibitor appraisals were appraised in the same	The Committee have made the

Role*	Section	Comment	Response
Professional 5	guidance	way as previous guidance, and added to the guidance already in place.	recommendation in the context of previous NICE guidance (see FAD section 1.1). In addition, this current topic is due to be part reviewed alongside technology appraisal guidance 130 and TA186 in 2011.
NHS Professional 5	Proposed date of review of guidance	TA198 (Tocilizumab) should also be included within this review. In addition, TA195 should be reviewed to include these new therapies for use in patients who have already failed on DMARDs and at least one TNF-inhibitor.	Comment noted. TA195 is due to be considered for review in June 2013 and TA198 is due to be considered for review in August 2013. The part of the golimumab guidance relating to the use of golimumab after a TNF inhibitor is to be considered for review alongside TA195.
NHS Professional 6	Appraisal Committee's preliminary recommendations	Agree with preliminary recommendations. Further information has been requested for two out of three indications (indication 1 and 3). The Appraisal committee is 'minded' not to recommend golimumab as a treatment option for rheumatoid arthritis in people who have had therapy with conventional DMARDs (indication 1) nor as a treatment option for rheumatoid arthritis in people who have had therapy with a TNF inhibitor and for whom rituximab is contraindicated or is withdrawn because of an adverse event (indication 3). This means that the committee has asked for further data/clarification from the manufacturer including a revised model. The recommendations for these two indications will become firm and may potentially change direction after this information is provided.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the critique by the evidence review group and the manufacturer's submissions, including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195 (see FAD sections 4.16 and 4.20).
NHS Professional 6	The technology	There may be a problem with dose escalation. The standard dose of golimumab is 50mg however for patients who weigh more than 100kg an increase to 100mg is permitted in the EMEA marketing authorisation. The committee suggested that the model should be adjusted to include the proportion of people likely to need this higher dose. If the acquisition cost is included in the model the ICER for	Comment noted. The Committee noted that following consultation on the appraisal consultation document, the manufacturer did not submit any additional data regarding the 100 mg

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		golimumab would be higher than that estimated in the base-case presented by the manufacturer.	dose, but instead proposed a patient access scheme what would provide the 100 mg dose at the same cost as the 50 mg dose in people for whom the higher dose is suitable. The Committee recognised that the patient access scheme has been accepted by the Department of Health (see FAD section 4.14)
NHS Professional 6	Manufacturer's submission	The long term adverse effects of golimumab have not been adequately studied. This technology is not a cost effective use of NHS resources for indication 2. The Evidence Review Group (ERG) conducted exploratory analyses for the group of people who had had previous treatment with both conventional DMARDs and a TNF inhibitor. These compared golimumab with rituximab. The ERG made modifications to the manufacturers model. These modifications seem appropriate and in effect increase the time between treatments for rituximab and remove the assumption that disease progresses at a faster rate on rituximab compared with TNF inhibitors. When these assumptions are changed the estimate of cost effectiveness in the manufacturer's first model is overturned. Where golimumab was previously associated with fewer costs and more QALYs than rituximab (golimumab dominated rituximab) the position changes so that rituximab is associated with fewer costs and more QALYs than golimumab (ie. rituximab dominates golimumab). Rituximab, currently approved for treatment of RA after failure of a first TNF inhibitor, is therefore likely to be both a cost effective alternative to golimumab and more affordable for PCTs (lower overall cost per head).	Comment noted. Committee concluded that golimumab's adverse event profile had not been shown to be different from that of the other TNF inhibitors (see FAD section 4.11). The Committee agreed that the ERG's amendments to increase the time between treatment intervals for rituximab and remove the assumption of a differential rate of underlying progression of disease were appropriate. The Committee noted that when these assumptions were changed rituximab was associated with lower costs and more QALYs than golimumab. The Committee considered that golimumab could not be considered a cost effective use of NHS resources where rituximab was a treatment option (see FAD section 4.19).
NHS Professional 6	Consideration of the evidence	Golimumab is no more effective than the other TNF inhibitors. The clarifications required could have major effects on the output from the model. Requests have been made for further information regarding the first and third indications. These are unlikely to show golimumab is more cost effective than alternatives but PCTS will need an opportunity to check this and comment again if needed. Without this data there is insufficient evidence to say whether golimumab is or is not a cost	The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, critique by the evidence review group and the manufacturer's submissions,

Role*	Section	Comment	Response
		effective use of NHS resources for indication 1 and 3. There were limitations to the quality of the research: Small short term RCTs of golimumab with methotrexate against placebo and methotrexate were combined in a mixed treatment analysis. Considerable uncertainties remain around the point estimates of effect and the evidence base is not considered 'sufficient' to inform these decisions.	including the additional analyses provided by the manufacturer following consultation on the appraisal consultation document. On the basis of the evidence submitted the Committee recommended golimumab as a treatment option to be used in the same way as the other TNF inhibitors appraised in technology appraisal no 130 and 195 (see FAD sections 4.16 and 4.20).