Rheumatoid arthritis - adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab - review [ID537]

Pfizer Response to Technology Assessment Report (TAR)
25th September 2013

Pfizer welcomes the opportunity to comment on the Technology Assessment Report (TAR) from The School of Health and Related Research (ScHARR) for the review of Rheumatoid arthritis - adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab - review [ID537]. The following response is based upon our best interpretation of the TAR in the absence of the economic model. There are fundamental aspects of the TAR that we have been unable to fully understand or critique due to the model being unavailable and insufficient clarity of methods reported in the TAR.

Overall, Pfizer has serious concerns regarding the remit and approach taken in the TAR and does not believe it presents suitable evidence to help inform the decision problem for the appraisal committee. Furthermore, we do not agree with the conclusions on cost effectiveness as being a reasonable interpretation of the evidence and we feel that the cost effectiveness of biological disease modifying anti-rheumatic drugs (bDMARDs) are being severely underestimated when compared to conventional disease modifying anti rheumatic drugs (cDMARDs) by the Assessment Group (AG). Pfizer have major concerns with how the overall clinical and cost effectiveness conclusions were reached for the following reasons:

- **Failure to present the incremental cost effectiveness of individual bDMARDs**
- **Combination of the clinical effectiveness for the moderate to severe population with the severe population**
- **Use of EULAR response as the primary efficacy measure**
- **Use of inappropriate registries to inform key model relationships**
- **Use of simplifying assumptions to inform key data inputs and parameters in the model**

Pfizer is concerned with the suitability of the TAR for the purpose of the decision problem. The modelling approach taken in the TAR does not present the incremental cost-effectiveness of the individual bDMARDs identified in the scope of the appraisal. Rather it presents the cost-effectiveness of a full treatment pathway for bDMARDs. The cost-effectiveness of the use of the first line bDMARDs cannot therefore be separated from the cost-effectiveness of the second and third line use of bDMARDs. This is a fundamental limitation that could underestimate the cost-effectiveness and prevent the Appraisal Committee from considering first line biologic therapy. Furthermore, the modelling of the sequential use of bDMARDs has been over simplified and evidence used is inconsistent versus existing NICE appraisals.

Finally, there are errors, inconsistencies and alternative analyses whose impact on the cost-effectiveness remains unknown due to the absence of the model. Taken individually, or as a whole, these could significantly impact the results and therefore need to be fully addressed.

Pfizer believes these issues have caused the results of the AG's economic evaluation to conflict with previous NICE appraisals of bDMARDs for the treatment of Rheumatoid Arthritis and significantly underestimate their cost-effectiveness. Given that the majority of the evidence base has not changed, Pfizer feels that it is the AG's methods and approach that are driving this conflict.

Pfizer maintain that the availability of the AG model is paramount to inform the TAR consultation and to prepare and fully participate in the first appraisal committee meeting. In particular, the following key points need to be further addressed with a full consultation opportunity on the AG economic model prior to the Appraisal Committee consideration at the meeting on 15th October:

1. Failure to present the incremental cost effectiveness of individual bDMARDs

1.1 The results presented in the TAR do not reflect the cost-effectiveness of first line bDMARD therapy by inherently including guidance from TA195 and TA247. The results presented therefore reflect the cost-effectiveness of a full treatment pathway for bDMARDs.

1.2 The modelling of sequential bDMARD treatments from TA195 and TA247 has been conducted in a simplistic manner and is unlikely to reflect the true cost effectiveness of the full treatment pathway of bDMARDs compared to cDMARDs.

2. Combination of the clinical effectiveness for the moderate to severe population with the severe population

2.1 The AG has made a decision to combine two populations defined in the review's scope moderate to severe and severe into one evidence network and this evidence network is used to analyse efficacy of EULAR and ACR responses. Combining populations in this manner results in an underestimation of bDMARD response for a severe RA population and will negatively impact the cost effectiveness of bDMARDs for the severe DMARD-IR population. Pfizer recommend that both EULAR and ACR evidence networks are re-analysed for separate DMARD-IR populations and the results for the severe DMARD-IR population are incorporated into the economic model.

3. Use of EULAR response as the primary efficacy measure

3.1 Significantly fewer trials report EULAR response compared to ACR response. This results in incomplete efficacy estimates for bDMARDs and favours more recently approved bDMARD treatments.

3.2 The model does not take into account moderate EULAR responders who have a 0.6-1.1 change in DAS28 and can reach clinical remission (DAS 28 <2.6). Pfizer argues that these responders should be included in the economic model and currently the AG's model does not reflect the true benefit of bDMARDs in more moderate disease.

3.3 ACR response is an appropriate response measure for economic modelling, and is in line with previous NICE appraisals and decision making using the best available evidence.

4. Use of inappropriate registries to inform key model relationships

4.1 The use of the ERAS database to inform HAQ progression for cDMARDs does not reflect patients with more established disease. The use of this dataset is likely to underestimate HAQ progression in patients on cDMARDs and 'non biologic therapy' in moderate to severe and severe RA populations in the model.

4.2 Inconsistent methods used to estimate HAQ progression for bDMARDs and cDMARDs adds further considerable uncertainty to results of the economic evaluation.

4.3 The VARA database used for mapping ACR to EULAR has low generalisability to the UK clinical setting and the use of this source adds considerable uncertainty to the results of the economic model.

4.4 The NDB registry used for relationships between HAQ and utility and HAQ and mortality is also likely to be unrepresentative to a UK clinical setting and adds uncertainty to the results of the economic model.

4.5 The NOAR registry has been used to estimate the link between HAQ and medical resource use (MRU) in the model. This dataset only includes a limited number of cost components

and other MRU relationships are more likely to capture the full resource impact of patients with RA.

5. Use of simplifying assumptions to inform key data inputs and parameters in the model

5.1 Evidence from registries around the world suggests there are differences in drug survival times between treatments. These differences in duration of response have not been explored by the AG in the economic model. The assumption that the duration of response with cDMARDs is equal to that of bDMARDs could underestimate the cost-effectiveness of bDMARDs.

5.2 The combination of monotherapy and combination therapy in one network is not reflective of clinical practice as these are distinct populations. The impact of the combined network should be explored and two separate sets of results presented for monotherapy options and combination therapy options.

5.3 There are a number of additional concerns that Pfizer has with the AG's modelling approach, assumptions, data inputs and reporting. Specifically, Pfizer suggests further sensitivity and scenario analyses should be explored by the AG to reduce uncertainty in the cost effectiveness. The restricted use of sensitivity and scenario analyses limits understanding of key model drivers and does not explore the full breadth of uncertainty in the decision problem.

In conclusion, Pfizer argues that the TAR is not suitable for the appraisal committee to address the decision problem. Significant new analyses are required to illustrate the cost-effectiveness of first line bDMARDs instead of the cost-effectiveness of the full bDMARDs treatment strategy; to present an ACR based economic model in line with previous NICE appraisals using the best available evidence; and to use the effectiveness for the severe RA population from a separate severe evidence network meta analysis.

The following sections provide further details on these key points for consideration.

Pfizer review of the Technology Assessment Report (TAR)

1. Failure to present the incremental cost effectiveness of individual bDMARDs compared to cDMARDs

1.1. The results presented in the TAR do not reflect the cost-effectiveness of first line bDMARD therapy by inherently including guidance from TA195 and TA247. The results presented therefore reflect the cost-effectiveness of a full treatment pathway for bDMARDs

The current AG modelling approach does not reflect the cost effectiveness of first line bDMARDs, but the cost effectiveness of the recommended NICE treatment pathways for bDMARDs, which inherently includes guidance from TA195[1] and TA247[2] (Section.6.3.2, pg.350-1). This applies to all three populations within the scope i.e. moderate to severe, severe and severe MTX-naïve. The key question for this appraisal is whether first line bDMARDs are cost effective versus cDMARDs; currently the answer provided by the AG has addressed whether the NICE bDMARD treatment pathways are cost effective. Pfizer recommends that the first line bDMARDs cost effectiveness is explored, as was done in TA130, in order to separate out the noise and uncertainty of the extra bDMARD treatments in the pathway. This is especially pertinent given the simplistic assumptions used by the AG to model additional treatment sequences in the model. Please see point 1.2 below.

In the moderate to severe, severe and severe MTX naive populations who **can** receive MTX the AG have currently assessed the cost effectiveness of the current NICE treatment pathway i.e. first bDMARD +MTX, rituximab +MTX, tocilizumab +MTX versus a MTX strategy. The cost effectiveness of the use of the first line bDMARDs cannot therefore be separated from the cost-effectiveness of the second and third line use of bDMARDs.

Furthermore, the bDMARD treatment pathway used is the NICE recommended pathway for severe RA. There is no such established treatment pathway for moderate to severe RA. As there is currently no NICE recommended treatment options for moderate to severe RA, the key decision is only whether the use of the first biologic is cost-effective for this population.

In the moderate to severe, severe and severe MTX naive populations who **cannot** receive MTX the AG have included a variant on the NICE treatment pathway. The current NICE recommended pathway is adalimumab, certolizumab, etanercept monotherapy followed by adalimumab or etanercept monotherapy if there has been inadequate response to the first bDMARD monotherapy. Pfizer notes that the AG has added in tocilizumab as a third bDMARD monotherapy, which is not recommended in TA195 or TA247. This therefore does not present the cost effectiveness of the current NICE treatment pathway in monotherapy or the cost effectiveness of the first bDMARD monotherapy either. Pfizer argues that adding in tocilizumab monotherapy goes beyond the remit of the scope by considering additional sequence of treatments, which will affect the cost effectiveness of the bDMARD treatment pathway in this population.

In all populations considered within the NICE scope the inclusion of the full NICE bDMARD treatment pathway may offer a less cost-effective option than the cost-effectiveness of first line biologics alone.

- **Pfizer suggests further scenarios are conducted to consider the cost effectiveness from the point of divergence for first line bDMARDs in all three populations for patients who can and cannot receive MTX as was done in TA130. These are presented below:**

1. **A scenario where the NICE treatment pathway is removed to see if this has any impact on the cost effectiveness of first line bDMARDs +MTX compared to MTX in patients eligible to receive MTX**

cDMARD strategy	bDMARD strategy
MTX	First line bDMARD +MTX
cDMARD	cDMARD
'Non biologic therapy'	'Non biologic therapy'

2. **A scenario where the NICE treatment pathway is removed to see if this has any impact on the cost effectiveness of first line bDMARDs monotherapy compared to cDMARDs in patients who cannot receive MTX**

cDMARD strategy	bDMARD strategy
cDMARDs	First line bDMARD monotherapy
cDMARD	cDMARD
'Non biologic therapy'	'Non biologic therapy'

1.2. The modelling of sequential bDMARD treatments from TA195 and TA247 has been conducted in a simplistic manner and is unlikely to reflect the true cost effectiveness of the full treatment pathway of bDMARDs compared to cDMARDs.

The AG has not modelled a reduction in clinical effectiveness and time on treatment for subsequent lines of therapy in the model (Section 6.3.11, pg360 and Section 6.3.15, pg 373-376). Reduced effectiveness for sequential lines of therapy has been modelled previously in NICE TA247 and can be clearly seen in RCTs in TNF inadequate responders (TNF-IR) in TA195. This approach is an oversimplification and is inconsistent versus these existing NICE appraisals. It is also likely to be unreflective of the true cost effectiveness of the NICE bDMARD treatment pathway compared to cDMARDs.

In this appraisal, the AG has assumed that the efficacy of rituximab will be equivalent to abatacept IV from the AG's NMA in Section 6.3.11, pg360 based on near equivalence of ACR response in a TNF-IR population from Malottki et al 2011[3]. This assumption does not reflect clinical reality. There is a clear difference in efficacy between the abatacept DMARD inadequate response (DMARD-IR) trials and the rituximab TNF-IR trial (Table 1). Furthermore, it is not clear from the TAR what efficacy estimates have been used for tocilizumab and MTX, which are used as the subsequent therapies after rituximab in the bDMARD treatment strategy. It is assumed that first line efficacy data for tocilizumab and MTX has been used by the AG. If so, this is likely to significantly overestimate the treatment response for these therapies in this position in the pathway. Furthermore, the AG in TA130 noted that it would be clinically inappropriate for patients to use MTX as a single therapy after failing bDMARDs combined with MTX and sulfasalazine was used instead.[15]

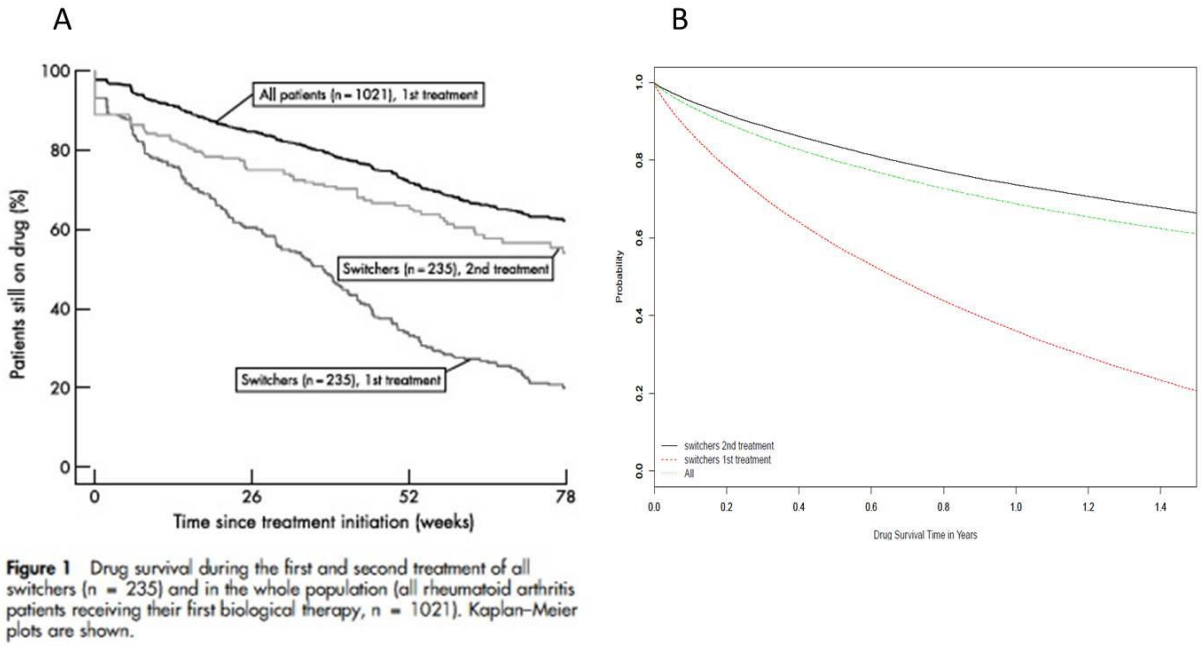
Table 1: ACR response for abatacept IV from a DMARD-IR population has been used for rituximab in a TNF-IR population.

Trial	(AIM) 6 months DMARD-IR population taken from the TAR		Abatacept IV (ATTEST) DMARD-IR population taken from the TAR*		Rituximab (REFLEX) (24 weeks)[35] TNF-IR population	
Intervention	PBO+MTX	Abatacept IV	PBO+MTX	Abatacept IV	PBO+MTX	Rituximab
% achieving ACR 20 response	39.7%	67.9%	41.8%	66.7%	18%	51%
% achieving ACR 50 response	16.8%	39.93%	20%	40.4%	5%	27%
% achieving ACR70 response	6.5%	19.8%	9.1%	20.5%	1%	12%

***excludes infliximab arm of the trial**

Registry data also suggests a reduction in time on treatment over time on subsequent TNF inhibitors[4], as utilised in the Pfizer model (Figure 1). The AG has not modelled this in their economic evaluation. The failure to take account of evidence of subsequent treatments in the AG model provides a biased estimate of the overall cost effectiveness considering the AG have modelled the NICE bDMARD treatment sequence in comparison to cDMARDs, as opposed to first line bDMARDs versus cDMARDs.

Figure 1: Treatment cessation in the Pfizer model based on registry data



A: Figure taken from Hjardem et al, 2007; B: Derived from the Pfizer economic model

- **If the full treatment pathway is part of the cost-effectiveness estimate, the reduction in effectiveness and time on treatment for subsequent lines of therapy should be modelled to represent the true cost effectiveness of bDMARDs by either adjusting the effectiveness from registry data or making use of available evidence from previous NICE appraisals (TA195 and TA247).**

2. Combination of the clinical effectiveness for the moderate to severe population with the severe population

2.1. The AG has combined two populations defined in the review's scope; moderate to severe and severe into one evidence network

The clinical evidence used to inform the economic model should reflect the populations being assessed in the economic model, namely both severe population and a moderate to severe population. It is noted that for the EULAR response and ACR response network meta-analyses (NMAs), the AG has combined the network for the moderate to severe population (defined as DAS20 >3.2 and <5.1) and severe (defined as DAS28 ≥5.1). No explanation has been given for joining the two populations in either the Methods Section 5.1, pg 57, or within the results Section 5.2, pg 68, although there is reference to the populations being combined on pg 70 in Section 5.2.1.1. Pfizer believes that the only rationale for merging the two populations is to allow a EULAR response network to converge.

Pfizer believes the AG should conduct a separate analyses of the severe DMARD-IR population as defined by the scope[5] removing all moderate trials from the network. The effect of combining both severe DMARD-IR and moderate to severe DMARD-IR populations will lead to an underestimation of efficacy in the severe DMARD-IR population.

- **Pfizer recommends both EULAR and ACR evidence networks be re-analysed for a severe DMARD-IR population and the results for the severe DMARD-IR population incorporated into the economic model.**

- **Pfizer recommends the removal of the moderate trials from the EULAR Response and ACR response networks so that the severe DMARD-IR population can be analysed.**

3. The evidence base for EULAR is severely restricted and diluted versus ACR

3.1. Significantly fewer trials report EULAR response compared to ACR response. This results in incomplete efficacy estimates for bDMARDs and favours more recently approved bDMARD treatments.

It is noted that the basecase EULAR response network (Section 5.3.2.1 EULAR – Main Trials, figure 5, pg 129), currently consists of 11 studies which rises to 15 studies in the largest sensitivity analysis (Section 5.3.2.2 EULAR – Main Trials plus Prior Biologics with AMBITION figure 6, pg 134). Three treatments being compared in this health technology assessment are missing from the basecase EULAR response network, CTZ, CTZ+ and ABA SC. Sensitivity analyses allow for the inclusion of CTZ+, however, there remains no data for either CTZ or ABA SC. The EULAR response network has fewer than half of the studies which are present in the ACR network where the basecase consists of 28 studies (Section 5.3.2.4 ACR – Main Trials, figure 8, pg 148) and the sensitivity analysis consists of 40 studies (Section 5.3.2.5 ACR – Main Trials plus Prior Biologics with AMBITION, figure 9, pg 153). Within the ACR basecase and sensitivity analyses only CTZ treatment is not present. This suggests

the ACR response network evidence base is larger and more inclusive than EULAR response and is likely to provide a network that converges for the efficacy of the treatments in a severe only DMARD-IR population. In addition, it is noted that the recent trials are more likely to report EULAR response, which suggests a bias in favour of the more recent bDMARDs.

Pfizer argues that the Swefot trial[6] be removed from the EULAR response network. Pfizer believes the Infliximab + MTX arm of the trial is outside of the appraisal scope. The protocol allows for participants randomised to Infliximab + MTX to switch to ETN should they experience an adverse event to infliximab. This has occurred in 5/128 participants and these have been included in the study analyses. This is not a pure Infliximab population and therefore Swefot does not meet the scope of this appraisal. In addition, a further 13 participants randomised to the infliximab + MTX arm of the Swefot trial increased the frequency of Infliximab from every 8 weeks to every 6 weeks. The scope does not allow for intensification of bDMARD therapy and as such this is further rationale for Swefot not being a valid trial for this evidence network.

Without the Swefot trial in the network, there would be no link to the ETN trials (LARA [7] and JESMR [8]) and combined bDMARDs trial TACIT [9] resulting in four further products being missing from the EULAR NMA basecase (ETN, ETN+, combined bDMARDs and intensification of cDMARDs). Introducing additional trials in the sensitivity analysis would allow CTZ+ into the network but none of the four treatments previously mentioned. We therefore believe that this is a further reason the EULAR response network is not appropriate to analyse bDMARDs for the treatment of severe RA in a DMARD-IR population.

Pfizer did not analyse EULAR response due to a lack of data which in our opinion meant such an analysis would not be robust. It is noted in the TAR that "In the case of the analysis of the EULAR data there were relatively few studies and too few to update the between study standard deviation" (page 67). Because of the sparse data set for the EULAR outcome, the TAR NMA used a 'weakly' informative prior distribution for the between study standard deviation (A half normal distribution with mean 0 and standard deviation 0.32). Pfizer believes the use of a weakly informative prior distribution is an indicator of poor model convergence and fit.

The ACR response NMA was used to generate an estimate of response for bDMARDs in the severe MTX naïve population due to only one trial presenting EULAR response evidence. Accordingly, no economic evidence for bDMARDs in combination with MTX in a severe MTX naïve population. With the Swefot trial removed, there would be no trials presenting a EULAR response for DMARD-IR moderate to severe population. The network for a DMARD-IR severe population basecase would not contain seven possible treatments in the base case. Therefore for two of the three populations identified within the scope of this appraisal, there are no evidence networks for the EULAR response and for the third population there is missing evidence for a number of treatments. This severely undermines the use of EULAR response as an appropriate measure of efficacy.

- **Pfizer recommends the use of ACR response as the most appropriate response measure for economic modelling using the best available evidence to minimise uncertainty**

- **Pfizer recommends the removal of the Swefot trial from the EULAR response network due to its design being out of scope**

- **Given the uncertainty associated with this analysis it is unclear why the EULAR NMA results would be used as a measure of effectiveness in the economic model and Pfizer recommends that ACR response is a more appropriate measure of effectiveness.**

3.2. The model does not take into account moderate EULAR responders who have a 0.6-1.1 change in DAS28 and can reach clinical remission (DAS 28 <2.6).

The model does not take into account moderate EULAR responders [10] who have a 0.6-1.1 decrease in DAS28 and can reach clinical remission (DAS 28 <2.6), or low disease activity (DAS 28 <3.1). The current NICE guidance is not in line with the BSR or EULAR guidelines for the treatment of RA with bDMARDs where bDMARD treatment can be initiated in moderate to severe disease and a target of at least low disease activity is expected after a 6 month trial [11, 12]. A number of these patients with moderate to severe disease (starting DAS28 of ≤3.2 <5.1) can reach clinical remission, or low disease activity using bDMARDs, despite obtaining a decrease in their DAS of less than 1.2. According to current NICE guidance, these patients will be required to stop their biologic treatment although reaching clinical remission, or low disease activity. These patients should be allowed to continue treatment. In addition these patients are currently not modelled in the economic model and this will lead to an economic underestimation to the value of bDMARD therapy.

- **Pfizer recommends that these moderate EULAR responders should be included in the economic model as currently the AG's model does not reflect the true benefit of bDMARDs in more moderate disease.**

3.3. ACR response is an appropriate response measure for economic modelling rather than a EULAR based model, and is in line with previous NICE appraisals and decision making using the best available evidence.

Pfizer believes that the ACR response is the most relevant outcome for modelling RA due to a number of limitations in the evidence base for EULAR response that have been outlined above. In terms of clinical validity and discriminatory ability the available literature suggests ACR and EULAR response are equivalent [13, 14]. Pfizer notes that the AG cite Van Gestel[10] to suggest that EULAR is superior to ACR response with better construct and discriminate validity (Section 3.1, pg 43). The AG fails to explicitly note that this study considered only ACR 20 responders and did not consider ACR 50 and ACR 70 responders and this is likely to explain the loss of construct and discriminate validity seen in this study. Indeed, both the European league Against Rheumatism and the American College of Rheumatology do not discriminate between the outcomes and recommend that both are collected in RCTs to measure response[16]. Pfizer argues that ACR and EULAR response are equally valid response measures to be used in the modelling of RA. Furthermore, ACR response is in line with previous NICE appraisals and decision making given that the majority of recent NICE appraisals have considered ACR based models.

- **Given the limitations in EULAR outlined above, Pfizer argues that ACR should be used as the initial effectiveness in the economic model to provide consistency with previous NICE decisions based on ACR economic models.**

4. <u>Inappropriate use and choice of registry data to inform key relationships in the model is likely to underestimate cost effectiveness of bDMARDs compared to cDMARDs</u>

4.1. The use of the ERAS database to inform HAQ progression for cDMARDs does not reflect patients with more established disease. The use of this dataset is likely to underestimate HAQ progression in patients on cDMARDs and 'non biologic therapy' in moderate to severe and severe RA populations in the model.

The use of the ERAS dataset to estimate cDMARD HAQ progression (Section 6.3.14, pg 370) has a number of limitations which Pfizer feel will underestimate progression on cDMARDs and increase the ICERs for a bDMARD strategy compared to cDMARDs. There are clear differences in the datasets used to estimate HAQ progression for bDMARDs and cDMARDs. ERAS and BSRBR contains patients with early RA and established RA respectively. The baseline characteristics (Table 2) in the two datasets are noticeably different in terms of disease duration and HAQ score and they are from different historical time periods. Similar issues exist with the NOAR and ERAN early RA datasets used by the AG to validate their analysis (pg.371).

The observational cohorts (ERAS / ERAN / NOAR) by definition look at a normal distribution of patients with inflammatory arthritis: to the left of the curve, there will be patients who don't need any treatment (disease is quiescent) and to the right will be some patients who would meet criteria for bDMARDs but do not receive them (patient choice, bDMARD not available i.e. pre 1999). The vast majority will be in the middle with mild-moderate disease. The BSRBR cohort are a group of patients to the right of the curve and are applicable to generate a HAQ progression for cDMARDs that would be useful as a comparator in a moderate to severe and severe population. The HAQ progression curve generated from the observational cohorts is not appropriate for the vast majority of the population who would not be eligible for bDMARDs. The BSRBR control cohort provides a better source to estimate HAQ progression on cDMARDs and should be utilised by the AG.

Table 2 Comparison of characteristics between the BSRBR and ERAS datasets

Characteristics	BSRBR [24]		ERAS [50]
	bDMARDs	cDMARDs	cDMARDs
Age	56 ± 12	60 ± 12	55 (IQR:45-64)
Female (%)	76	72	65
Disease duration	12 years (6-19)	7 years (1-15)	8.1 months
DAS28	6.6 ± 1.0	5.0 ± 1.4	NR
HAQ	2.1 ± 0.6	1.5 ± 0.8	1.0 (IQR 0.5-1)
RF+. %	65	58	62.9

Furthermore, the AG has identified a number of limitations with the ERAS database as a source to estimate HAQ progression for cDMARDs on page 372. These include only 15 years of follow up in the cohort, baseline characteristics not matching the data used in the cost effectiveness analysis and the dataset not including inadequate responders to cDMARDs. Pfizer also acknowledges and agrees with the AG that some of these limitations will apply to the studies used previously to estimate mean HAQ progression for cDMARDs. Nevertheless, these studies provide consistency across previous NICE appraisals.

Pfizer would like to note some further limitations with the ERAS dataset that may lead to underestimation of HAQ progression from this source. Patients were enrolled in ERAS between 1986 and 1998[17] and a number of biases may be introduced as a result of the historic nature of the cohort. One such bias is the high percentage of surgeries and joint replacements recorded in the dataset. At 10 years follow up the cohort reported that 27% of the patients had orthopaedic surgery. Major joint surgery was performed in 12% and excision anthoplasty and/or joint fusion were performed in 5%. Overall, 9% of the cohort had multiple joint surgeries. [18] These interventions are likely to either halt

or more likely significantly improve HAQ levels in the cohort and could explain the levelling off in HAQ seen in the analysis from around 10 years in the assessment group's analysis.

Another limitation is the significant loss of observations seen over time in the ERAS cohort which may impact the HAQ trajectories estimated by the AG. The AG's estimate is based upon Norton et al 2013[17] who employed a similar analysis over a 10 year period. In the study only 61% of patients in ERAS completed the 10 years follow up. Given the AG analysis is over 15 years; Pfizer suggests that the AG clarify the number of observations between 10 and 15 years that the analysis is based upon. Pfizer argues that potentially more healthy patients are remaining in the cohort over time and biasing the analysis given patients with higher HAQ scores are more likely to die. This could explain the diminishing effect seen in HAQ progression over time as healthy patients remain in the cohort and reduce the mean HAQ score over time. It is not clear from the TAR whether anything was done to explore this potential bias in the data.

- **The ERAS dataset is inappropriate to estimate HAQ progression for cDMARDs and will lead to an underestimation of HAQ progression, whilst increasing uncertainty in model results. The BSRBR control cohort should be utilised to provide an estimate of HAQ progression for cDMARDs. Previous studies used to estimate HAQ progression for patients in cDMARDs also have limitations and are also likely to underestimate HAQ progression. Given uncertainty in this estimate previous values used in NICE appraisals should be used to maintain consistency in approach.**

4.2. Inconsistent methods used to estimate HAQ progression for bDMARDs and cDMARDs adds further considerable uncertainty to results of the economic evaluation.

Pfizer notes that the AG has employed two different approaches to estimating HAQ progression for cDMARDs and bDMARDs. These differences in methods lead to further uncertainty to model results given the approaches are not comparable. The AG has estimated HAQ progression for cDMARDs based on HAQ class trajectories using a growth mixture model approach (pg. 370-72), whilst for bDMARDs it estimated HAQ progression for Moderate and Good EULAR responders using a Autoregressive Latent Model (pg 365-370). It is unclear what impact the use of different methods of estimating HAQ progression will have had on model results.

- **Pfizer request a consistent approach for estimating HAQ progression for bDMARDs and cDMARDs should be used by the AG. Currently, it is not clear what impact the different methods are having on model results and whether they may be biasing one class of treatments over the other.**

4.3. The VARA database used for mapping ACR to EULAR has low generalisability to the UK clinical setting and the use of this source adds considerable uncertainty to the results of the economic model.

Pfizer welcomes the attempt by the AG to use ACR in a scenario analysis to address the wider evidence base given the limitations highlighted with EULAR (Section 6.3.11 pg 359-360). However, Pfizer has a number of concerns regarding the choice of dataset and estimation of the relationship between ACR and EULAR used in the AG model. The concerns can be summarised as follows:

- Low generalisability of the VARA database to a UK population being treated with bDMARDs which may introduce a number of confounders to the ACR to EULAR relationship.

- Limited reporting of the ACR to EULAR relationship lacks transparency and doesn't demonstrate whether there is a strong relationship between the two outcomes.
- Use of an additional mapping relationship will increase uncertainty in model results and ACR should be used directly in the model to explore uncertainty in the relationship.

It has been previously noted that there may be issues of external validity with RA registry data. Kremer et al have previously written: 'the patient populations should ideally be representative of the population at large in the country or area from which the database is derived. In order to achieve representativeness, either the majority of patients in a particular area, or an appropriate selected random sample, should be studied. If not, there is the potential for bias as patients with particular characteristics may be over or underrepresented.' [19]. Pfizer are concerned that the choice of US registry data by the AG does not consider these concerns and that underlying confounders and difference in clinical practice have not been controlled for in their analyses.

The AG provides no justification of why the VARA database was chosen to inform the relationship between ACR and EULAR. Given that ACR is not recorded in the BSRBR it is clear the AG will have tried to identify other sources of data. However, the choice of the VARA database is concerning given the very low generalisability to a current UK clinical practice. The registry enrols US veterans who are mainly males with lower HAQ scores, more moderate disease activity, have a higher number of co-morbidities and have a higher percentage of rheumatoid factor positive patients than those treated with bDMARDs in the UK (Table 3). Given these clear differences between the BSRBR and VARA databases there are likely to be a number of confounders in the analysis that may affect the relationship between ACR and EULAR, especially in a severe population.

Table 3 comparative characteristics between the BSRBR and the VARA databases[24]

Characteristics	BSRBR		VARA	
	Bio	Comp	Bio	Comp
Age	56 ± 12	60± 12	64± 11	68± 12
Female	76	72	11	8
Disease duration	12 (6-19)	7 (1-15)	14± 11	14 ± 12
DAS28	6.6 ± 1.0	5.0 ± 1.4	3.7 ± 1.4	3.7 ± 1.5
HAQ	2.1 ± 0.6	1.5 ± 0.8	1.0 ± 0.6	1.0 ± 0.7
RF+. %	65	58	84	77

There is very limited reporting of how the ACR to EULAR relationship has been estimated by the AG. We realise that the ACR to EULAR analysis has been marked academic in confidence and this could explain the limited reporting of methods. Given this is an important relationship which informs one of the main scenario analyses for the AG's economic model, Pfizer suggests that there should be more transparency in methods and reporting of the analysis. A previous review of RA modelling has noted that the choice of primary measure will only have a marked impact on model results where the correlation between measures is weak, assuming that data sources and definitions of adequate response are comparable[20]. From the literature it is unclear how well the ACR and EULAR response correlate, although it has been noted that they have similar discriminatory potential in determining response to treatment [14].Even assuming there is a good correlation between ACR and EULAR, there is still likely to be additional noise and uncertainty inserted into the model from using a mapping relationship.

Accordingly, Pfizer would recommend that the AG also run a scenario where ACR is mapped directly to HAQ in the model rather than using three different mapping relationships to reach final outcomes (i.e. ACR to EULAR, EULAR to HAQ and finally HAQ to utility/costs). Firstly, this would provide an exploration of the uncertainty in the relationship between ACR and EULAR given the limitations in the data, the reporting of the analysis and the additional mapping step that is required to run this

scenario. In addition, this would enable the Appraisal Committee to directly compare to previous NICE decisions and to identify the main drivers in the cost effectiveness between the AG's model and previous recent manufacturer models used in NICE appraisals and the majority of current manufacturer's models in this appraisal. [21, 22, 23]

- **Pfizer recommends that ACR is applied directly in the model rather than mapping from ACR to EULAR given the low generalisability of the dataset to the UK and unnecessary uncertainty an additional mapping relationship will add to the model. Practically, this will provide a comparison to previous models used in NICE appraisals and the majority of manufacturer models in this appraisal.**

4.4. The NDB registry used for relationships between HAQ and Utility and HAQ and mortality is also likely to be unrepresentative to a UK clinical setting and adds uncertainty to the results of the economic model.

Pfizer has similar concerns regarding the representativeness and generalisability of the US National Data Bank for Rheumatic Disease (NDB) dataset used to estimate the HAQ to utility and HAQ to mortality relationships in the model (Section 6.3.18 pg 377-381 and Section 6.3.20 pg 382-383). The HAQ scores in the NDB bDMARD cohort is 1.1 ± 0.7 and is considerably lower than the BSRBR bDMARD cohort with a mean 2.1 ± 0.6[24]. Again the use of biologics is likely to be considerably different to the UK clinical practice. Indeed, the AG note that 'in the US NDB just 1% of observations exceed a HAQ of 2.5', as a justification for low numbers of patients progressing to higher HAQ scores. Pfizer would argue that this is indicative of earlier use of bDMARDs in line with their licenses and fewer patients are allowed to progress to high HAQ levels in the US. It is unclear what effect that this will have on the relationship between HAQ and utility estimated by the AG, but Pfizer suggests that there may be a limited number of observations informing the relationship between HAQ and utility at higher HAQ levels.

Pfizer believes that the representativeness of the NDB dataset is likely to be low, but acknowledges it is a large dataset and this does provide benefits. It is not clear from the TAR what methods have been undertaken by the AG to control and explore these underlying biases in the NDB dataset when estimating the relationship between HAQ and utility. The HAQ to mortality relationship is from a published source and these concerns will not have been explored in this reference. The use of the NDB dataset adds a number of uncertainties to the economic evaluation and it is not clear what impact these will have on model results.

- **Pfizer argues that, despite sophisticated analysis by the AG in a large dataset to estimate HAQ to utility in the model, questions remain around the generalisability and representativeness of the patients in the NDB to the UK clinical setting. It is unclear whether these differences have been adequately controlled for by the AG. Pfizer argues that previous UK studies estimating HAQ to utility should be used in the basecase given this uncertainty and to allow consistency to previous NICE appraisals.**

- **Other mortality estimates like Brennan et al 2007[27] used in the Pfizer submission should also be used given the uncertainty of this estimate with regards to a UK population.**

4.5. The NOAR registry has been used to estimate the link between HAQ and medical resource use (MRU) in the model. This dataset only includes a limited number of cost components and other MRU relationships are more likely to capture the full resource impact of patients with RA.

The AG has used the NOAR database to estimate medical resource use (MRU) in the model (Section 6.3.17, pg 376-377). The NOAR dataset used for MRU has been criticised previously by the ERG in TA198 [25] as being no longer valid for contemporary practice and for determining inpatient facilities due to the dataset being from the early 1990s. Furthermore, the ERG suggested that there was wide practice variation in the dataset with many patients rarely requiring inpatient care. No outpatient, GP visits or other medications costs are included in the current AG estimate and this may underestimate the cost of RA at each HAQ level.

Pfizer understands that there are limited sources to inform this relationship. Pfizer notes that the Kobelt 2002[26] included a broader range of MRU including hospitalisations, surgical interventions, outpatient visits, medication, and drug monitoring from the ERAS dataset and this is likely to be more appropriate source than the NOAR relationship due to a more complete collection of resource use associated with RA. Pfizer realises the use of early RA cohorts is problematic for estimating costs of RA in more severe disease and Pfizer suggests that other MRU relationships should be explored, such as Brennan et al 2007[27] and Malottki et al 2011[3] to determine the uncertainty in this input.

- **Pfizer suggest that the NOAR database is unlikely to capture all medical resource use data associated with RA. Pfizer recommends that other MRU relationships are used instead of the NOAR to explore the uncertainty in this approach.**

5. Use of simplifying assumptions to inform key data inputs and parameters in the model

5.1. Evidence from registries around the world suggests there are differences in drug survival times between treatments. These differences in duration of response have not been explored by the AG in the economic model. The assumption that the duration of response with cDMARDs is equal to that of bDMARDs could underestimate the cost-effectiveness of bDMARDs.

Pfizer disagrees with the AG assumption that patients on cDMARDs and bDMARDS will have the same drug survival. Pfizer notes that from their own analysis of overall drug survival from the BSRBR that patients with DAS28>5.1 in the etanercept + MTX cohort had longer overall time on treatment compared to the control cohort, reproduced in Table 143, pg 293 of the TAR. The AG cite in Section 6.3.15 that there is little data on the duration of response for patients receiving cDMARDs. Pfizer argues that the there is considerable evidence for the time on treatment for cDMARDs [28, 29, 30]. However, we believe the issue the AG found was that there was insufficient evidence to support the modelling approach based on EULAR response and therefore have had to rely upon a simplifying assumption. This is likely to underestimate the benefit that bDMARDs provide and could underestimate their cost effectiveness.

The assumption that there is no difference in time on treatments based on EULAR response for bDMARDs by the AG does not take into account the best available evidence. The AG argue in Section 6.3.15, p374 that only enough data was available for infliximab, etanercept and adalimumab to inform the input for time on treatment for bDMARDs from the BSRBR. However, differences in time on treatment were not implemented because of significantly shorter time on treatment for adalimumab and etanercept compared to infliximab. Pfizer is concerned with this approach, as a systematic review undertaken to inform the time on treatment for bDMARDs input for the Pfizer model concluded that 'in studies which only enrolled bDMARD naïve patients, ETN consistently exhibited higher rates of drug survival than both ADA and INF between 12 to 60 months.' [47, 51] Furthermore, etanercept demonstrated significantly better time on treatment in two European

registries compared to adalimumab and infliximab[31, 32] and one further registry against infliximab[33]. This assumption that there is no difference in time on treatment is likely to underestimate the benefit of etanercept and underestimate its cost effectiveness not only versus cDMARDs (given the pooling of bDMARDs), but also versus adalimumab and infliximab individually. Given the previous AG in TA130[30] explored different time on treatment scenarios based on the available evidence, Pfizer suggests the current AG should do the same given the new evidence to inform this input.

- **Pfizer argues that given the access to the entire BSRBR database, the AG should explore the difference in drug survival. Difference in follow up times for the individual treatments could be explored through survival analysis techniques. Otherwise, this simplifying assumption should be explored in a sensitivity analysis to see what impact this has on economic results.**

5.2. The combination of monotherapy and combination therapy in one network is not reflective of clinical practice as these are distinct populations. The impact of the combined network should be explored and two separate sets of results presented for monotherapy options and combination therapy options.

Pfizer notes that the AG has combined both bDMARD monotherapy and combination therapy (bDMARD + cDMARD) in the evidence networks sections of the TAR (page 129 Section 5.3.2.1 EULAR – Main Trials and page 148 Section 5.3.2.4 ACR – Main Trials).The potential effect modification by concomitant use of DMARDs/MTX has not been explored by the AG. Thorlund et al 2012[34] states that lumping monotherapy and combination therapy should be avoided without controlling for concomitant use of cDMARD.

"If the monotherapy and combination therapies have been combined within a network then one of the three approaches are recommended to be undertaken:

(1) Use meta-regression to control for the effect of concomitant MTX–DMARD
(2) Analyse monotherapy and combination therapy in separate treatment networks
(3) Analyse monotherapy and combination therapy as different treatments, but in the same network.

Provide sufficient rationale for the chosen approach. Consider additionally using a second of the above three approaches as sensitivity analysis."

The AG appears to have only used approach three; however, no rationale has been given as to why this approach has been undertaken.

Furthermore, whilst it may be credible to join the monotherapy and combination therapies in one network, Pfizer believes it is inappropriate to rank all treatments in one table when in clinical practice these are distinct populations with different treatment options. Pfizer therefore believes it is appropriate to have two separate sets of results for ranking monotherapy options and ranking combination therapy options.

- **Pfizer recommends that the AG also apply approach 2 as advocated by Thorlund et al 2012 to validate their approach of combining monotherapy and combination therapy treatments in one network.**
- **Pfizer recommends having two separate sets of results for monotherapy and combination therapy.**

5.3. **There are a number of additional concerns that Pfizer has with the AG's modelling approach, assumptions, data inputs and reporting that are highlighted in the section below. Specifically, Pfizer suggests further sensitivity and scenario analyses should be explored by the AG to reduce uncertainty in the cost effectiveness. The restricted use of sensitivity and scenario analyses limits understanding of key model drivers and does not explore the full breadth of uncertainty in the decision problem.**

Other concerns with the TAR/model/ modelling approach	**Pfizer comment and request for action**
Issues with trials included in the basecase DMARD-IR ACR network for populations 2 and 3	• Pfizer questions the inclusion of the STAR study [42] in the DMARD-IR population 2/3 analyses (Table 13 Page 31). The population of the STAR trial does not fulfil the criteria of the scope for this assessment. The study was conducted to evaluate the safety and efficacy of adalimumab for up to 24 weeks in patients with active RA receiving chronic concomitant standard antirheumatic therapy (e.g., traditional DMARD, corticosteroids, NSAID, and/or analgesics). The ADA+ population in this study is a mixture of participants receiving ADA monotherapy (57/318 (17.9%)) and ADA + (261/318 (82.1%). The placebo population is also a mixed group. Of the 318 randomised to receive placebo therapy, 48/318 (15.1%) received no cDMARD therapy during the study. Given that both ADA and ADA+ are being assessed separately in the network against cDMARD therapy, the STAR study cannot be analysed within this evidence network because of its mixed populations. In addition, the population of the STAR trial was not truly cDMARD-IR, with 26/318 (8.2%) of participants randomised to receive ADA and 23/318 (7.2%) participants randomised to placebo being cDMARD naïve. A number of studies were not included in the basecase analysis because a percentage of their participants had not used previous cDMARDs. This further strengthens the concerns around the STAR study having a legitimate population for this evidence network. • **Pfizer recommend the removal of the STAR study as it is not within the scope of this current appraisal.**
Issues with trials included in the sensitivity analysis DMARD-IR ACR network for populations 2 and 3	• We would like to highlight that the efficacy estimates of certolizumab pegol + MTX in the ACR response sensitivity analysis NMAs may lead to an overestimation of its benefit and these should be treated with caution due to the uncertainty around its true benefit (Section 5.3.2.5 pg 153 – 160 and Section 5.3.2.6 pg 160 – 167). Specifically, participants from the RAPID 1[52] and RAPID 2[53] trials are excluded 8 weeks before the primary efficacy endpoint and treated as non responders if they had not exhibited an ACR20 response at either week 12 or 14 and were classed as non responders at week 16. However, in these 8 weeks it is possible that some patients would have achieved an ACR20 response and were incorrectly assumed to have a no response. This is likely to affect the control arm to a greater extent due to the higher withdrawal rate (63-81%) compared to the intervention arms (17-21%).

	It has been shown that methotrexate is most effective when step-up therapy is employed (as it is in the majority of other trials). The restriction on dose increases may have resulted in patients being taken into rescue therapy from the control arm that would have responded by week 24. This imbalance in withdrawals may have had an impact on the treatment effects measured by these studies. The ITT primary outcome at 24 weeks suggested a greater treatment effect for certolizumab pegol compared to placebo than was the case before early escape[54]. • **Pfizer recommend that the RAPID 1 and RAPID 2 trials are removed from the sensitivity analyses due to the study designs potentially overestimating the treatment effect of certolizumab pegol.**
Inclusion of tofacitinib in the NMA for populations 2 and 3	• Pfizer questions the presence of the tofacitinib data in the evidence tables and network diagrams throughout the result section of the TAR (Pg 153 –pg 167). This contradicts pg 55 of the TAR: " *Relevant comparators* The relevant comparators within the final scope differ according to the population considered. The scope stated that tofacitinib would be included if NICE had issued positive guidance prior to the report's completion, but this did not occur and therefore tofacitinib was not evaluated. " Pfizer recognize that the tofacitinib trials may be used to inform the network [43, 44, 45]. However, tofacitinib does not have a marketing authorisation with the EU and is therefore not a legitimate comparator for this appraisal and as such, any data related to this arm should be removed from the analysis. This would be consistent with the data seen from the AUGUST II trial[46] where any arms with a treatment not defined in the scope are not seen in any analysis, ie, phase II drug (atacicept) from AZ (data on page 81 of the report).
Inclusion of all the TACIT trial data	• Pfizer also questions the relevance of the inclusion of the results of the multiple bDMARD arm of the TACIT trial in the EULAR response NMA as this was not in the scope of the appraisal (Section 5.3.2.1 EULAR – Main Trials pg 129). Whilst we agree that the Intensification of cDMARD arm of The TACIT trial[9] maybe relevant to inform the EULAR response network, the scope does not allow for a multiple bDMARD arm as a comparator. In addition, participants in whom one TNF inhibitor is stopped another may be used. The scope does not allow for sequential use of bDMARDs and as such any data related to this arm should be removed from the analysis. This would be consistent with the data seen from the AUGUST II trial where any arms with a treatment not defined in the scope are not seen in any analysis.
Relevant data is missing for ETN+ in the ACR network	• Pfizer believes that there is relevant information missing from the network (Section 5.3.1 population 1 (MTX-naïve) for ETN and recommend this is added to the network. In Pfizer's submission 24

MTX naïve population 1	week data from the COMET trial was presented [47]. At week 24, the number of participants exhibiting ACR 20, 50 and 70 responses to ETN+MTX were 224/274 (81.8%), 167/274 (61.0%) and 103/274 (37.6%) respectively. This is compared the number of participants exhibiting ACR 20, 50 and 70 responses to cDMARD monotherapy 159/268 (60.3%), 102/268 (38.1%) and 47/268 (17.5%) respectively. • **Pfizer believes that this data should be included in the ACR response network and feels that this will have a significant impact on the ACR response analysis for population 1 in a MTX naïve population.**
Issues with trials included in the DMARD-IR ACR network for populations 1	• Pfizer believes that the PREMIER trial [48]does not fit the criteria of the scope and recommend its removal from the NMA of the MTX naive population. The PREMIER trial specifically allows for an increase to weekly dosing for ADA at week 16 if an ACR 20 response has not been seen in participants. A weekly dose increase occurred in 69/274 (~25%) of participants in the ADA monotherapy arm and 29/268 (~11%) of participants in the ADA + MTX arm. An increase in ADA dose is not within the ADA licence [49]. In addition, an increase in bDMARD dose is not in scope with this appraisal. • **Pfizer recommend that the PREMIER trial is removed from the evidence network and analysis.**
Potential Missing data EULAR response Network for populations 2 and 3	• Pfizer note that the LA RA data for a good EULAR response is not presented and therefore question as to whether it has been used to inform the EULAR response network (Table 19 EULAR response data used in the MTC for populations 2 and 3, pg 115). Pfizer believes this should be used within the AG's analyses. From Machado et al 2012[7] 131/279 (47%) achieved a good response in the group randomised to receive ETN+ compared to 17/142 (12.0) achieving good response in the population randomised to receive an intensification of cDMARDs.
Implicit assumption that relationships estimated from ERAS dataset hold across all populations.	• ERAS dataset has been used to inform mean pain scores and its variance estimated for each HAQ score to inform the utility related HAQ relationship (Section 6.3.18, pg378) and HAQ change conditional on EULAR response (see Section 6.3.13, pg 364). • It is unclear whether these relationships estimated in an early RA population are equally valid in moderate to severe and severe population given the low generalisability of this dataset to these populations. • These relationships are only briefly reported in the TAR and it is not clear what methods have been used to estimate them or how strong the relationships are between outcomes. • **Pfizer suggests further details of how these relationships were estimated and the strength of relationships.**

No consideration of sequences for patients in which rituximab is contraindicated or inappropriate due to an adverse event	• The AG has not explored differences in the treatment sequence as specified in the NICE guidance (TA195) considering a population sequence in which rituximab is contraindicated or inappropriate due to an adverse event. • This will provide a different sequence of treatments as people who fail the initial biologic may move to etanercept or adalimumab, infliximab, abatacept or golimumab. • Tocilizumab as a third biologic in the sequence is not a possible option after a second biologic failure. • **Pfizer argues that the cost effectiveness of this sequence should also be presented as this will be different to the results presented for patients in which rituximab are contraindicated or inappropriate due to an adverse event.**
No reporting of model validation and if an external peer review of the model was undertaken	• No reporting of how the AG's model was validated and quality checked. In some areas of the report it is not entirely clear what methods have been taken by the assessment group and reproducibility of the model is felt to be low. • Given that there is no access to the model this makes the transparency of the model extremely low and Pfizer is concerned that there has been no independent validation of the model to identify potential errors in the model. • **Can the AG report how the model has been validated and quality checked.**
Patients in the Moderate to Severe population of the BSRBR are not representative of a Moderate to Severe population seen in RCTs or patients in clinical practice	• The AG sampled from patients who are MTX experienced from the BSRBR including those patients with a DAS28 score between 3.2 and 5.1. Section 6.3.8, pg 353. • Both Pfizer (pg217 TAR) and Abbvie (pg214 TAR) have noted within their submissions the limitations of the bDMARD cohort from the BSRBR with a DAS28 <5.1 due to them being a very select group of patients with non-normal characteristics due to patients not being eligible for bDMARDs based on NICE guidance. Hyrich et al 2009[39] have suggested that "it is possible that these patients [with a DAS28 <5.1] are fundamentally different from patients who receive these agents [TNF inhibitors] in countries without these restrictions, meaning the results may not be generalisable to the wider population". • **Pfizer suggests that the mean patient characteristics are taken from the moderate trials i.e. Etanercept PRESERVE or certolizumab CERTAIN and then a covariance matrix from the BSRBR severe population is used to preserve the relationship between baseline characteristics. This approach was utilised in the Pfizer submission.**
Clarification of whether the baseline characteristics for the bDMARD and cDMARD cohorts	• It is not clear whether the AG have used the initial patient characteristics from the control cohort and the bDMARD cohort of the BSRBR or a combined cohort of both cDMARDs and bDMARDs. • **Pfizer seeks to clarify this and suggests that only the bDMARD patient cohort is applicable to simulate patients given that the cDMARD cohort has different baseline characteristics to the**

have been combined	**bDMARD cohort.**
MTX dose in the model and the assumption that MTX will be escalated from the lowest dose to the maximum dose	• The AG have assumed in Table 185, pg 355, that people on MTX will start on 7.5mg per week escalated by 2.5mg per week up to 20mg per week. Pfizer notes that MTX is used in multiple places in the treatment sequence for population 2 and 3 in the model. This is likely to underestimate the cost of MTX throughout the model. Pfizer feels it is very unlikely that patients will be started on the lowest dose of MTX, as they are likely to have already received MTX as part of their initial DMARD therapy. • **Pfizer argues that a higher starting dose of MTX should be assumed throughout the model for MTX.**
Underestimation of 'non-biologic therapy' and rescue therapy in the model	• Non biologic therapy has been assumed by the AG to be an approximation of cDMARD therapy (leflunomide, gold and cyclosporine etc) in Table 185, pg 355. The monitoring assumptions for this treatment have not been reported by the AG. • Pfizer acknowledge the difficulty of accurately costing the non biologic therapy/ palliative care/rescue therapy costs. Pfizer have made a similar assumption in their economic model around triple cDMARD use. However, we feel it is important to note that these assumptions are likely to represent an underestimation of the total costs on palliative care and rescue therapy. • A recent Pfizer advisory board has suggested that there may be a number of additional costs that may be more appropriate to this treatment line. These included pain medication, physiotherapy and surgery could be considered to treat the symptoms of disease at this stage. It was further suggested that biologics would likely to be redundant (by association so would conventional DMARDs) as inflammation is no longer the predominant feature of the disease and the structural damage is likely to be significantly progressed (Pfizer data on file, available on request). Given these additional costs, Pfizer suggests that the additional cost of £720 per year assumed by the AG is likely to be an underestimation of the true costs. • Furthermore, Pfizer are concerned that AG's analysis of cDMARD HAQ progression in the model means that relatively few patients will ever have a high HAQ score and by association high costs of medical resource use in the model. • **Accordingly, Pfizer feels that the costs of palliative care in the AG model has been underestimated and is likely to be in favour of the cDMARD strategy compared to the bDMARDs strategy.**

Assumption that bDMARDs will all have the same monitoring costs as MTX and that these will be equal to the monitoring costs for MTX overestimates the cost of bDMARDs	• The AG has made an assumption that monitoring costs are assumed equal for MTX and bDMARDs on pg 356 and 357. It is not clear what monitoring costs have been assumed for the other treatments included in the model and are presented in Table 185, p355. The AG has not reported whether they got clinical input into these assumptions. • Pfizer is concerned by this simplifying assumption made by the AG. The monitoring tests and costs of monitoring for bDMARDs and cDMARDs vary between individual treatments in both classes[40, 41] • Furthermore, Pfizer is concerned by the assumption that methotrexate monitoring in the first 6 months has been applied to biologics. Pfizer do not believe that the frequency of monitoring will occur this frequently for bDMARDs. Furthermore, some of the monitoring will either be done at home via homecare delivery for subcutaneous bDMARDs or during administrations of IV bDMARDs and therefore this is additional cost that is unlikely to fall on the NHS or be included in current administrations. • Similarly, Pfizer does not believe the recurring monitoring cost for bDMARDs will be as regular as for MTX. Clinical advisors have suggested that the monitoring for bDMARDs will occur around 2-3 months after the first 6 months. (Pfizer advisory board, available on request) Accordingly, Pfizer feels that that the AG has overestimated the monitoring costs for bDMARDs compared to MTX and is likely to be detrimental to the bDMARD cost effectiveness versus cDMARDs. • **Pfizer recommend that reduced monitoring costs should be assumed for bDMARDs compared to MTX in line with previous NICE appraisals (TA130 and TA195). Furthermore, correct testing and monitoring costs for individual treatments should be applied by the AG from available sources and guidelines.**
Simulating the expected pain score associated with HAQ	• The AG has simulated the expected pain score based on the HAQ score in Section 6.3.18 page 378. The AG report that the estimation of EQ-5D utility scores is substantially more accurate when based on HAQ and pain than on HAQ alone. • Pfizer feels that this is somewhat contradictory. The AG is improving predictability of the relationship between HAQ and utility but is still using HAQ to improve this relationship and not independent pain values. In effect they are still using HAQ alone to estimate the impact on utility. • **Pfizer argues this does not make this source any more robust than the sources used by the manufacturers based on HAQ alone.**
Stability of the assessment groups model given their test on the appropriate number of patients to run when generating results	• The AG has indicated that 3000-5000 patients are needed to produce relatively stable ICERs when reproducing analyses in Section 6.3.21 pg 383. A test using 10,000 patients is provided to show the stability of the model between two runs illustrating discounted costs, discounted QALYs and discounted ICERs s in Figures 100, 101 and 102. The figures show a considerable amount of variability between treatments at 10,000 patients. CTX+MTX appears to move from most cost effective treatment out of 7 treatments to the 4th or 5th most

	cost effective strategy. • **Pfizer is concerned that the AG model results have not been run using a sufficient number of patients given the variability of results. Pfizer suggest that further testing be carried out to see if this is the case.**
Same serious infection rate for all bDMARDs, but a differential serious infection rate for cDMARDs	• The AG has used a different rate of serious infections between cDMARDs and bDMARDs in the model (Section 6.3.19 pg 381). However, the AG has assumed serious infections rate between bDMARDs is the same. The reference used by the AG for the serious infection rate reports a significant difference between certolizumab pegol and the control[38]. • In contrast the AG argue that time on treatment should be the same between cDMARDs and bDMARDs due to similar toxicities (Section 6.3.15 pg 381-382). • **Pfizer argues there should be consistency in approach to applying serious infections and time on treatment in the model.** • **Pfizer argues that given difference in the rates for serious infections between bDMARDs the individual rates from Singh et al should be used.**
Pfizer suggests a number of further scenarios and sensitivity analyses are undertaken to reflect the uncertainty in the literature, methods and model assumptions	• The restricted use of sensitivity and scenario analyses limits understanding of key model drivers and does not explore the full breadth of uncertainty in the decision problem. • **Scenarios that explore the cost effectiveness of first line bDMARDs rather than the NICE treatment pathway of bDMARDs compared to cDMARDs.** • **The use of ACR mapped directly to HAQ in the model given the uncertainty in using the VARA dataset. This will also allow a direct comparison with recent NICE appraisals and the majority of manufacturer submissions in this appraisal.** • **Modelling a scenario for patients who have a contraindication or AE to rituximab and progress down an alternative treatment pathway on the basis of NICE guidance in TA195.** • **A scenario modelling the reduction in efficacy and time on treatment for subsequent lines of therapy as used in TA195 and TA247.** • **Cost relationships used in previous NICE appraisals given the limitations with the NOAR dataset: Kobelt 2002 used in TA280, Brennan 2007 and Malottki et al 2011 used in TA195.** • **Use of mean patient characteristics for moderate to severe population from moderate trials like etanercept PRESERVE[36] and certolizumab pegol CERTAIN[37] instead of the BSRBR given the limited number of observations and limitations with the cohort in this population** • **Rebound assumption where patients are assumed to return to their pre-treatment baseline HAQ.** • **Exploration of higher costs attached to non-biologic therapy/rescue therapy to explore the uncertainty in resource use attached to this treatment in the AG model.** • **Differential rate of serious infections for bDMARDs in the model, as**

	per the reference used by the AG, which showed a significance difference between certolizumab pegol and control[38]

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