Rheumatoid arthritis - adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab - review [ID537]
Pfizer Response to additional analyses from the Decision Support Unit and Assessment Group
2nd April, 2015

Pfizer welcomes the opportunity to comment on the Decision Support Unit (DSU) *Report on Progression of Disease in People with Rheumatoid Arthritis Treated with Non-Biological Therapies* from The School of Health and Related research (ScHARR), University of Sheffield (referred to as document 2) and the addendum to the ScHARR Assessment Group (AG) report *Assessing how the results from the DSU report on HAQ progression affect the cost per QALY gained ratios* (document 3). Pfizer note that several authors of the Technology Assessment Report (TAR) contributed to the DSU report and indeed declared a conflict of interest. Therefore, Pfizer consider the DSU report an extension of analyses included in the original TAR.

Overall Pfizer is disappointed that the DSU/AG continues to propose Health Assessment Questionnaire (HAQ) progression estimates derived from the ERAS cohort. This is despite Pfizer and other consultees raising concerns with this approach in response to the original TAR and at the meeting with the DSU on 1st December 2014. In comparison to the scope of this appraisal, the majority of patients included in the ERAS cohort have less severe disease (as measured by Disease Activity Score [DAS]) and have received fewer prior conventional disease modifying anti-rheumatic drugs (cDMARDs). More importantly, these patients exhibit slower HAQ progression, which leads to an underestimation of the resultant cost-effectiveness estimates for biological disease modifying anti-rheumatic drugs (bDMARDs). Notwithstanding the limitations of the ERAS cohort, Pfizer believe the ERAS sub-analysis represents the closest approximation to the populations included in the scope of the appraisal. However, we would suggest that further validation of analyses on this sub-population should be undertaken. This should include but not limited to a description of patient characteristics for each trajectory class, probabilities of class membership and testing of alternative modelling approaches such as linear mixed effects regression modelling.

In addition, we disagree with the DSU/AG's non-linear interpretation of HAQ progression from ERAS. We believe that the most relevant analyses presented by the DSU/AG continue to support the linear approximation of HAQ progression previously accepted by NICE and included in our cost-effectiveness model. This position was substantiated by a recent publication by Norton et al (2014), which adopted an alternative analytical approach to that preferred by the DSU/AG. Importantly, it stratified HAQ progression by DAS and adjusted for changes in treatment over time, which accounted for some of the limitations associated with the ERAS/ERAN dataset. Linear estimates of HAQ progression for patients with severe disease were found to exceed those accepted in previous Technology Appraisals. Consequently we are confident that the model results included in our original submission remain credible and that etanercept is a cost-effective treatment for patients included in the scope of this appraisal.

Moreover,, Pfizer continue to question the validity of the AG economic model and remain sceptical regarding the resultant base case results produced including the proposed lower bound incremental cost-effectiveness ratios (ICERs) presented in document 3. Despite the correction of previously identified coding errors, results remain widely divergent from the

Pfizer model, even for scenarios where identical cDMARD HAQ progression estimates were applied. The results of our most recent testing of the AG model has identified a number of potential reliability issues. One of the most impactful was uncertainty surrounding the relationship between pain and HAQ, which impacts on utilities. Testing the model using the original NDB analysis and linear HAQ progression returned an ICER for etanercept of approximately £29,000 per quality-adjusted life-year (QALY) in the severe cDMARD inadequate response population. This is substantially lower than the corresponding linear base case ICER for etanercept of £39,068/QALY reported in the updated TAR (Table 182). Further details on this and other reliability issues relating to the AG model are presented in the separate pro-forma.

Given the continued uncertainty with the AG model we are disappointed that despite the Appraisal Committee's request for tri-angulation of the DSU/AG model results with manufacturer models, that this has not been completed as part of this addendum work.. To this end, Pfizer have rerun their economic analyses utilising the linear HAQ progression estimates from the DSU ERAS sub-analysis and Norton et al (2014) in the cost-effectiveness model previously submitted by Pfizer. For the population in which etanercept is currently recommended by NICE (severe disease activity following treatment with cDMARDs, TA130) all ICERs were below £30,000/QALY when compared to cDMARDs. Furthermore, ICERs for other populations in scope were below £30,000/QALY in all but the most conservative scenarios tested. These findings contrast with the base case for etanercept in the updated TAR, which for the AG's preferred HAQ progression approach exceeded £60,000/QALY in all populations.

Furthermore, Pfizer would like to emphasise that the reports reviewed here have only addressed one of our key areas of concern raised within our response to the original TAR, which was that use of the ERAS database to inform HAQ progression for cDMARDs does not reflect patients with more established disease. We would like to take this opportunity to raise our additional concerns with the validity of the analyses undertaken by the AG in order to ensure that the Appraisal Committee takes these points into account at the next committee meeting in May 2015. These are summarised as follows:

1. The AG's cost-effectiveness model compared a full treatment pathway for bDMARDs compared to cDMARDS alone. This was not representative of NICE guidance and under-estimated the cost-effectiveness of bDMARD treatment.
2. Clinical effectiveness data for moderate and severe populations have been combined for the purposes of the evidence network. This underestimates bDMARD response in a severe rheumatoid arthritis population and will underestimate the cost-effectiveness of bDMARDs for the severe cDMARD inadequate responder population.
3. Use of EULAR response as the primary efficacy measure is inconsistent with previous NICE appraisals and confounded by substantially fewer trials reporting this outcome. ACR response should be used in line with previous NICE appraisals.
4. A number of registries of low generalizability to the UK informed the AG's economic model, such as the VARA database used for mapping ACR to EULAR This introduced uncertainty that should be explored in sensitivity analyses.
5. Simplifying assumptions were made in the AG's model that could underestimate the cost-effectiveness of bDMARDs. For example the inclusion of monotherapy and combination therapy in a single evidence network for the model. We have yet to review the results of sensitivity analyses exploring these key assumptions.

In light of the points raised regarding the new reports and also our previous response, Pfizer continue to argue that there are important limitations with the DSU/AG approach that lead to an underestimation of the cost-effectiveness of bDMARDs. We continue to believe that progression of HAQ in the submitted Pfizer economic model is credible and relevant to the populations included in scope. This is supported by the most relevant findings from the DSU report and also the recent publication by Norton et al (2014). Implementing these new estimates of HAQ progression in the Pfizer model continues to suggest that etanercept represents value for money to the NHS in all populations within the scope of this appraisal. Therefore, the ICERs for etanercept presented in this response should be considered alongside estimates from the AG at the forthcoming Appraisal Committee meeting.

Pfizer review of the DSU report

The following sections provide further details on the key points for consideration regarding document 2. Additional comments are included in the Factual inaccuracies and other points section on page 12 of our response.

1. **The ERAS cohort preferred by the DSU is not representative of the populations included in the scope of the appraisal and cannot be relied upon for decision making. Furthermore, the DSU preferred analysis did not account for important changes in cDMARD treatment over time.**

Pfizer supports the conclusion within the DSU report (Doc. 2, p.67) that "there is no study that reports how HAQ progresses in rheumatoid arthritis (RA) patients on non-biologic therapies that coincides entirely with the requirements of the cost effectiveness analysis". Consequently, Pfizer is concerned that the DSU's preferred analysis continues to use data from the whole ERAS cohort and not the sub-analysis, which despite limitations is more representative of the populations in scope. This underestimates HAQ progression experienced by patients who receive cDMARDs and consequently underestimates the cost-effectiveness of a bDMARD strategy compared to cDMARDs.

Consistent with the maintenance of response observed in BSRBR, the AG and Pfizer applied no progression of HAQ for patients receiving bDMARDs. Given the purpose of the BSRBR to collect data on patients receiving bDMARDs, this data can be considered representative of patients included in scope. However, ERAS recruited patients with recently diagnosed RA and so patients differ substantially from those in the scope of this appraisal and recruited into the BSRBR cohort. Table 1 describes the patients included in each cohort. Key differences are as follows:

- ERAS included patients in the early stages of RA who had substantially shorter disease duration than patients who initiated bDMARDs in BSRBR.
- Mean HAQ at baseline in ERAS (1.14) was substantially lower than that from the BSRBR (2).
- Mean DAS at baseline in ERAS was substantially lower (4.5) than that from the total or severe disease activity BSRBR cohorts (6.6 or 6.2).
- No patients at baseline in ERAS had failed 2 prior DMARDs and only 16% met this criterion over the entire observation period (Doc. 2, Table 5, p.27). Patients in BSRBR have on average failed more than 2 DMARDs irrespective of disease activity.

Table 1. Comparison of BSRBR and ERAS cohort characteristics

	BSRBR			**ERAS**	
	Total	**Severe**	**Moderate**	**Total cohort**	**Post 2 DMARDs**
Age	56.2	57.3	58.0	55.13	55.54
Female	0.8	80%	70%	67%	74%
HAQ	2	1.6	1.5	1.143	1.414
DAS28	6.6	6.2	4.4	4.501	4.317
DAS>5.1	NR	100%	0.0	NR	24%
Disease duration (yrs)	13.3	9.4	10.2	8.2	5.7
Previous DMARDs	3.9	2.8	2.9	0	NR
Failed 2 DMARDs	NR	NR	NR	0	100%

Source: adapted from tables 2, 3 and 23 presented in Doc. 2

Additionally, the historic nature of the ERAS cohort (patients enrolled between 1986 and 1998) may have introduced a number of biases:

- Current NICE (2015) recommendations are for newly diagnosed patients with active rheumatoid arthritis to receive a combination of cDMARDs (including methotrexate and at least one other cDMARD). Patients included in ERAS were largely managed using a sequence of sulfasalazine followed by methotrexate (Norton et al 2012). Only 42% of patients having received methotrexate. Given the efficacy of methotrexate in newly diagnosed RA patients and its delayed initiation, modelling HAQ trajectories from baseline using the ERAS cohort is of limited relevance to current practice and will underestimate HAQ progression.
- Surgery and joint replacement were common (Musa et al 2008). At 10 years follow up it was reported that 27% of 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. These interventions are likely to either halt or more likely improve HAQ levels long-term and their impact has not been differentiated from cDMARDs.

Consequently, only a very limited proportion of the ERAS cohort can be considered reflective of the populations included in scope. As acknowledged by the DSU, similar if not more substantial limitations apply to the other databases appraised by the DSU (ERAN, LEIDEN, BARFOT and NDB datasets, Doc. 2, p.25). Therefore, the reliability of latent class growth modelling (LCGM) to differentiate trajectories of HAQ progression must be questioned when only a very small sample of patients relevant to the appraisal were included in the preferred analysis.

In recognition that an *"alternative view is to restrict analysis to those data drawn from relevant patients"* the DSU undertook a sub-analysis of ERAS patients who failed 2 DMARDs (characteristics reported in Table 1). Pfizer agree that such an approach was more likely to generate relevant HAQ progression estimates. Since only a small minority of patients in ERAS were relevant to the scope of the appraisal it is likely that data from non-relevant patients unduly influenced findings from the DSU's preferred LCGM. Nonetheless, there a number of important limitations with the ERAS sub-analysis:

- Only approximately 92 patients from the sub-analysis cohort of 380 would be eligible for bDMARDs according to current NICE guidance (TA130) as only 25% of this cohort had DAS>5.1. The number of patients that would meet criteria for inclusion in the severe naïve or moderate-severe populations is also ambiguous.
- The DSU stated that the time point at which the third cDMARD commenced was unknown and the duration of follow-up available for patients post-2 DMARDs is unclear.
- Patient characteristics for each predicted class for the sub-analysis have not been presented by the DSU. These are necessary to compare class membership with the entire cohort analysis presented in Table 1 of Norton et al (2012). Probabilities of class membership for the sub-analysis have also not been presented. These are required to assess the continued relevance of a 4 class model.

- Alternative methods of estimating HAQ progression were not tested in the sub-analysis. Given that the DSU identified the majority of BSRBR patients as members of HAQ trajectories class 1 or 2, Pfizer believe the testing of a 3-4 class model is of limited relevance to the sub-analysis cohort. Fewer classes and alternative methods of estimating HAQ progression, such as linear mixed effects regression models, should be tested.

Notwithstanding the limitations outlined above, of the analyses undertaken by the DSU, Pfizer believe the ERAS sub-analysis represents the closest approximation to the populations included in the scope of the appraisal. However, we would suggest that further validation of analyses on this sub-population should be undertaken. This should include but not limited to a description of patient characteristics for each trajectory class, probabilities of class membership and testing of alternative modelling approaches such as linear mixed effects regression modelling.

2. Results from the DSU analyses indicate that approximating HAQ progression as linear remains a valid approach in patients with moderate/severe disease activity treated with cDMARDs.

In all previous Technology Appraisals in this area (TA130, TA186, TA195, TA225, TA247) it was assumed within cost-effectiveness models that progression of HAQ for patients on cDMARDs is linear. Over the course of these appraisals this approach was validated in discussion with numerous clinical experts. For the current appraisal the AG have proposed a change to a non-linear modelling of HAQ progression using LCGM. This was justified by the AG on the basis of LCGM incorporating patient characteristics as predictors of HAQ progression and the absence of any restrictions imposed on how the rate of HAQ progression changes over time. However, Pfizer note that the choice of covariates or clinical validation of the plausibility of predictions has not been fully discussed within the DSU report, which is inconsistent with methods guidance from the DSU (Kearns et al 2012). Pfizer believe that the non-linear shape of the observed and projected HAQ trajectories can be explained by the initial treatment effect observed in a cohort identified at diagnosis and long term attrition within the sample. Therefore, the linear approximation validated with clinical experts and used in the Pfizer economic model remains relevant.

The DSU explain that *"in the majority of the datasets, there is an initial drop in HAQ, creating a J-shaped curve. This is because in all datasets except the NDB, patients were recruited at or shortly after diagnosis and generally put onto therapy at that point or shortly after".* Consequently, Pfizer consider that data from this non-linear period should not be used to inform HAQ progression for the populations in scope who are identified as cDMARD inadequate responders. Furthermore, the DSU indicate that the period from year 2 to year 8 "is where generally there is greater certainty due to the larger number of observations" (Doc. 2, p.32). This is consistent with the acknowledgement from the DSU that the predictive ability of the LCGM ERAS sub-analysis diminished beyond year 8 (Doc.2, p.57 and Figure 21). Similar limitations can be observed with the full ERAS cohort LCGM for which predictive ability appears to diminish after year 10 (Doc. 2, Figure 8, p.42).

For the DSU's preferred analysis it is indicated that the majority of patients relevant to the appraisal scope are included in HAQ trajectory classes 1 and 2. Examination of these classes and for the time period of most relevance (years 2 to 8) in both the DSU preferred

analysis (Doc. 2, Figure 8, p.42) and the sub-analysis (Doc. 2, Figure 21, p.57) suggests that HAQ progression is approximately linear.

This is supported by data presented in section 2 of the report from Krishnan et al (2004) which presents the annual change in HAQ for 6,000 patients from multiple datasets in the US and Canada. Upon review of Figure 3 in the DSU report, it appears that HAQ at baseline may influence the trajectory at which HAQ progresses. While the median suggests that HAQ increases at a decreasing rate, HAQ at baseline is fairly low (Doc. 2, Figure 3, p.17). More interestingly, the 75th and 90th percentiles, which have a baseline HAQ more reflective of patients who receive bDMARDS in the UK indicate that HAQ increases in a linear fashion over 18 years of follow-up.

Pfizer therefore conclude that although simplistic, a linear approach to modelling HAQ progression in patients requiring bDMARD treatment is reasonable. Furthermore, the linear progression estimates presented by the DSU (Doc. 2, Table 14, p.42 and Table 27 p.58) and summarised below (Table 2) indicate that the change in HAQ of 0.125 over 2.7 years (~0.045/year) accepted in previous Technology Appraisals was a reasonable approximation. This is despite aforementioned limitations with the applicability of the ERAS cohort to patients included in scope. Consequently, Pfizer consider the cost-effectiveness analyses included in our original submission as reflective of the long-term value of etanercept in the treatment of rheumatoid arthritis.

Table 2. Annual rates of HAQ change reported by the DSU for ERAS cohorts

Analysis		**Population sampled from BSRBR (ΔHAQ/year)**		
	Time period analysed (years)	**Total**	**Severe**	**Moderate**
ERAS cohort	After t=2	0.0326	0.0293	0.0264
	t=2 to t=8	0.0617	0.0551	0.0480
ERAS sub-analysis (post 2 DMARDs)	After t=2	0.0401	0.0406	0.0362
	t=2 to t=8	0.0494	0.0489	0.0389

The HAQ trajectories for ERAS patients most relevant to the appraisal (classes 1 and 2) were approximately linear during the time periods associated with the most robust data (years 2 to 8). Pfizer believe that this data continues to support the linear approximation of HAQ progression previously accepted by NICE and included in our cost-effectiveness model. Therefore, Pfizer recommend that the linear estimates presented by the DSU in Table 27 of their report be considered alongside the values previously accepted in NICE appraisals and utilised in our model. Note Pfizer have tested the most relevant DSU HAQ progression values in our economic model and results are reported in point 5 below.

3. **The validity of the linear approach to the approximation of HAQ progression is supported by a recently published analysis of a UK patient cohort by Norton et al. (2014). This showed that linear rates of HAQ progression in severe patients exceeded those accepted in previous Technology Appraisals.**

The analysis by Norton et al (2014) provides an alternative approach to estimating HAQ progression for cDMARDs in patients relevant to the scope of the appraisal. Pfizer

recommend that the DSU review the methods employed and consider the publication an additional source of HAQ progression estimates for use in the appraisal.

The analysis by Norton and colleagues combined the ERAS (n=1,460) and ERAN (n=1,236) cohorts and grouped patients by DAS28 into low (≤3.2), moderate-low (>3.2 and ≤4.2), moderate-high (>4.2 and ≤5.1), and high (>5.2) disease activity over follow up. Similar to the preferred LCGM analysis by the DSU a large proportion of patients included in the analysis would not meet the scope of this appraisal. However, to allow for differential rates of progression by treatment over time, interaction terms were included for all DMARD related variables with time and DAS group. Treatment with corticosteroids and orthopaedic surgery were also controlled for. Results showed that for patients similar to those included in the scope of this appraisal, HAQ progression estimates accepted in previous Technology Appraisals (0.045/year) may have been conservative (Table 3).

Table 3. Impact of disease activity and treatment on progression (Norton et al 2014)

Disease activity	∆HAQ/year	95%CI
Low (DAS28≤3.2)	0.014	0.005 to 0.024
Moderate-Low (3.2<DAS28≤4.2)	0.039	0.029 to 0.049
Moderate-High (4.2<DAS28≤5.1)	0.064	0.053 to 0.074
High (DAS28>5.2)	0.080	0.066 to 0.093

Inclusion of time dependent covariates is an important differentiator of the analysis by Norton et al (2014) and Pfizer are concerned that they appear not to have been included in the DSU's preferred LCGM. The DSU state: "*The covariates used to predict latent class membership are the same as in Norton et al [2012]: age, gender, DAS, symptom duration, rheumatoid factor, and fulfilment of ACR criteria, all at baseline*" (Doc. 2 p.41). The higher HAQ progression rates (after year 2) estimated by the DSU for the ERAS sub-analysis compared to the whole ERAS cohort support these concerns (Doc. 2 Table 27 vs. Doc 2. Table 14).

There are limitations with the data available from Norton et al 2014 as the publication is currently only in abstract form. Nonetheless, the linear HAQ progression estimates from it suggest that the DSU not accounting for changes in treatment over follow-up has underestimated the rate of HAQ progression and consequently cost-effectiveness of bDMARDs in the AG model.

Norton et al (2014) combined two of the UK patient cohorts appraised by the DSU/AG (ERAS and ERAN). The publication is important to this appraisal as the analytical approach employed differed from that adopted by the DSU/AG in several respects. It stratified HAQ progression over time by DAS and controlled for changes in treatment, including cDMARDs, generating estimates of HAQ progression that correspond to patients who would be potentially eligible for bDMARDs. The availability of the publication was raised by Pfizer at the meeting on 1st December and it is unclear to Pfizer why this important analysis was not included in the DSU report. Pfizer recommend that the DSU review the methods employed and consider the publication an additional source of HAQ progression estimates for use in the appraisal.

Pfizer review of the AG report assessing how the results from the DSU report on HAQ progression affect the cost per QALY gained ratios

The following sections provide further details on the key points for consideration on document 3. Additional comments are included in the Factual inaccuracies and other points section on page 12 of our response.

4. **The analyses presented by the DSU/AG as a plausible lower bound on the ICER are based on analyses of patients not representative of the populations included in the scope of the appraisal and have not been justified.**

Document 3 outlines the impact on the revised base case ICERs of implementing HAQ trajectories for subgroups with the highest latent drop out, as identified by the DSU. The AG state that these "can be taken as a credible upper bound of the HAQ trajectory for any subgroup of patients". Pfizer are concerned that no justification has been provided for this statement and that alternative plausible lower bound ICERs have not been presented.

The HAQ progression trajectories implemented in the AG model suffer from the same limitations regarding characteristics of the analysis population as outlined for the DSU's preferred analysis (See point 1 above). Furthermore, no clinical rationale was presented for the varying shape of the curves.

Given the wide range of analyses undertaken by the DSU, the scope of the cost-effectiveness analyses presented in this report is extremely limited. Pfizer consider that additional analyses are required to inform the Appraisal Committee of the full impact of the DSU report on HAQ progression (Document 2).

Pfizer seek from the DSU/AG a clinical rationale as to why the HAQ trajectories of patients with the highest latent drop out offer a credible upper bound for use in cost-effectiveness analysis. The current report provides only a limited assessment of different HAQ progression estimates and should not be regarded as a plausible lower bound of cost-effectiveness by the Appraisal Committee. In the absence of a patient cohort that corresponds to the populations included in the scope of the appraisal Pfizer suggests that scenario analysis be undertaken in the AG cost-effectiveness model using linear estimates from the DSU sub-analysis of patients of greatest relevance to the appraisal and also estimates from Norton et al's (2014) treatment history adjusted analysis of ERAS/ERAN.

5. **Cost-effectiveness estimates from the AG model remain associated with considerable uncertainty. Pfizer is therefore concerned that results from the AG model using the new HAQ estimates have not been validated against other models, as requested by the Appraisal Committee in the DSU specification.**

NICE commissioned the DSU to research *"What is (are) appropriate estimate(s) for the rate of underlying disease progression for people with rheumatoid arthritis while on treatment with (1) conventional DMARDs and (2) palliative care / non biological therapy (that is the rate*

of progression for 'last-line' treatment after the failure of biological and conventional DMARDs)?"

Within the DSU specification the Appraisal Committee outlined five key areas for research that would attempt to address the aforementioned questions and indicated that the DSU/AG would provide six deliverables/outcomes. Whilst it appears that the DSU/AG have addressed the majority of the analyses outlined in the remit, they have not undertaken a review of the respective HAQ estimates in the manufacturer models. This request was stated in the *exact analyses required* and the *DSU deliverables/outcomes* sections of the DSU specification.

Pfizer believe that this request, although optional, was of vital importance to differentiate the impact of uncertainty associated with HAQ progression estimates from that associated with other causes in the AG model. In particular numerous modelling errors were identified in the previous review of the AG model by consultees. Following Pfizer's assessment of the recently updated model it was identified that the selection of the relationship between pain and HAQ is unclear and an important driver of results. Modelling the original NDB Quadratic Regression relationship included in the model generates an ICER for etanercept with methotrexate vs cDMARDs of £29,000/QALY when linear cDMARD HAQ progression is applied. This is substantially lower than the corresponding linear base case ICER for etanercept of £39,068/QALY reported in the updated TAR (Table 182).

Furthermore, the model visual basic code remains opaque and HAQ progression is not presented as a model output. As a result implementation of the HAQ progression class membership using BSRBR patient baseline characteristics cannot be verified or compared against long term projections from manufacturer models. In addition our previous response to the TAR identified important differences with regards to treatment sequences and model assumptions employed. Consequently cost-effectiveness estimates from the AG model remain associated with considerable uncertainty and cannot be relied upon for decision making.

Therefore, to inform the considerations of the Appraisal Committee Pfizer have addressed the question in the DSU/AG specification regarding testing the estimates of HAQ progression in the manufacturers' models, in this case the Pfizer model. Since the Pfizer model was not designed for the inclusion of four latent class growth trajectories of HAQ progression the approach adopted by the AG cannot be fully replicated. Nonetheless, as outlined in point 2 above, assuming linear progression of HAQ for patients included in scope appears a reasonable approximation. On this basis, and despite limitations with their derivation, the linear estimates provided by the DSU for the ERAS sub-analysis have been implemented in the Pfizer model. In addition Pfizer have undertaken a scenario analysis implementing the DAS and treatment history adjusted HAQ progression rates presented in Norton et al (2014).

For patients with severe disease activity and previously treated with DMARDs our analyses indicated that etanercept compared to a cDMARD strategy was cost-effective with ICERs below £30,000/QALY for all HAQ progression estimates tested (Table 4). In the severe DMARD naïve population ICERs (Table 4) for etanercept compared to a cDMARD strategy were below £30,000/QALY for all scenarios except the most conservative HAQ progression rate (0.0406). A similar situation was observed for patients with moderate disease activity and previously treated with DMARDs, where only the most conservative scenario (0.0362)

returned an ICER above £30,000/QALY (Table 5). The ICER was not observed to exceed £31,000/QALY for any population or HAQ progression estimate. Pfizer therefore continue to believe that our original submission remains relevant and that etanercept is cost-effective for all patients included in the scope of the appraisal.

Table 4. Scenario analyses undertaken in the Pfizer model: Severe populations included in scope

Analysis	HAQ progression estimate (ΔHAQ/year)	Severe DMARD naïve (£/QALY)	Severe post DMARDs (£/QALY)
Pfizer base case	cDMARD: 0.046* Palliative care: 0.06	27,882	20,520
ERAS sub-analysis (post 2 DMARDs) (Doc. 2, Table 27)	0.0406	30,871	22,175
	0.0489	27,681	20,639
Norton et al. 2014 (DAS28>5.2)	0.08	20,307	16,832

*Estimate based on a change of 0.125 over 2.7 years reported in TA195.

Table 5. Scenario analyses undertaken in the Pfizer model: Moderate-severe population included in scope

Analysis	HAQ progression estimate (ΔHAQ/year)	Post DMARDs £/QALY
Pfizer base case	cDMARD: 0.046* Palliative care: 0.06	24,727
ERAS sub-analysis (post 2 DMARDs) (Doc. 2, Table 27)	0.0362	30,811
	0.0389	28,722
Norton et al 2014 (3.2<DAS28≤4.2)	0.039	28,722
Norton et al 2014 (4.2<DAS28≤5.1)	0.064	20,337

*Estimate based on a change of 0.125 over 2.7 years reported in TA195.

Pfizer requests that the new cost-effectiveness analyses undertaken by Pfizer and presented in this response be considered at the Appraisal Committee meeting alongside those from the AG. Notwithstanding limitations with the DSU's HAQ progression estimates, cost-effectiveness analyses undertaken using the Pfizer model indicate that ICERs based upon the most relevant DSU HAQ progression estimates (ERAS sub-analysis) are consistently below £30,000/QALY and that etanercept remains value for money for the NHS.

Factual inaccuracies and other points

Document and location	Description of problem	Description of proposed amendment
DSU Report, Section 2, Context and Literature, p.16-18	Comparisons are made between HAQ progression estimates reported in the literature and that of 0.045 accepted in previous NICE Technology Appraisals. However, there is no discussion of the relevance of the patients studied to the populations in scope.	Include, where available, information regarding the severity of disease and prior treatment history so as to allow informed comparison of HAQ progression rates.
DSU Report, Section 3, p.18	The authors state *"Our suggested data sources were discussed and presented in two workshops held in 2014, attended by clinical experts, economists with experience of this area, as well as patient and manufacturer stakeholders."* Pfizer were informed of, and attended only a single meeting with the DSU on Monday 1st December 2014. This meeting was used to present the data sources identified by the DSU, and ask if manufacturers were able to identify any additional sources. Could NICE please confirm that there were two DSU meetings held in 2014, and if manufacturers were invited to the earlier other meeting?	Amend text to clarify that only a single meeting occurred with manufacturers.
Impact of DSU HAQ progression report (Document 3), Section 3, p.7	A cross reference is made to section 2.3.2 of the DSU report (doc. 2). This section is not present in the DSU report.	Amend text to correct the cross-reference. Pfizer have interpreted this as an intended cross-reference to section 3.2.3 of the DSU report.
Impact of DSU HAQ progression report (Document 3), Section 2, p.5	The base case HAQ progression illustrated in Figure 2 does not correspond to that presented in either the DSU report or revised AG report.	Clarification of the source of Figure 2 is requested.

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