Wyeth comments on the Appraisal Consultation Document for adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after failure of a TNF-α inhibitor.

Wyeth welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (RA) after failure of a TNF-α inhibitor.

Whilst it would appear that the relevant evidence has been taken into account Wyeth has a number of concerns regarding the interpretation of the clinical and cost effective evidence and therefore do not consider that the provisional recommendations of the Appraisal Committee are sound or constitute a suitable basis for the preparation of guidance to the NHS.

Executive Summary

Our concerns are set out below and explanation of each point is set out in the section following the Executive Summary.

1. There is no evidence that patients who do not respond to their first TNF-α inhibitor experience any further HAQ improvements on conventional DMARDs.
2. Balance of evidence in relation to HAQ values for a second TNF-α inhibitor has fundamentally changed and it is now not appropriate to consider BSRBR data as the primary source.
3. There have been serious breaches of NICE processes with regards to including rituximab as a comparator which has led to inappropriate analysis, and changing the discount rates which has introduced bias in the analysis which may have misled the appraisal committee.
4. Wyeth has update its economic model to incorporate consideration of these key points which clearly demonstrates that etanercept is not only cost-effective as a first-line TNF-α inhibitor, but also when used as sequentially after the failure of a first TNF-α inhibitor vs. non-biologic DMARDs and rituximab. This is substantiated by an analysis by the University of Sheffield on behalf of the BSR.

Wyeth believes that the current ACD is perverse in its consideration of the evidence, and that the institute has not followed its own procedures. This has led to an inappropriate preliminary recommendation for rheumatoid arthritis patients in England and Wales.

Comments

Point 1

There is no evidence that patients who do not respond to their first TNF-α inhibitor experience any further HAQ improvements on conventional DMARDs.

Studies identified by the DSU on the effectiveness of non-biologic DMARDs after TNF-α inhibitor failure investigated the use of novel treatments, in people in whom TNF-α inhibitor treatment had failed in comparison with placebo when added to an ongoing DMARD. The ACD correctly states that the placebo arm of these studies are not measuring the effect of an individual DMARD, but may provide an indication of the effect of conventional DMARDs when used in TNF-α inhibitor failures (mean Health Assessment Questionnaire (HAQ) improvement of 0.11). This improvement in HAQ can not be attributed to a switch to DMARDs as the patients in the study continued to receive DMARDs plus an added placebo. The improvement seen must be attributed to placebo effect and protocol driven care instead. Therefore this is inappropriate evidence to utilise this effectiveness values within the cost-effectiveness modelling.

This has led to an overestimation of the HAQ improvements of conventional DMARD therapy in patients whom have experienced a lack of efficacy with a TNF-α inhibitor, driving higher cost-effectiveness ratios.

In the updated review of the effectiveness of conventional DMARDs after TNF-α inhibitor failure the DSU was not able to identify any evidence that directly considers the effectiveness of non-biologic DMARDs in the population of interest. Evidence from the BSRBR suggests that the response from a DMARD post TNF-α inhibitor maybe only slightly different in terms of EULAR response. However, new evidence from the BSRBR is available demonstrating no further improvement based on HAQ.

Appropriate evidence for no HAQ improvement on conventional DMARDs

Hyrich, et al. used data from the BSRBR to assess whether switching improves longer term outcomes, by comparing changes in HAQ scores one year following lack of response to a first TNF-α inhibitor[1]. This study concluded that patients with long-standing disease who do not respond to their first TNF-α inhibitor, discontinue this drug and receive no further biologic treatment in the subsequent 12 months do not experience any further mean improvement in

HAQ score over this period. Patients who continue on their first TNF-α inhibitor despite suboptimal improvement in disease activity gain further improvements in HAQ, however the best improvement was seen in patients whom switched to a second TNF-α inhibitor.

Table 1: Mean changes in HAQ scores for patients whom discontinued anti-TNF-α therapy and did not start a subsequent anti-TNF-α agent or other biologic drug during the next 12 month (stoppers) as reported by Hyrich.

Group	HAQ at start of 1st anti-TNF mean (S.D.)	HAQ when classified as non-responder mean (S.D.)	Mean change in HAQ score on 1st anti-TNF mean (S.D.)	HAQ measured 12 months after non-response mean (S.D.)
Stoppers	2.21 (0.48)	2.19 (0.51)	-0.03 (0.37)	2.19 (0.56)

Whilst the ACD implies a reasonable response based on EULAR response, this recent publication by Hyrich and colleagues from the BSRBR demonstrates no HAQ improvement. In the absence of any evidence on return to a conventional DMARD the BRAM should be rerun with a zero HAQ multiplier as the base case. Any short-term improvement must be so small that it will be less than 0.045 which is the accepted measure for HAQ deterioration for DMARD therapy.

Point 2

Balance of evidence in relation to HAQ values for a second TNF-α inhibitor has fundamentally changed and it is now not appropriate to consider BSRBR data as the primary source.

The mean HAQ improvements reported by salient studies support the use of higher effectiveness values for a second TNF-α inhibitor.

In the present technology appraisal, evidence for the clinical effectiveness of the use of a second TNF-α inhibitor was taken from a systematic review completed by the DSU.

The lower HAQ improvement from the BSRBR data drives the higher cost-effectiveness values. The literature search by the DSU found a number of articles showing that the HAQ improvements in these patients were greater than in the data from the BSRBR.

The majority of studies identified from the literature considered eligible for inclusion in the full analyses reported DAS and EULAR scores. Only a minority reported HAQ scores. The

largest data sources for HAQ scores with sequential TNF-α inhibitors were the ReACT trial and the BSRBR. Due to population included in the register and the timing of collection of the efficacy measures the BSRBR should not be used to inform the effect size of a second TNF-α inhibitor. The ReACT study in contrast identifies HAQ values collected at the appropriate time points. However, it may underestimate the true treatment effect for etanercept following adalimumab or infliximab, given the reasons mentioned elsewhere in this document. The HAQ changes observed in the different data sources are provided in table 2.

Table 2: HAQ changes observed in studies.

Study	**Number of patients**	**Baseline HAQ**	**HAQ at measurement**	**HAQ change**
Hyrich 2008 (BSRBR)	868	1.98	1.83	-0.15 (-0.05; -0.26)
BOSS survey	25	1.5	1.1	0.4
RADIUS[2]	155	INF-ETA 1.49 ETA-INF 1.57	INF-ETA 1.08 ETA-INF 1.44	INF-ETA -0.41 ETA-INF -0.13
SSATG[3]	1st TNF 1306 2nd TNF 378 3rd TNF 89	1st TNF 1.35 2nd TNF 1.4 3 TNF 1.61	1st TNF 1.01 2nd TNF 1.09 3rd TNF 1.35	1st TNF -0.34 2nd TNF- 0.31 3rd TNF -0.26
ReACT	899	Prior TNF (all) 1.85 Prior INF 1.83 Prior ETA 1.89 Prior ETA & INF 1.93	Prior TNF 1.30 Prior INF 1.32 Prior ETA 1.46 Prior INF&ETA 1.53	Prior TNF -0.55 Prior INF -0.51 Prior ETA -0.43 Prior INF&ETA -0.40
Haraoui[4]	25	1.53	1.08	-0.45
Favelli[5]	8	NA	NA	-0.49
Bennett[6]	70	2.07	1.73	-0.34

The mean HAQ improvements reported by these studies support the use of a higher effectiveness value for the TNF-α inhibitors which will result in lower cost-effectiveness results.

These findings together with no HAQ improvements on non-biologic DMARDs influences the cost-effectiveness results of the two TNF-α inhibitor strategy compared to a single TNF-α inhibitor and then DMARD, or rituximab as shown in the outputs from the Wyeth model in table 3. These results indicate, that the use of sequential TNF-α therapy is a cost-effective use of NHS resources, and should therefore be recommended.

Table 3: Cost-effectiveness results for different HAQ changes for TNFs vs. DMARDS and rituximab.

Discount rate: Costs 3.5%, Outcomes: 3.5%										
Mean HAQ change	**0.15**	**0.26**	**0.31**	**0.40**	**0.41**	**0.43**	**0.44**	**0.48**	**0.51**	**0.55**
ICER Vs DMARD	£34,847	£27,788	£27,788	£23,538	£23,538	£23,538	£23,538	£23,538	£20,744	£20,744
ICER vs Rituximab	Dominated	£27,377	£27,377	£10,526	£10,526	£10,526	£10,526	£10,526	£8,463	£8,463

Discount rate Cost: 6%, Outcomes 1.5%										
Mean HAQ change	**0.15**	**0.26**	**0.31**	**0.40**	**0.41**	**0.43**	**0.44**	**0.48**	**0.51**	**0.55**
ICER Vs DMARD	£20,102	£16,233	£16,233	£13,841	£13,841	£13,841	£13,841	£13,841	£12,242	£12,242
ICER vs Rituximab	Dominated	£24,753	£24,753	£6,966	£6,966	£6,966	£6,966	£6,966	£5,342	£5,342

NB: Please note that, because HAQ is measured in increments of 0.125, the model's outputs are not sensitive to small differences in HAQ change.

Secondary loss of efficacy demonstrates higher efficacy for 2nd TNF.

In the ReACT study, Bombardieri, et al. evaluated the effectiveness and safety of adalimumab in patients with RA who previously discontinued TNF-α antagonists for any reason in clinical practice. They reported an over all mean HAQ improvements of 0.33 – 0.55 at week 12 for patients whom required switch. These patients included those with intolerance to, no response, or lost response to a TNF-α inhibitor over time. The average weighted mean HAQ response was the lowest in patients whom showed no response to TNF-α inhibitor (0.44), and highest in patients with a loss of response (0.51). There is no reference within the ACD to the fact that the range of ICERs for sequential TNF-α inhibitor therapy in patients with secondary loss of efficacy is less than for those with primary efficacy failure.

By incorporating these HAQ change estimates into our model, it was demonstrated that a second TNF-α inhibitor would be considered cost-effective, when compared against either a conventional DMARD or rituximab. Specifically, it was shown that, when a HAQ change of 0.4 was used for the second TNF-α inhibitor, cost-effectiveness ratios of £13,841 (versus DMARD) and £6,966 (versus rituximab) were observed. When discount rates of 3.5% were used, the ICERs were £23,538 and £10,526 respectively (Table 3).

Again, this estimation of HAQ change indicates that the use of a second TNF-α inhibitor would be considered to be a cost-effective use of NHS resources.

Current cost effectiveness analyses in the ACD of the sequential use of TNF-α inhibitors have failed to estimate the full cost-effectiveness of two sequential TNF-α inhibitors compared with one TNF-α inhibitor and a standard DMARD

The Birmingham Rheumatoid Arthritis Model (BRAM), like the Wyeth RA model, was designed to estimate the costs and benefits (in terms of QALYs) derived from a sequence of treatments of RA and to compare the costs and benefits of different treatment sequences. However the analysis of the sequential use of TNF-α inhibitors conducted to date only counts costs and benefits from the point of initiation of a second TNF-α inhibitor thus failing to capture the full cost effectiveness of a sequence of two TNF-α inhibitors. Given that the benefit derived from a second TNF-α inhibitor would be expected to be dependent on its relative effectiveness compared with the first TNF-α inhibitor (see below) this serves to underestimate the total cost effectiveness of a more effective TNF-α inhibitor followed by a less effective TNF-α inhibitor compare with the converse (i.e. a less effective TNF-α inhibitor followed by a more effective treatment). This bias would be avoided if the BRAM was rerun for each combination of first and second TNF-α inhibitor and corresponding comparator sequence of TNF-α inhibitor followed by return to standard DMARD, counting costs and benefits from the point of initiation of the first TNF-α inhibitor.

Some HAQ improvement values utilised in the further cost effectiveness analysis of sequential TNF-α inhibitors, have been extrapolated from the ReAct study inappropriately

From its systematic review the West Midlands Health Technology Assessment Group identified a rank order for the effectiveness and cost effectiveness of the initial use of the available TNF-α inhibitors (etanercept > adalimumab > infliximab). It is reasonable to assume that differences in the effect on HAQ between the various TNF-α inhibitors observed during initial treatment would also be manifest in a second course of therapy following lack or lost of response to the first.

This interpretation is supported by the albeit limited evidence identified in the update report by the Decision Support Unit (DSU) on the sequential use of TNF-α inhibitors dated January 2008. In particular the large open label trial of the effectiveness of adalimumab in patients with a history of TNF-α inhibitor therapy (ReAct) clearly identifies that response to adalimumab is greater in patients failing infliximab than in patients failing on etanercept

treatment. Whilst utilising HAQ improvements for sequential use of adalimumab after failure of either etanercept or infliximab from this study would seem entirely appropriate to assume the converse i.e. the same effect for etanercept and infliximab after failure of adalimumab is without foundation, would lead to an underestimation of the relative effectiveness of etanercept and should be used with caution.

Point 3

There have been serious breaches of NICE processes with regards to including rituximab as a comparator which has led to inappropriate analysis, and changing the discount rates which has introduced bias in the analysis which may have misled the appraisal committee.

Inclusion of rituximab as a comparator

Rituximab was not considered as part of the original scope of this appraisal. Therefore it should not be included for consideration.

Rituximab has not assessed within the BRAM to the same extent as the existing TNF agents. This could have biased the analysis and led to an inappropriate decision by the appraisal committee.

Strong medical reasons to prefer sequential TNF-α inhibitor use over the use of rituximab.

The manufacturers of licensed TNF-α inhibitor drugs are required to follow up and collect safety data on patients in their RA clinical trial programmes. Safety data from these databases have supported the long-term use of this drug class for the treatment of moderately to severely active RA, with the adalimumab and etanercept safety databases contributing 16,973 and 6,448 (early RA + longstanding RA) patient years of clinical trial and clinical practice experience, respectively.

The European licence for rituximab in RA states that rituximab should be given in combination with methotrexate. It does not provide any option for the treatment of patients who are intolerant of MTX with rituximab monotherapy. This leaves these patients, according to current NICE RA guidance, with no options but to return to treatment with ineffective traditional DMARDs and corticosteroids, many of which they would have already failed.

The administration of rituximab requires admission to a day ward, which must be equipped with full resuscitation equipment. Adalimumab and etanercept in contrast can be administered at home, which is more convenient for the patient.

Published data from the rituximab clinical trial safety database are currently limited, and non-responders to rituximab have severely limited treatment options as the safety of further biologic therapy in patients with low or no circulating peripheral B cells is largely unknown.

Therefore, not recommending a sequential use of TNF-α therapy will further severely limit the already limited treatment options for patients with RA.

A nine month dosing interval for rituximab, compared with 7 months seen in clinical practice, results in overestimation of its cost-effectiveness vs. second TNF-α inhibitor.

The current cost-effectiveness analyses of TNF-α therapy vs. rituximab are based on a cost of rituximab taken from TA126, which was based on a mean retreatment period of 9 months.

Roche have also published an analysis of the open label extension study which included additional repeated treatment courses in order to establish the optimum frequency of repeated treatment with rituximab[7]. This analysis identified a consistent period for 30 weeks between first and second retreatment courses (30.9 and 30.1 weeks respectively).

An estimate of time between multiple repeat treatment courses is more representative for inclusion in a long-term treatment model than an estimate based on time to first retreatment only.

A period of 30 weeks (210 days) is the most appropriate estimate of the interval between repeat rituximab treatment courses. This value should be included in the economic model of the long-term cost-effectiveness of rituximab in patients who have failed at least one TNF-α therapy. Inclusion of this increased dosing frequency in the Wyeth economic model results in the following estimates of cost-effectiveness (Table 4).

Table 4: Cost-effectiveness of a second TNF-α inhibitor vs. rituximab

	Discount Rate: Costs 6% Outcomes 1.5%				**Discount Rate: Costs 3.5% Outcomes 3.5%**			
	Mean HAQ change	**QALY gain**	**Incremental costs (£)**	**ICER (£)**	**Mean HAQ change**	**QALY gain**	**Incremental costs (£)**	**ICER (£)**
1st TNF to 2nd TNF	0.15	-0.21	-238	1158 (SW)	0.15	-0.14	-468	3294 (SW)
	0.26-0.31	-0.05	261	Dominated	0.26-0.31	-0.02	190	Dominated
	0.4-0.48	0.1	778	7553	0.4-0.48	0.1	872	9031
	0.51-0.55	0.25	1287	5104	0.51-0.55	0.21	1543	7290

NB: "(SW)" refers to the ICER being located in the south-west quadrant of the cost-effectiveness plane (i.e. the treatment is less costly, but less effective than the comparator).

It is inappropriate to change the discount rate from that used in TA130.

The consideration of TNF-α inhibitors for sequential use was part of the original scope of the technology appraisal for etanercept, adalimumab and infliximab in RA. In order to avoid delay in issuing guidance on the use of these technologies after traditional DMARDs, the use of these technologies for sequential use was deferred. Therefore, this ACD merely extends the guidance in TA130 and does not represent a new appraisal. This status is backed up by the Institute not issuing a new scope, nor inviting consultees to submit updated evidence for the consecutive use of TNF-α inhibitors.

Therefore, it is surprising that the Institute has changed its decision-making criteria for this extension to TA130. Using the discount rate originally used in TA130 would have resulted in considerably lower incremental cost-effectiveness ranges for all the TNF-α inhibitors, thereby making it more likely that the TNF-α inhibitors would have been recommended for sequential use. Further, an additional comparator, rituximab, was added to this extension of TA130 and consultees were not invited to submit evidence with regards to this agent versus our own.

Consequently, the analysis should be re-run using the original discount rates. In addition, we enclose in our response (Table 4) data comparing etanercept with rituximab which we believe will materially affect the provisional recommendations in the ACD.

Effect of the tone of the Overview on the Appraisal Committees decision making

Wyeth are concerned that the balance of the Overview prepared for the Appraisal Committee may inadvertently lead the Committee to not recommend the sequential use of TNF-α inhibitors. For example the net effect of changing the discount rate was not explained within

the report. With all else being equal this serves to raise the incremental cost effectiveness ratios of analysis performed to inform this ACD compared with values used to inform TA130.

The Overview repeatedly refers to the use of an initial HAQ improvement of 0.11 for DMARDs derived from the abatacept study as 'assuming no treatment effect while on conventional DMARDs'. This is misleading; utilisation of a zero for HAQ improvement would assume no treatment effect. This scenario actually assumes a treatment effect of up to a third of that seen on sequential TNF-α inhibitors despite the lack of evidence to attribute such benefit.

Wyeth also believe that it should be make clear to the appraisal committee that the results presented from the BRAM do not include costs of hospital admissions or joint replacement surgery which would serve to further lower the incremental cost effectiveness ratios for TNF-α inhibitors compared to standard DMARD therapy.

Point 4

Wyeth have update its economic model to incorporate consideration of these key points which clearly demonstrates that etanercept is not only cost-effective as a first-line TNF-α inhibitor, but also when used as sequentially after the failure of a first TNF-α inhibitor.

Results from the updated economic model demonstrate cost-effectiveness of sequential TNF- α inhibitor use compared with conventional DMARDs and rituximab.

A deterministic Markov model was developed to predict the lifetime costs and health outcomes associated with treatment for patients with RA in the United Kingdom. Two treatment sequences are considered side by side. It is important to consider the impact of treating patients with different treatment sequence combinations so a number of alternative scenarios were studied.

For each treatment the initial (i.e. first six months), medium-term (first three years) and long-term (after three years) effects on the Health Assessment Questionnaire (HAQ) score are predicted. HAQ scores at each time period determine each patient's utility (QALYs), resource use and mortality.

Effectiveness data (HAQ progression, serious adverse events and mortality) were derived from a combination of the results from the published literature cited in this appraisal. The TNF-α inhibitor data was pooled to establish the effectiveness of an average TNF-α inhibitor

for use as a first TNF-α inhibitor therapy and then the effectiveness of a second TNF-α inhibitor was varied across a range of values to incorporate the range of values reported in the literature. Costs were also pooled in this way to create a generic cost of a standard TNF-α inhibitor. Unit cost data were drawn from established national (UK) databases, and were multiplied by resource use to predict the total cost. Resource use was estimated through published data and expert clinical opinion. Costs and outcomes were both discounted at 3.5% in the base case and then discounted at 6% costs and 1.5% outcomes in an alternative scenario.

The cost-effectiveness results of the two TNF-α inhibitor strategy compared to a single TNF-α inhibitor and then DMARD strategy are shown in the table below. The table also shows the cost effectiveness of switching between each TNF-α inhibitor. The comparison with rituximab has been shown previously (Table 4). Please note that, because HAQ outcomes are measured using increments of 0.125 units, the model's outcomes are not sensitive to very small changes in HAQ inputs. As such, results are presented for ranges of HAQ changes.

Table 5: Summary of cost-effectiveness results vs DMARDs

	Discount Rate: Costs 6% Outcomes 1.5%				**Discount Rate: Costs 3.5% Outcomes 3.5%**			
	Mean HAQ change	**QALY gain**	**Incremental costs (£)**	**ICER (£)**	**Mean HAQ change**	**QALY gain**	**Incremental costs (£)**	**ICER (£)**
ADA to ETA	0.15	0.58	9026	15441	0.15	0.42	11399	26969
	0.26-0.31	0.76	9534	12468	0.26-0.31	0.56	12079	21496
	0.4-0.48	0.94	10060	10647	0.4-0.48	0.7	12781	18237
	0.51-0.55	1.12	10580	9435	0.51-0.55	0.84	13476	16104
ADA to INF	0.15	0.35	6675	19288	0.15	0.26	8231	31971
	0.26-0.31	0.49	6969	14110	0.26-0.31	0.37	8615	23021
	0.4-0.48	0.64	7276	11357	0.4-0.48	0.49	9015	18401
	0.51-0.55	0.78	7581	9674	0.51-0.55	0.6	9411	15622
ETA to ADA	0.15	0.39	9592	24649	0.15	0.28	12144	42909
	0.26-0.31	0.54	10357	19018	0.26-0.31	0.4	13153	32702
	0.4-0.48	0.7	11152	15929	0.4-0.48	0.52	14201	27251
	0.51-0.55	0.85	11926	14020	0.51-0.55	0.64	15222	23930
ETA to INF	0.15	0.3	5869	19478	0.15	0.22	7343	33205
	0.26-0.31	0.43	6135	14310	0.26-0.31	0.32	7696	24025
	0.4-0.48	0.55	6413	11571	0.4-0.48	0.42	8063	19299
	0.51-0.55	0.68	6689	9903	0.51-0.55	0.51	8428	16466
INF to ADA	0.15	0.43	10792	25046	0.15	0.32	13516	42836
	0.26-0.31	0.60	11631	19362	0.26-0.31	0.45	14610	32684
	0.4-0.48	0.77	12503	16217	0.4-0.48	0.58	15747	27223
	0.51-0.55	0.94	13352	14261	0.51-0.55	0.71	16854	23877
INF to	0.15	0.58	8890	15382	0.15	0.42	11263	27091

ETA	0.26-0.31	0.75	9382	12524	0.26-0.31	0.55	11924	21779
	0.4-0.48	0.92	9892	10760	0.4-0.48	0.68	12607	18589
	0.51-0.55	1.09	10396	9580	0.51-0.55	0.81	13282	16494
1st TNF to 2nd TNF	0.15	0.49	9035	18448	0.15	0.36	11326	31684
	0.26-0.31	0.66	9594	14476	0.26-0.31	0.49	12062	24524
	0.4-0.48	0.84	10173	12167	0.4-0.48	0.63	12825	20479
	0.51-0.55	1.01	10742	10680	0.51-0.55	0.76	13575	17916

NB: "(SW)" refers to the ICER being located in the south-west quadrant of the cost-effectiveness plane (i.e. the treatment is less costly, but less effective than the comparator).

Additional model using different methods demonstrates the cost-effectiveness of the use of a second TNF-α inhibitor.

Economic modelling carried out using the BSRBR data of sequential TNF-α inhibitors indicates that use of a second TNF-α inhibitor is equally cost-effective as the use of a first one. [8] This analysis is based on 629 patients receiving a second TNF-α inhibitor from the BSRBR data.

The response to a second TNF-α inhibitor was modelled using Disease Activity Score (DAS) response, which is a different approach to that applied by NICE/BRAM and the manufacturers which assumes that mean HAQ improvement is the key driver. Further this model takes into account the shorter duration of therapy with a second TNF-α inhibitor vs. the time on therapy with a first TNF-α inhibitor. The NICE analysis assumes the duration of therapy on a second TNF-α inhibitor to be equivalent to that on a first agent, which raises the costs for these therapies and therefore leads to higher cost-effectiveness results.

The BSR analysis comparing 2 TNF-α inhibiotrs in a sequence with conventional therapy results in an incremental cost per QALY of £24,570. Probabilistic sensitivity analysis gives an 85% chance that the true cost-effectiveness is less than £30,000. This is a substantially lower cost/QALY as from the BRAM model on which the committee based its decision.

In comparison to analyses based on the BSRBR data, using this DAS driven model, the model which led to the current ACD probably reduces the size of effect of the second TNF due to its focus on the mean HAQ reduction, produces a greater effect for conventional DMARDs, as well as increasing the cost of the TNF-α inhibitor side of the equation through the assumption of equivalent duration of treatment. This combination drives higher cost-effectiveness results for consecutive TNF-α inhibitor use.

Additionally, the patients enrolled in the BSRBR have longer disease duration. The mean disease duration was 12 years at which time the reversibility of HAQ is limited. [9] The patients enrolled in the BSRBR have been the more severe established cases, but now these have been treated patients with shorter disease duration and thus a greater potential for HAQ improvement will be receiving treatment. Consequently the BSRBR data represent a worse case scenario. By using a DAS driven model Brennan et al have avoided this weakness of HAQ driven models for late stage disease.

A further strength of this analysis is that[10] the control cohort of patients not receiving TNF-α inhibitors is used to estimate the efficacy of conventional DMARDs. These patients may have a higher response as patients whom received a previous TNF-α inhibitors. This analysis supports the cost-effectives of the sequential use of TNF-α inhibitors.

Conclusion

In conclusion Wyeth maintains that the analyses which led to this current ACD were insufficient. The institute must use the same discount rate as used in TA130.

Further, the institute should to take into account the higher effectiveness of a second TNF-α inhibitor as reported from recent clinical trials, and apply a zero HAQ improvement for non-biologic DMARDs.

In addition the institute may choose to perform subgroup analyses in patients whom experience intolerance to TNF-α inhibitor, no response, or lost response over time, which will lead to a range of cost-effectiveness result which will be more in favour for the sequential use of TNF-α inhibitors.

Taken together these requirements will lead to lower cost-effectiveness results for the consecutive use of TNF-α inhibitors and the decision that such use would represent cost effective use of NHS resources.

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