

**ANKYLOSING SPONDILITIS: A COMPARISON OF COST
EFFECTIVENESS MODELS**

REPORT BY THE NICE DECISION SUPPORT UNIT.

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1. Background

On the 21st February the Appraisal Committee met to consider comments on the ACD of etanercept, infliximab and adalimumab for ankylosing spondylitis. At that meeting, a report prepared by the Decision Support Unit (DSU) and a paper tabled by the Assessment Group, Liverpool Reviews and Implementation Group (LRiG), were considered.

The DSU reported work that had implemented a number of corrections to the three manufacturer models and then applied a common set of parameter values to each. These parameter values had been agreed at the previous committee meeting. The purpose of this was to attempt to identify whether differences between the results of the three manufacturer models and the independent assessment group persisted once this common set of values were used.

The specific parameter values which were implemented were:

- i) No improvement in BASFI or BASDAI for patients not on anti-TNF α therapy
- ii) BASFI progression prevented whilst on anti-TNF α therapy
- iii) BASFI progresses at 0.07 per annum when patients are not on anti-TNF α therapy
- iv) Annual withdrawal rate of 7% from anti-TNF α therapy
- v) Baseline BASDAI/BASFI averages 6.5/5.6
- vi) Utility model as in the Schering Plough submission
- vii) Assessment group parameters for cost parameters (drug costs only)
- viii) 20 year time horizon

The results of this were that the manufacturer models all gave relatively consistent results for each of the drugs

For Schering Plough (SP) the ICERs over 20yrs for etanercept/adalimumab were £27k or £24k and for infliximab were £58k and £50k. Two figures are presented because SP presented two different versions of the model which reflected two different trials. In fact, the two versions were structurally identical and parameter values were also very similar.

The Wyeth model gave results of £20k for etanercept and £39k for infliximab. Abbott gave results of £17k for adalimumab and £43 for infliximab (over a 30 yr time horizon).

These ICERs were very different from those reported by the independent assessment group. Using a similar set of parameters the results for etanercept/adalimumab were £42k and for infliximab £82k.

Therefore, there appear to be differences between the results of the LRiG model and the three manufacturer models which cannot be explained by the set of parameter values examined and implemented in all models. Whilst the SP model indicates that infliximab is not cost effective, the model is important because it yields results for etanercept/adalimumab that are consistent with the other manufacturer models.

The purpose of this additional report is to attempt to resolve the reasons for the remaining differences.

A number of steps are described in this report.

In section 2, we examine the LRIg model in order to fully understand the implied assumptions of the adopted approach. In section 3, we explore the reasons for differences between the Abbott and LRIg models, supplementary to the LRIg report tabled at the February committee meeting. In section 4, we identify the reasons for differences between the Schering, Wyeth and LRIg models. In doing so we revisit some of the assumptions listed above and provide evidence for one particular approach. These model differences are discussed in section 4 and the key issues for committee consideration outlined in section 5.

2. Assessment group model

2.1 Clinical efficacy in the LRIg model

The key clinical efficacy variable in the LRIg model, in common with the three industry models, is response. It is assumed that all people who are responding remain on treatment, however a marked placebo effect, 17.1% response in the placebo arm, is identified by LRIg.

The mean BASDAI and BASFI scores for cohorts at any point in time are assumed to be functions of the proportion of people responding. A quadratic form has been assumed for this on the basis of declining mean BASDAI/BASFI scores in the first 12 week period of the trial.

The assumption of a quadratic form for the above relationship has some interesting implications and leads to some difficulties in maintaining logical consistency within the model, these are explored further below. This is particularly true when the quadratic equations, together with the constant declining response rates are used to project BASDAI/BASFI forward over a 20 year period.

It should be noted that the long term efficacy is based entirely on these two assumptions (Quadratic link of BASDAI/BASFI to response rate and declining response). Whilst it may be fair to criticise the LRIg model on the above account, the industry models are based upon equally frail assumptions (i.e. constant BASDAI, linear progression BASFI, declining response) and could be criticised accordingly.

It should be noted that throughout the assessment report LRIg are consistent in presenting their long term analysis as “exploratory”.

2.1.1 BASDAI

At any point in time, because each cohort can theoretically be divided into two mutually exclusive and exhaustive subgroups of responders and non-responders, the mean BASDAI can be expressed as a linear function of the proportion of responders at that time.

$$D(t) = D_r(t) x(t) + D_{nr}(t) (1-x(t)) \quad (1)$$

Where $x(t)$ is proportion of responders at time t
 $D(t)$ is mean BASDAI at time t
 $D_r(t)$ is mean BASDAI at time t in responders
 $D_{nr}(t)$ is mean BASDAI at time t in non responders

Now LRiG also assume that $D(t)$ is a quadratic function of $x(t)$

$$D(t) = a x^2(t) + b x(t) + c \tag{2}$$

Where a and b are given in the LRiG model spreadsheet and c is assumed to be equal to the assumed constant $D_{nr}(t)$. Now (1) and (2) can be rearranged to give:

$$D_r(t) = a x(t) + (b+c) \tag{3}$$

In the control arm $x(t)$ is constant (say $x_p = 17.1\%$) therefore the BASDAI for responders is also constant. However in the treatment arm $x(t) \rightarrow x_p$ as t increases. This is demonstrated in the figures below. Figure 1 shows the profile of mean BASDAI for treatment and control in the LRiG model. Figure 2 shows the implied mean BASDAI in the response and no response groups under treatment and no treatment.

Figure 1: Mean BASDAI in the treatment and control cohorts in the LRiG model.

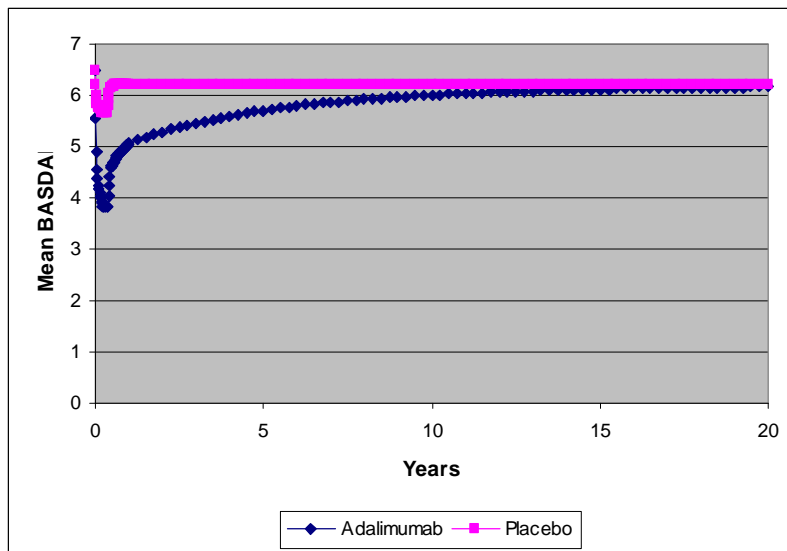
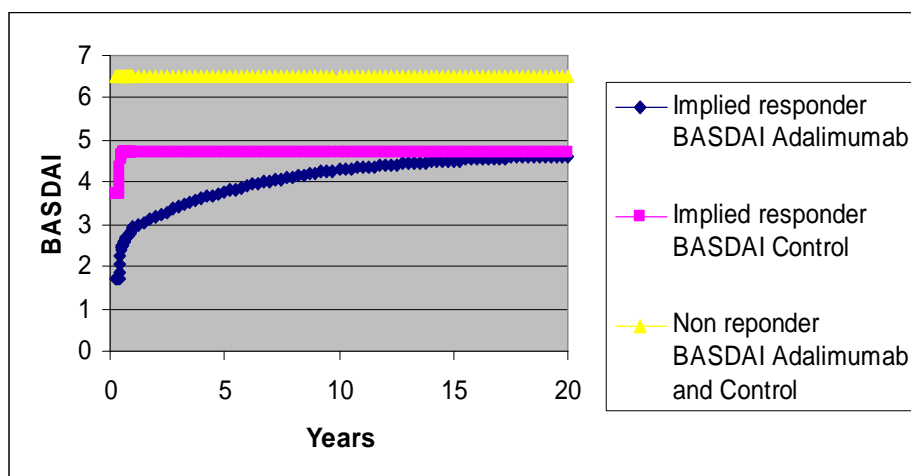


Figure 2: Mean BASDAI in responders and non responders in the treatment and control cohorts in the LRiG model.



Thus we have the potentially counter intuitive situation that

- the mean BASDAI for responders in the treatment arm is lower than responders in the control arm. Presumably this is verifiable in the study period.
- the mean BASDAI in non responders in both treatment and control arms and responders in the control arm are all constant over the full 20/30 years, whilst the mean BASDAI in the treatment arm responders increases and tends towards that found in the control arm responders.

The internal inconsistency arises from

- the crude classification into binary response / non response.
- Assumption that BASDAI in responders remains constant over time.
- Mean cohort BASDAI is reducing over time.

The internal inconsistency leads from LRiG's attempt to compensate for the naïve model structures proposed in the industry submissions.

2.1.2 BASFI

The LRiG model starts with an identically structured quadratic model of mean BASFI in each cohort dependent on proportion responding. The above discussion is equally valid for the modelling of BASFI, however there is also the added complexity of long term progression in BASFI.

Annual progression in BASFI is superimposed onto the quadratic model. This annual progression is assumed to be linear (at 0.07 BASFI points per year) and is applied to both responders and non responders equally, thus the mean BASFI is simply increased by 0.07 each year. The overall mean BASFI and the implied BASFI in responders and non responders are presented in Figure 3 and Figure 4.

Figure 3: Mean BASFI in the treatment and control cohorts in the LRiG model.

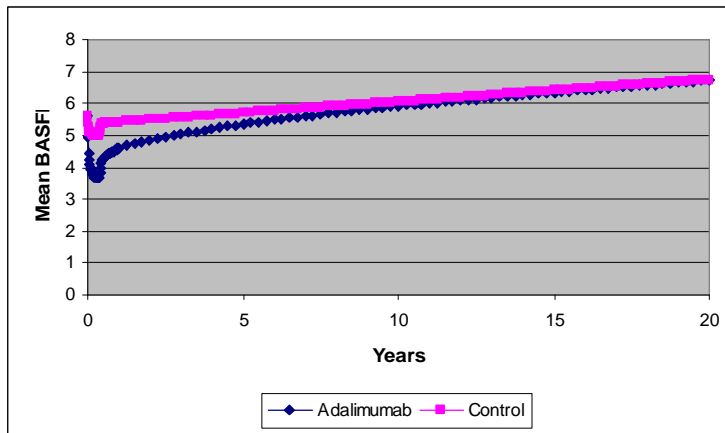
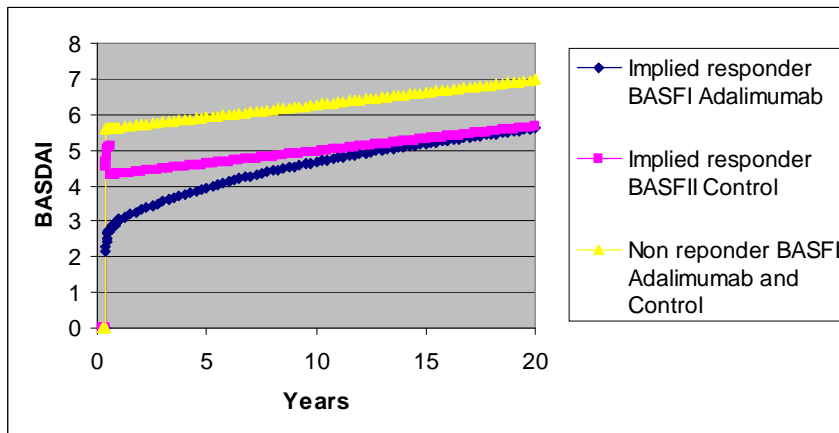


Figure 4: Mean BASFI in responders and non responders in the treatment and control cohorts



In order to estimate the impact of progression prevention in treatment responders a further cumulative adjustment is then made to remove a proportion of the annual progression each year. The proportion of the total 0.07 annual progression is calculated as the difference between the proportion responding and proportion not responding in each cohort. Note that whilst responders in the treatment arm are assumed not to progress, non responders in the control arm are assumed to still progress. This assumption has not been discussed.

2.2 Quality of life

Three similar models of quality of life are implemented in the LRiG model, the baseline analysis uses the ‘Schering-Plough’ model. The Schering-Plough model is a linear model. The model implemented agrees with the description in LRiG assessment report, that is:

$$Q = 0.877213 - 0.038409 \times \text{BASDAI} - 0.032252 \times \text{BASFI} - 0.02789 \times \text{Male} + 0.001681 \times \text{Age}$$

The baseline model assumes males aged 40. Age does not increase over the 25 years in the model, however since this is a linear factor the effect cancels out in the incremental analysis.

2.3 Costs

Acquisition costs simply calculated from the weekly cost of drug multiplied by the average number on treatment for each weekly (year 1) and quarterly (> year 1) period

Administration costs zero for adalimumab.

Monitoring costs: Minor possible error in implementation or lack of clarity in report. The LRiG report Table 7-1, defines monitoring costs to be £25 quarterly plus a further £25 every 6 monthly. The model implements this for the first year then the twice yearly cost is included every quarter in further years. Thus the 6 monthly costs are double counted. Makes a small impact on 20 year cost effectiveness.

TB monitoring and therapy cost: The LRiG model implements a cost for treating new incident cases of TB in each period of the model, this is not inconsistent with the description in the LRiG report. The monitoring costs are only included in the initial time period and at week 6 in the model. Two points of issue a) not sure of the justification for monitoring costs occurring as one off costs at 2 time points when treatment costs occur b) a minor discrepancy exists as the report refers to monitoring costs occurring in month 6, in the model they are implemented in week 6. These issues are unlikely to make substantial differences to the results.

Adverse event costs: The LRiG model implements a cost for treating new incident cases of adverse events in each period of the model, this is not inconsistent with the description in the LRiG report.

AS treatment costs: The LRiG model implemented is consistent with the methods described in the report. Treatment cost is modelled as an exponential function of BASFI. It should be noted that all other models include BASDAI in the modelling of costs. LRiG justify not using BASDAI since “BASDAI... appears to fluctuate but not increase over time”(page 123 of Assessment Report). This is inconsistent with their own model of BASDAI which specifically, due to the quadratic formulation, does increase over time in the cohort who remain on treatment. As a costing issue this is unlikely to be a significant factor.

2.4 Summary of the LRiG model assessment

The model is, by and large, consistent with the model description presented in the LRiG report. Whilst there are a few minor issues with the implementation of the model, we have found no major errors of implementation that have a major impact on the cost effectiveness estimates generated. In one or two places the implementation is difficult to follow and perhaps the report could be clearer. This is particularly true of the modelling of BASDAI and BASFI.

3. Comparison of the Abbott and LRiG models for adalimumab

An assessment of the differences between the LRiG model and the Abbott model has previously been undertaken by the Liverpool team and their assessment has been fully documented elsewhere. The DSU team has further examined some of the issues raised by the LRiG work on reconciliation of the two models.

A comparison scenario is defined for the LRiG model:

- Long term withdrawal rate 7% per annum
- Long term control responder multiplier 0 (i.e. no response in control arm)
- Schering-Plough utility model
- Proportion of BASFI progression rate 0%

Note that this scenario represents a base for comparison between the models and this does not imply that the DSU support this scenario as representing the ‘best model’ scenario for decision making. The cost per quality adjusted life year in the original models and in the comparison scenario are presented below.

	Abbott model	LRiG model
Original reported (20yr adjusted Abbott)	£23,259	£92,598
Comparison scenario	£24,403	£41,787

The LRiG model has three elements:

- Clinical efficacy of treatments in terms of BASDAI and BASFI
- Model linking BASDAI/BASFI to utility
- Model of costs

The different cost models lead to very similar profiles of cost over the 20 year time horizon, this is despite the Abbott model being based solely on BASDAI effects and the LRiG on BASFI effects. These differences have only a marginal impact of the economics.

The different utility models lead to very modest differences between the LRiG and Abbott models. The Abbott utility moves the cost per QALY gained from £41,800 in the LRiG model under the comparator scenario to £38,800.

The major differences between the models therefore lie in the modelling of the BASDAI/BASFI over the time horizon of the model. There are a number of issues included in this modelling. These include:

- response in the control arm
- long term quadratic modelling of BASFI and BASDAI
- first year BASFI /BASDAI effects
- long term progression of BASFI

The impact of different assumptions regarding the effect of therapy on long term progression has been dealt with elsewhere.

3.1 *Control arm response*

The 17% response found in the control arms of the adalimumab trials has a major impact on the economics. Including the 17% control arm response shifts the comparator scenario from £41,800 to £62,200. This effect could be caused by a number of issues including transient placebo effects or regression to the mean. However even if it is believed that it is appropriate to adjust the comparator arm then a strong justification is required to not also adjust the treatment arm similarly. No justification is provided, therefore the 0% spontaneous long term response in the control arm is a very favourable assumption.

3.2 *Quadratic modelling of BASDAI / BASFI*

The inconsistencies introduced by the quadratic model on long term BASDAI and BASFI progression have been discussed above. The impact of replacing the quadratic model with a linear model after 1 year is given below.

The BASDAI and BASFI values derived from the LRiG model at 12 months for responders and non responders are:

BASDAI non responders = 6.5
 responders = 2.91 (responder BASDAI @ 12 months)
 BASFI non responders = 5.6
 responders = 3.01 (responder BASFI @ 12 months).

Using these values in a linear model similar to the industry models results in the cost effectiveness moving from £41,800 to £30,100

3.3 *First year BASDAI and BASFI*

Following a similar process of replacing the quadratic model with a linear model in the first 12 months gives the following:

BASDAI non responders = 6.5
 responders = 1.7 (responder BASDAI @ 20 wks)
 BASFI non responders = 5.6
 responders = 2.15 (responder BASFI @ 20 wks).

With a cost per QALY of £21,800.

This resolves the differences between the Abbott and LRiG models.

It should be noted here that there is also a further issue to note that withdrawals between week 12 and week 52 are taken from the Abbott trial rather than the assumed 7% (or 10% or 15%) annual drop out rate. Since this is done in both the Abbott and the LRiG models this does not arise as a discrepancy, however a) this may give rise to differences to the other industry models and b) it is not clear whether this data will be subject to the same biases as the other post 12 week data.

4. Wyeth and Schering Plough models

The general structure of the two models submitted by SP and Wyeth are similar. Both are individual sampling models which attribute a response in terms of BASFI and BASDAI to a proportion of patients on treatment. Each individual patient continues along a BASDAI and BASFI pathway until they withdraw and the models then incorporate an element of rebound at the point of withdrawal.

The SP model is simpler to amend than the Wyeth model partly because it does not include patient covariate adjustments and since both models gave very similar results when each of the 3 strategies was analysed, we have chosen to concentrate on the SP model to illustrate differences with the LRiG model. In fact, SP presented two slightly different versions of their model which represented two different trials (ASSERT and BRAUN). Since these were structurally equivalent we have only undertaken changes on the BRAUN version of the SP model. Additionally, manipulation of the Wyeth model would require substantial alteration of the Visual Basic code.

4.1 Additional amendments to the Schering model.

In the previous DSU report we reported the results of implementing corrections to the model that were identified by LRiG and the application of some parameter values that were common to those presented for the LRiG model. We have now identified some additional issues within this model that are not consistent with the LRiG model and been able to implement additional common parameters. The results of these changes are described in Table 1. Note that these changes are incremental i.e. each change is added to those made in previous rows.

Table 1: Impact on ICER from SP model according to parameter changes

	ICER vs no treatment (£/QALY)	
	IXB	ETP/ALB
LRiG	82350	41787
1. SP after DSU corrections/parameter changes	58148	27201
2. No long term BASFI gain from treatment	59430	28280
3. Number of patients remaining on treatment	61380	28797
4. Baseline BASDAI/BASFI	57889	27081
5. BASDAI on treatment worsens	74187	34942
6. BASFI on treatment worsens	95607	45861
7. SMR included	92845	45843

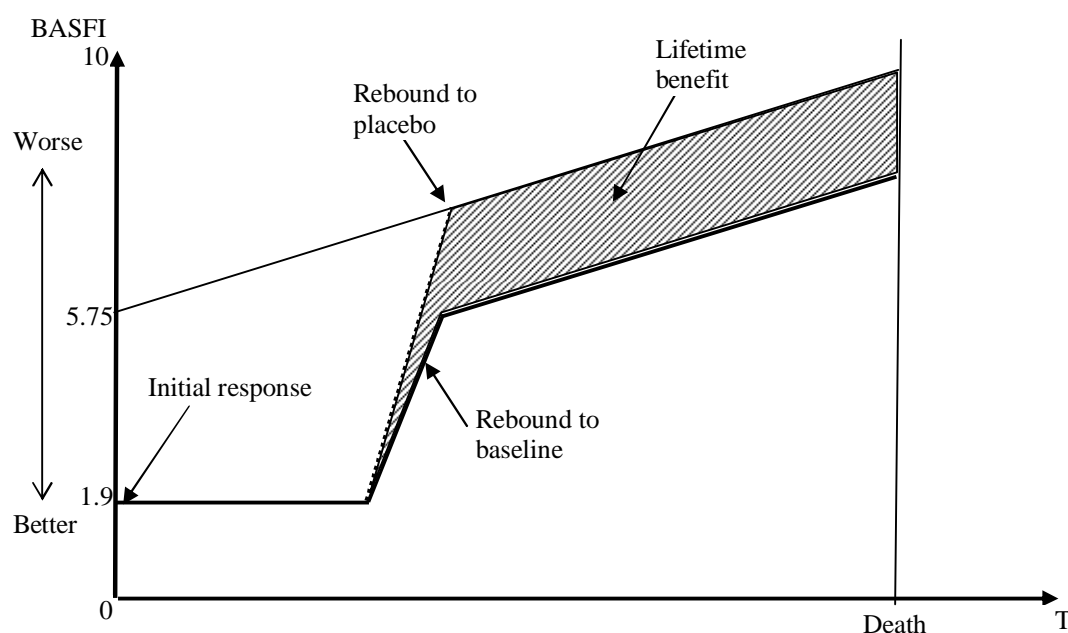
The starting point for the analysis produces an ICER of £58k for infliximab and £27k for etanercept. The parameter values which underlie these figures are as submitted in the original SP submission, with corrections made by the DSU and the following parameter changes:

- i) 4 vials per infliximab infusion
- ii) 20yr time horizon
- iii) 7% withdrawal per annum

Each of these assumptions are equivalent to those implemented by LRIg which produce the ICERs presented in the first row of Table 1.

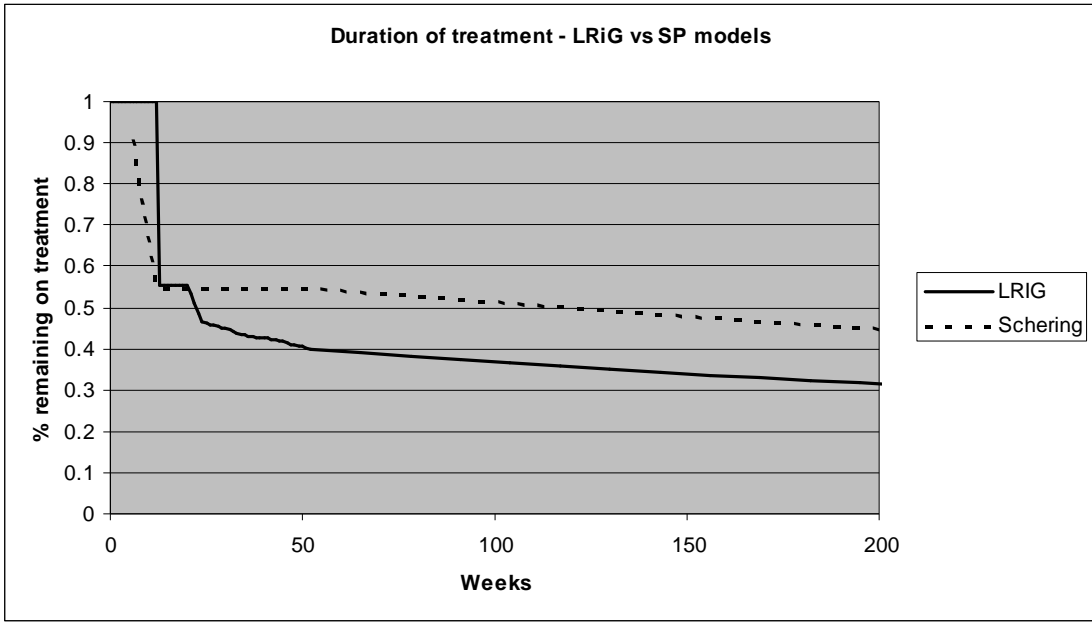
One of the errors identified in the SP model by LRIg that was corrected by the DSU previously, concerned BASFI in the treatment cohort. In making this correction, we assumed that when a patient withdraws from treatment, BASFI increased back to the mean baseline level of the no treatment cohort. This approach attributes a lifetime benefit to TNF- α therapy as illustrated in Figure 5. In the LRIg model, this benefit is assumed not to occur. The SP model was therefore amended so that patients rebound to current no treatment BASFI at withdrawal. This increases the ICERs only slightly as shown in analysis 2.

Figure 5: Impact of differing BASFI rebound assumptions



It was also identified that, despite the implementation of a common 7% per annum withdrawal rate, the SP model maintained a higher proportion of patients on treatment than LRIg due to different starting points as illustrated in Figure 6. Analysis 3 indicates that the ICERs increase slightly as a result of this change.

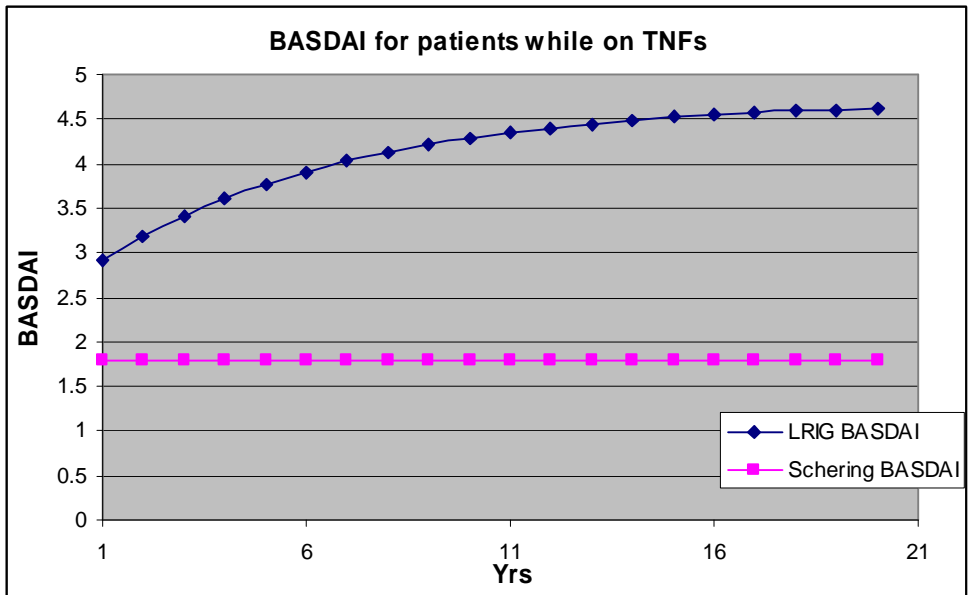
Figure 6: Duration of treatment



The small improvement in ICERs shown in analysis 4 indicates the effect of changing the baseline BASDAI/BASFI from 6.3/5.4 to 6.5/5.6 as used in the LRiG model. This approximately offsets the increases in ICERs caused by the two previous changes.

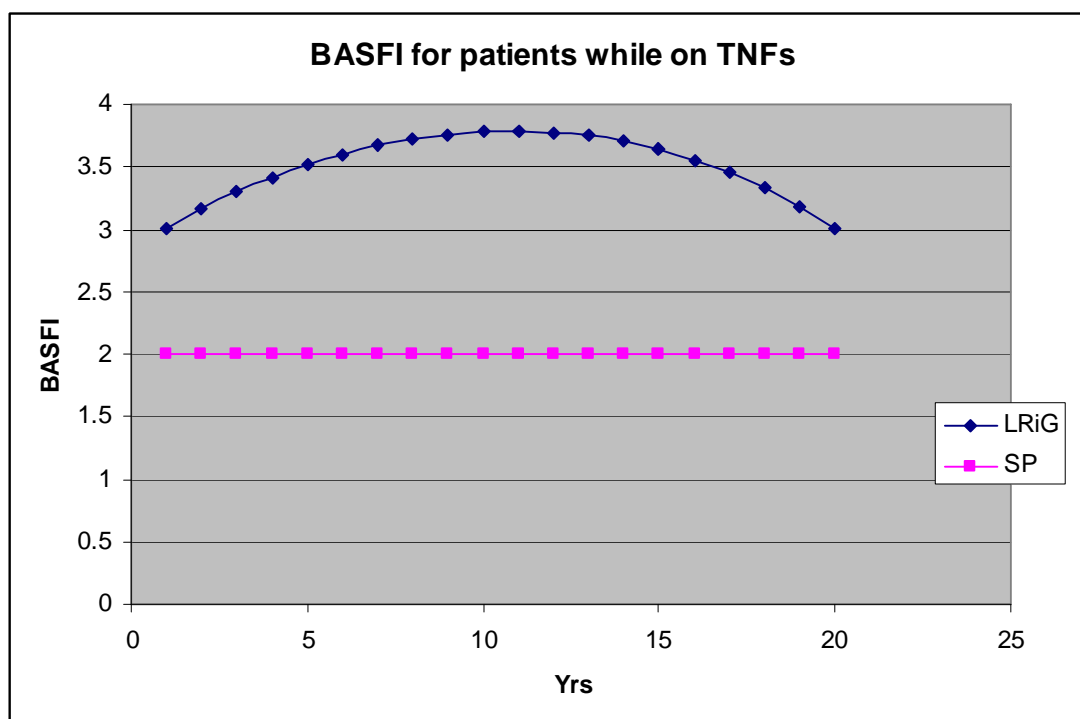
Two differences which have substantial changes on the model outputs were then implemented. In the SP model, it is assumed that the BASDAI for patients who remain on treatment is stable. In the BRAUN version BASDAI remains at a mean of 1.8 for the duration of treatment. This contrasts with the rising mean score in the LRiG model as illustrated in Figure 7. Here, BASDAI is 2.9 at year 1 and rises to 4.3 at year 10. Implementing the LRiG profile into the SP model (analysis 5) results in significant increases in ICERs to £74k and £35k for infliximab and etanercept/adalimumab respectively.

Figure 7: Mean BASDAI while on treatment - LRiG vs SP models



A similar difference between the models occurs with BASFI. The SP model maintains all patients at a mean of 2 whilst they remain on treatment. This is contrasted with the LRiG approach in Figure 8. Incorporating this change into the SP model is shown in analysis 6 which results in ICERs higher than those generated by the LRiG model.

Figure 8: Mean BASFI while on treatment – LRiG vs SP models



Finally, it was noted that the SP model uses general population mortality rates. This contrasts with each of the other submitted models which all use standardised mortality rates of 1.5. Incorporating this final adjustment into the SP model (analysis 7) leads to ICERs of £93k for infliximab (£11k higher than LRiG) and £46k for etanercept/adalimumab (£4k higher than LRiG).

4.2 Cross checking the impact of BASDAI/BASFI in LRiG

We input the same mean BASFI and BASDAI profiles for patients on treatment that are presented in the SP Braun model into the LRiG model. This holds the BASDAI constant at 1.8 while on treatment and BASFI constant at 2. The ICER obtained was £22k for etanercept/adalimumab, which compares to £20k in the Wyeth model and £27k in the SP Braun model and £24k in the SP Assert model.

For infliximab in the LRiG model, using the same flat BASDAI and BASFI profiles whilst on treatment yields an ICER of £48k. This compares to £50k or £58k in the SP models.

As an additional test of the consistency of this approach across the models, we estimated the mean BASDAI and BASFI while on treatment in the Wyeth model. The values were 1.9 and 0.9 for BASDAI and BASFI respectively. Inputting these values

into the LRiG model and holding patients on treatment at this level mirrors the Wyeth approach and yields an ICER of £18k. The equivalent figure from the Wyeth model was reported in the previous DSU report at £20k.

Table 2 summarises the findings across the different models according to the BASDAI/BASFI profiles incorporated.

Table 2: Summary of ICERs (£000's) from models according to BASDAI/BASFI assumptions

	MODELS				
	LRiG	Abbott	Wyeth	S-P (Assert)	S-P (Braun)
BASDAI/BASFI profile on treatment					
<i>Adalimumab/Etanercept</i>					
LRiG model	42				46
Abbott model		17			
Wyeth model	18		20		23
SP model	22			24	27
<i>Infliximab</i>					
LRiG model	82				93
SP model	48			50	58

5. Discussion

It is not surprising that it is the course of BASDAI and, to a lesser extent BASFI, that are identified as the key drivers of the differences in results between all the manufacturer models and the LRiG model. Previous work which implemented common parameter values indicated this was likely to be the case and LRiGs own reconciliation with Abbott also identified these profiles as the key difference. In particular, the models differ in terms of the course of BASDAI and BASFI in responders while they remain on treatment.

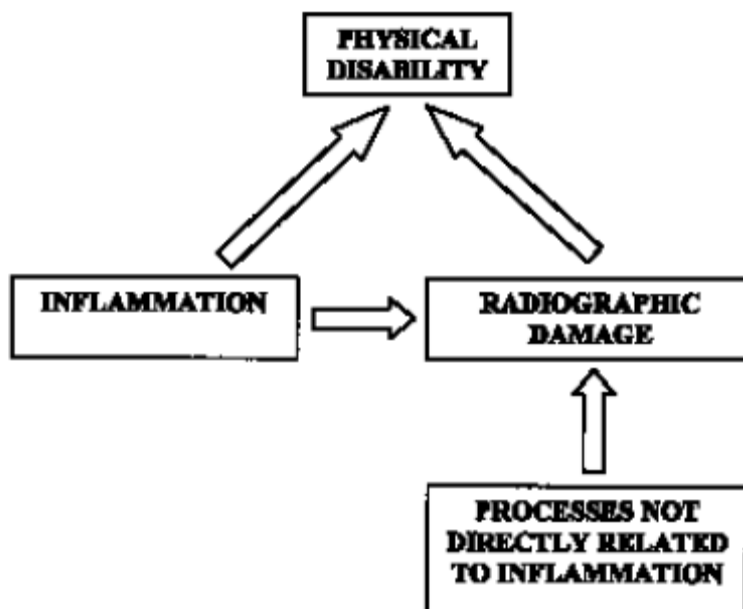
As the assessment report describes, there is little evidence on the course of disease progression in patients with AS. Since TNF antagonists have only recently been used in patients with AS, there is even less evidence on how their intervention might alter the natural course of disease.

The industry submissions offer little evidence to support the assumption that there is no progression when using a TNF antagonist. In both the Wyeth and SP submissions, evidence is offered from the open label extensions of the trials. For example, the Schering submission states that those who remain on treatment in the open label extension period of the Braun trial (i.e. beyond 12 weeks) and would classify as BSR responders, mean BASDAI improves from 1.9 (12 weeks) to 1.5 (1 and 2 years). Similarly, BASFI improves slightly from 2.2 (12 weeks) to 2.1 (1 yr) and 2 (2 yrs). However, this is based on just 13 patients at 2 years of the 18 that qualified for continuation at 12 weeks. In addition, the open label extension gives rise to significant risk of bias since patients frequently drop out when their condition deteriorates.

The zero rate disease progression on treatment has to some extent been ‘borrowed’ from rheumatoid arthritis (RA). In RA, while modelled only in terms of physical disability (HAQ), it was closely linked to the underlying impact of treatment on radiological progression. Figure 9 shows the conceptual relationship. While in RA,

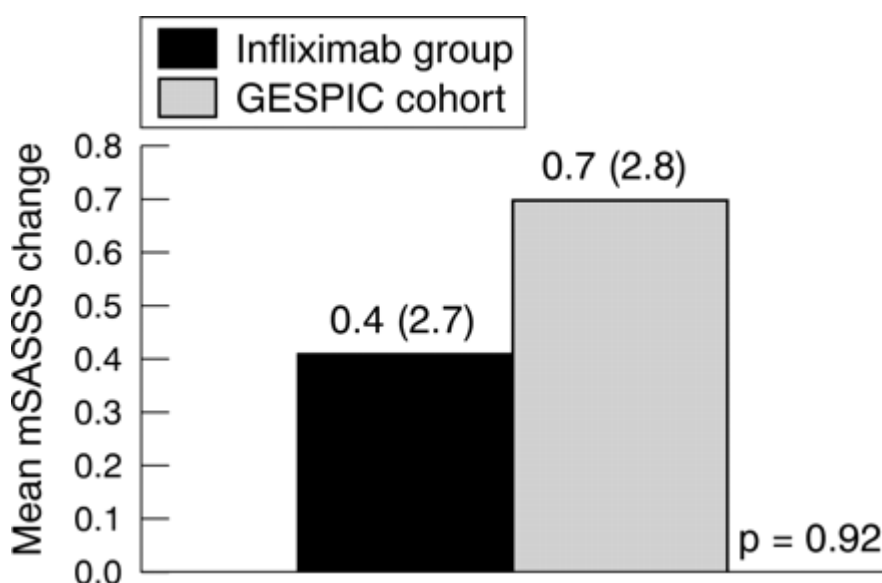
TNF antagonists have prevented radiological progression, even in patients that do not respond to treatment, the evidence in AS is more limited.

Figure 9: Conceptual relationship between disease activity, radiographic progression and physical function in inflammatory arthritis (Landewe and van der Heijde D)



For example, the 2-year evidence on infliximab finds that while progression is reduced in terms of modified Stokes AS Spinal Score as compared to patients on non-TNF antagonist treatment, some progression remains.(Figure 10)

Figure 10: Comparison of radiological progression in patients receiving infliximab compared to a cohort not receiving TNF therapy at 2 years (Baraliakos et al.)



Therefore there is some evidence to suggest disease progression is possible in patients responding to treatment but what the level of progression is remains unknown. The LRiG analysis uses data from a short term trial and so cannot equally be relied upon

for an accurate measure of progression, although it must be noted that the Assessment Report highlighted these caveats around long term modelling.

6. Summary of key issues

The most optimistic approaches to modelling incorporate a zero progression rate in both BASDAI and BASFI whilst on treatment. As the Assessment group point out, this is one of many alternatives that could be plausible and it is our view that this is a key issue for clinical opinion and future analysis. The Assessment Group adopted a quadratic modelling approach on the basis that this most closely fitted the IPD data over 52 weeks. Criticisms of this have arisen primarily because of the apparent inconsistencies that arise once this is used to extrapolate over the long term.

In the set of parameters that were provided to the DSU as those which the committee had previously discussed and agreed upon as those which should form the base case, was “BASFI progression prevented whilst on treatment”. We have demonstrated that implicit in the LRiG model is a changing BASFI profile over time for responders. LRiG do have an option that allows an additional 0.07 annual progression rate to be excluded from responders and it is this option that the ICER of £42k per QALY refers to.

However, it is interesting to note that if BASDAI and BASFI are assumed to remain constant after one year for responders in the LRiG model the ICER is £30,100. **Any** progression over time while on treatment will cause the ICER to rise above this level. It is not possible to judge whether the rate of progression included in the LRiG base case model that causes the ICER to rise to £42k is biased upwards rather than downwards.

Furthermore, it must also be recognised that these figures are based on the favourable assumption of excluding the 17% of apparent responders in the placebo group with no comparable adjustment made to the intervention group. Adjustment for this issue also leads to a higher ICER.

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