The cost-effectiveness of etanercept in patients with severe ankylosing spondylitis in the UK

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\textbf{Objectives.} To examine the costs and benefits associated with long-term etanercept (ETN) treatment in patients with severe ankylosing spondylitis (AS) in the UK in accordance with the BSR guidelines.

\textbf{Methods.} A mathematical model was constructed to estimate the costs and benefits associated with ETN plus non-steroidal anti-inflammatory drugs (NSAIDs) compared with NSAIDs alone. Individual patient data from Phase III RCTs was used to inform the proportion and magnitude of initial response to treatment and changes in health-related quality of life. A retrospective costing exercise on patients attending a UK secondary care rheumatology unit was used to inform disease costs. Published evidence on long-term disease progression was extrapolated over a 25-yr horizon. Uncertainty was examined using probabilistic sensitivity analyses.

\textbf{Results.} Over a 25-yr horizon, ETN plus NSAIDs gave 1.58 more QALYs at an additional cost of £35 978 when compared with NSAID treatment alone. This equates to a central estimate of £22 700 per QALY. The incremental cost per QALYs using shorter time periods were £27 600, £23 600 and £22 600 at 2, 5 and 15 yrs, respectively. Using a 25-yr horizon, 93\% of results from the probabilistic analyses fall below a threshold of £25 000 per QALY.

\textbf{Conclusions.} This study demonstrates the potential cost-effectiveness of ETN plus NSAIDs compared with NSAIDs alone in patients with severe AS treated according to the BSR guidelines in the UK.

\textbf{Key words:} Tumour necrosis factor, Health status, Cost effectiveness, Cost utility, Economic evaluation, Ankylosing spondylitis.

\textbf{Introduction}

Ankylosing spondylitis (AS) is a chronic progressive inflammatory disease that causes irreversible skeletal damage. Recent evidence-based recommendations developed by the European League against Rheumatism (EULAR) and the Assessment of Ankylosing Spondylitis (ASAS) Working Group included the use of non-steroidal anti-inflammatory drugs (NSAIDs) anti-rheumatic drugs, treatments with biological agents, simple analgesics, local and systemic steroids, physiotherapy and surgery [1]. The mainstays of treatment, however, are NSAIDs and physiotherapy. Typically presenting in young males, long-term prognosis is poor with some patients experiencing severe loss of physical function, high levels of pain and large reductions in health-related quality of life (HRQoL) [2–5]. AS is associated with reductions in working hours, changes in career and early retirement from the work force [4, 6–7]. Published evidence suggests costs accrued by AS patients are driven by the disease and its consequences on their capacity to work [8–9]. Consequently, any treatment that can provide prolonged and sustained relief from symptoms and future disability has the potential to improve patients’ chances of remaining in full employment and to reduce the need for surgery; thus providing financial benefits to both patients and society.

For patients failing the only drug therapies available (NSAIDs), tumour necrosis factor (TNF)-blockers are currently the most promising treatment option and the only alternative for individuals with active progressive disease. Anti-TNF agents have been shown to be efficacious in treating AS patients and under the British Society for Rheumatology (BSR) guidelines [10] for patients diagnosed using the modified NY, USA criteria [11] are eligible for treatment and, if they have failed, two or more NSAIDs are taken sequentially at maximum tolerated dosage; and have a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) $\geq 4$ units (scale 0–10, 10 = worse); and a spinal pain visual analogue scale (VAS) $\geq 4$ units. Patients are assessed at 3 monthly intervals and if they fail to respond (where response is defined as: a reduction of BASDAI to 50\% of the pre-treatment value or a fall of $\geq 2$ units and a reduction of the spinal VAS by $\geq 2$ units) treatment is withdrawn. These criteria are similar to those published by ASAS [12], which were recently updated by Braun et al. [13].

In budget-constrained healthcare systems, policy decision makers require evidence on the potential cost-effectiveness of novel interventions and three studies reporting the cost-utility of anti-TNF agents in AS patients have been published. The first examined the use of infliximab in the UK, using a 2-yr horizon in the basecase and a 30-yr horizon in sensitivity analyses [14]. This model was then adapted to examine the use of infliximab in Canada [15]. The second examined the use of either infliximab or etanercept (ETN) in The Netherlands using a 5-yr horizon [16]. The basecase results for infliximab ranged from £9.6k per QALY using a 30-yr horizon and £32.8k per QALY using a 2-yr horizon [14]; to €190k (€180k) per QALY using a 5-yr horizon [16]. The 5-yr basecase result for ETN was estimated to be in the region of €118k (€97.6k) per QALY [16]. Based on these results, the question; do anti-TNF agents provide value for money in AS patients remains unresolved.

The aim of the current study is to provide evidence on the potential costs and benefits associated with long-term (25-yr) ETN treatment for patients with severe AS in the UK in accordance with the BSR guidelines [10]. The time horizon reflects the chronic nature of the disease as stipulated by the National Institute of Health and Clinical Excellence (NICE) [17] and a National Health Service (NHS) perspective involving direct healthcare costs only was employed as indicated in the NICE reference case [18].

\textbf{Method}

\textit{Overview}

The model uses both the BASDAI and the Bath Ankylosing Spondylitis Functional Index (BASFI) to represent response and
The current study has been constructed around these relationships and utilizes changes in BASDAI and BASFI measurements to predict corresponding changes in disease costs and HRQoL.

The model (Microsoft Excel 2005) compares ETN plus NSAIDs with NSAIDs alone following BSR guidelines for ETN [10]. Patient level data from phase III randomized controlled trials (RCTs) informs clinical effectiveness and HRQoL changes [21–23]. Long-term disease progression is based on published evidence and the costs and benefits accrued over a 25-year horizon are used to calculate an incremental cost per QALY. As the pathway is extrapolated beyond the RCT evidence, results are also presented using shorter horizons. Costs and benefits are discounted at 3.5% in accordance with UK guidelines [24].

Data
The pivotal clinical efficacy evidence is derived from a large multicentre European RCT where patients were randomized to receive: ETN 25 mg twice weekly (n = 150), ETN 50 mg once weekly (n = 155) or placebo (n = 51) for 12 weeks [21]. As there was no significant difference in outcomes, data from the two ETN arms were pooled. This evidence is supported by data from a predominantly US RCT where patients were randomized to receive ETN 25 mg twice weekly (n = 138) or placebo (n = 139) for 24 weeks supplemented by 3-year evidence from an open-label extension [23, 25].

HRQoL data collected during the European study are used to model changes in utilities. As over 88% of patients in the placebo arms of the RCTs received NSAIDs these data have been used to inform the comparator arm (Table 1). AS disease costs are derived from a retrospective (12 month) costing exercise examining the direct health care utilization of AS patients (n = 147) attending a UK Rheumatology centre in Stoke [26].

Clinical pathway
In accordance with the BSR recommendations, it is assumed that all patients have tried and failed to respond to at least two consecutive NSAIDs and have a BASDAI measurement ≥40 (scale 0–100) prior to entering the model [10].

To continue to receive ETN, patients must respond to treatment where response is defined as: a reduction of BASDAI to 50% of the pre-treatment value (or a fall of ≥20 units) and a reduction of the spinal VAS by ≥2 units. Based on the RCT evidence, 67 and 55% respond to ETN while 24 and 16% of the comparator arm are deemed responders at weeks 12 [21] and 24 [21–22], respectively. It is assumed that 10% withdraw from ETN each year [27, 28]. On withdrawal from ETN treatment it is assumed that patients continue to receive NSAIDs.

Estimating benefit
The magnitudes of initial efficacy were derived from patient level data using patients with a baseline BASDAI of greater or equal to 40 [21–22]. The mean BASDAI and BASFI measurements at weeks 12 and 24 for responders and non-responders to treatment (as defined by the BSR criteria) are provided in Table 2.

For responders to treatment, open-label data suggests that initial response to ETN are sustained over a further 3 yrs [23, 25]. For patients who continue responding to treatment, it is assumed that their BASDAI and BASFI measurements remain constant at the levels observed at week 24 in the RCTs. For patients who withdraw from treatment, it is conservatively assumed that BASDAI and BASFI measurements revert back to baseline values immediately on withdrawal.

Beyond 6 months, while patients with AS will suffer from a natural progression in disability, evidence on possible changes in BASDAI and BASFI measurements are scarce. Evidence for natural progression of the disease is derived from a cross-sectional survey of over 1000 UK AS patients, which recorded a mean absolute change in BASFI of 0.7 (scale 0–100) per annum [14]. Similar rates have been reported from a 5-year longitudinal study in 74 UK patients in which BASFI increase by 1.26 (95% CI 0.13, 2.29) units per annum [29].

With mortality risk equal in both arms; age- and sex-related lifetables were adjusted using a standardized mortality ratio of 1.50 [30–31].

Quality of life
Life years were transformed into utility using a relationship derived from the BASDAI, BASFI and EQ-5D data collected.
during the European RCT (utility = 0.923 – 0.004*BASFI – 0.004*BASDAI, R² = 0.52).

**Estimating resource use**

A costing study on 147 patients attending the Staffordshire Rheumatology centre, Haywood Hospital, Stoke, was undertaken to establish the total annual costs attributable to patients with AS [26]. Hospital records (obtained December 2003 to June 2004) were examined retrospectively to assess the direct healthcare resources (including medications, hospitalizations and physiotherapy) used over the previous 12 months. Costs were assessed using a micro-costing approach starting with a detailed inventory and measurement of resources consumed by the patient. Prescription drug and hospital costs were taken from various sources [32–34]. A relationship between BASDAI and BASFI measurements and annual costs was used to estimate the costs offset by improvements in disability (Table 3).

Costs associated with NSAIDs were assumed to be included in the annual disease costs as 85% of patients in the Stoke cohort received NSAIDs. The annual cost of ETN plus monitoring was £9,372, with a start-up cost of £71 in the first 3 months.

**Results**

Possible annual AS disease costs ranged from £439 to £3.2k (BASDAI/BASFI, 0–100) with a 10 unit increase incurring a mean increment of approximately £138 for measurements of 40 and below; and a mean increment of approximately £476 for measurements of 70 and above. Figure 1 shows the changes in mean annual costs and utility profiles of patients in the ETN and comparator arms over the 25-yr period.

**Cost effectiveness**

At 2 yrs, the total incremental discounted QALYs gained by a cohort of 1000 patients (Table 4) was 368 at an additional cost of £10 152k resulting in an incremental cost utility ratio (ICUR) of £27.6k per QALY. The ICUR decreases over time and by 25 yrs, the incremental benefits accrued by the ETN cohort has increased to 1585 QALYs at an additional incremental cost of £35978k, giving an ICUR of £22.7k per QALY.

**Sensitivity analysis**

The results of a series of one-way sensitivity analyses (Table 5) are summarized in a tornado diagram (Fig.2). The length and position of the horizontal bars denote the range of ICURs produced by varying a specific parameter over its plausible range. Three variables have a large impact on the 25-yr results. First, when using the 95% confidence intervals to represent benefits associated with HRQoL (S/a 2) ICURs range from £15.7k to £34.7k per QALY. Second, when varying the annual withdrawal rate from ETN treatment (S/a 5) ICURs range from £15.1k per QALY if the annual withdrawal rate is decreased to 5% per annum, to £29.4k per QALY if the annual withdrawal rate is increased to 15% per annum. Third, when using the 95% confidence intervals for disease costs (S/a 3) ICURs range from £13.6k to £24.9k per QALY.

Monte-Carlo simulations were performed to examine the overall uncertainty in all the variables simultaneously and Fig. 3 shows the results at several points in time. As each symbol depicts...
Discounted Incremental Cost per QALY

<table>
<thead>
<tr>
<th></th>
<th>Incremental £10 152 034</th>
<th>£19 280 748</th>
<th>£32 818 855</th>
<th>£35 978 245</th>
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</thead>
<tbody>
<tr>
<td>Comp</td>
<td>£2 889 706</td>
<td>£7 109 054</td>
<td>£18 596 422</td>
<td>£26 538 439</td>
</tr>
<tr>
<td>ETN</td>
<td>£13 041 740</td>
<td>£26 389 802</td>
<td>£51 415 277</td>
<td>£62 516 684</td>
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Total Discounted Costs

<table>
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<tr>
<th></th>
<th>Comp 817</th>
<th>1831</th>
<th>4266</th>
<th>5700</th>
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<tr>
<td>ETN</td>
<td>368</td>
<td>815</td>
<td>1453</td>
<td>1585</td>
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Total Discounted QALYS

<table>
<thead>
<tr>
<th>Time horizon (years)</th>
<th>2</th>
<th>5</th>
<th>15</th>
<th>25</th>
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</thead>
<tbody>
<tr>
<td>ETN</td>
<td>1185</td>
<td>2646</td>
<td>5739</td>
<td>7285</td>
</tr>
<tr>
<td>Comp</td>
<td>817</td>
<td>1831</td>
<td>4266</td>
<td>5700</td>
</tr>
</tbody>
</table>

Table 4. Breakdown of costs and time horizons incurred for a cohort of 1000 patients over 4 time periods

Discussion

With the majority of incremental cost utility ratios (ICURs) falling below £25k per QALY, this study demonstrates ETN treatment in AS patients in the UK under BSR guidelines could be viewed as cost effective under NICE thresholds [25].

As with many economic evaluations of novel interventions, one of the most challenging aspects of this research has been identifying robust sources of evidence. In particular, our literature searches and reviews revealed a dearth of AS specific evidence including: long-term natural disease progression; long-term disease progression whilst responding to treatment; AS related disease costs and utilities. The following sections discuss the limitations of the current model in terms of the available evidence and the implications of this on the estimated ICURs. The priorities for further research are summarized in Table 6.

As BASDAI and BASFI measurements are used consistently in both short- and long-term studies of AS patients they provide a common metric to merge evidence from disparate sources. Our research corroborates earlier published results suggesting strong correlations between BASDAI and BASFI measurements and associations between these and AS disease costs and utilities. We use changes in both these variables to estimate corresponding changes in costs and utilities associated with AS.

Based on comparatively short-term (3-yr) open label data [25] we assume that continued responders to ETN experience no increases in BASDAI and BASFI measurements. We performed several analyses to explore the impact of this assumption. The results are reasonably robust to changes in the rate of progression for responders to treatment. If it is assumed that the decline in function for responders to treatment is half that of the comparator cohort i.e. an increase of 0.35 units for responders and 0.70 units for non-responders/comparator per annum, the resulting ICURs increases by just 2%. If it is assumed that the functional decline is equal for all patients in the model (i.e. an increase in BASFI of 0.7 units per annum) the ICUR increases by just 4%. If no disease progression is modelled for any patients in the model, the resulting ICUR remains well below a £30k threshold at £25.7k per QALY.

An associated area of uncertainty involves the magnitude of changes to BASDAI and BASFI measurements on withdrawal from treatment. We assumed that these measurements revert to pre-treatment levels immediately on withdrawal from treatment. We believe this is a reasonable assumption as under the BSR recommendations; patients who experience an increase in BASDAI measurements would be withdrawn from treatment in general clinical practice. Long-term observational studies should provide evidence on whether the guidelines for anti-TNF agents are adhered to in general clinical practice; the magnitude of changes in BASDAI and BASFI measurements on relapse; any possible time delay in relapse and the different rates of disease progression for responders and non-responders to treatments. Long-term studies should also provide answers as to whether the efficacy observed in RCTs is transferred into prolonged effectiveness in general clinical practice. Evidence from long-term studies in RA show no change over time in the incidence rate for severe adverse events in individuals receiving ETN and there are no data to suggest that the long-term safety profile for individuals with AS will differ from those with RA [37, 38].

The disease costs used in the current evaluation are representative of the medical costs accrued by patients with AS attending a secondary care rheumatology unit in the UK [26]. Using BASDAI/BASFI measurements of 20, 50 and 80, the corresponding annual disease costs are estimated to be £0.5k, £1.1k and £2.0k. A recent UK costing study estimated total annual (including both direct and indirect costs) disease costs of approximately £3.5k, £9.5k and £30.0k for BASDAI/BASFI measurements of 20, 50 and 80, respectively [14]. If only hospital and medication costs are included we estimate these figures would
reduce to approximately £0.6k, £1.4k and £3.0k per annum. Boonen et al. [16] reported similar annual costs of €1.7k and €4.7k (£1.1 and £3.1) for BASDAI <40 and ≥40, respectively. With the exception of patients at the severe end of the disease scale, both sets of figures are comparable with those used in our study.

The mean BASDAI score in the Stoke sample was 42.5 (range 0.2–91.7) and the mean BASFI score was 44.4 (range 0.0–92.9). As the sample encompasses the full spectrum of disease severity the results should be generalizable to other cohorts. However, unlike the Bath cohort, none of the patients in the Stoke sample received joint replacements hence it is possible that we underestimate the potential costs for patients at the extreme end of the disease scale. In addition, the relatively small sample size (n = 147) precluded subgroup analyses. The regression used could be strengthened by additional research involving a larger sample size.

AS primarily affects patients of working age and evidence implies that indirect costs are the greatest contributors to costs incurred by these patients [7–8]. In this instance it may be appropriate to use a societal perspective taking into account costs such as loss of wages, loss of productivity, early retirement and perhaps the impact on benefits such as the HRQoL of the primary career. However, this is difficult to quantify in practice and while some countries view inclusion of work related costs as absolutely necessary other countries consider their inclusion unrealistic. As the current study was conducted to inform policy decision

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**Table 5. Results of one-way sensitivity analyses**

<table>
<thead>
<tr>
<th>Time horizon (years)</th>
<th>Incremental costs</th>
<th>Incremental QALY</th>
<th>Incremental cost-effectiveness ratio</th>
<th>Percentage change from base case</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base case</td>
<td>2</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>£10 152 034</td>
<td>£35 978 245</td>
<td>368</td>
<td>£27 594</td>
</tr>
<tr>
<td>1. Discount rates</td>
<td>Undiscounted costs and benefits</td>
<td>£10 296 063</td>
<td>£44 500 001</td>
<td>375</td>
</tr>
<tr>
<td></td>
<td>Costs and benefits discounted at 6%</td>
<td>£10 054 979</td>
<td>£31 720 422</td>
<td>363</td>
</tr>
<tr>
<td>2. Health-related quality of life</td>
<td>LCI</td>
<td>£10 152 034</td>
<td>£35 978 245</td>
<td>502</td>
</tr>
<tr>
<td></td>
<td>UCI</td>
<td>£10 152 034</td>
<td>£35 978 245</td>
<td>239</td>
</tr>
<tr>
<td>3. Disease costs</td>
<td>LCI</td>
<td>£11 099 386</td>
<td>£39 495 657</td>
<td>368</td>
</tr>
<tr>
<td></td>
<td>UCI</td>
<td>£4 348 438</td>
<td>£21 560 682</td>
<td>368</td>
</tr>
<tr>
<td>4. Disease progression</td>
<td>No progression for any patients</td>
<td>£10 161 394</td>
<td>£36 824 499</td>
<td>366</td>
</tr>
<tr>
<td></td>
<td>BASFI at 0.35 for responders to ETN and 0.7 for comparator and non-responders</td>
<td>£10 152 034</td>
<td>£36 031 712</td>
<td>368</td>
</tr>
<tr>
<td></td>
<td>BASFI at 0.7 for all patients</td>
<td>£10 152 034</td>
<td>£36 088 442</td>
<td>368</td>
</tr>
<tr>
<td>5. Long-term annual withdrawal rate from ETN</td>
<td>annual withdrawal rate decreases to 5%</td>
<td>£10 125 338</td>
<td>£33 976 378</td>
<td>376</td>
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<tr>
<td></td>
<td>annual withdrawal rate increases to 15%</td>
<td>£10 166 062</td>
<td>£36 968 423</td>
<td>363</td>
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**Table 6. Priorities for further research**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Issue</th>
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<tbody>
<tr>
<td>Anti-TNF agents: efficacy</td>
<td>How ETN works in clinical practice—including withdrawal based on BSR criteria</td>
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<tr>
<td></td>
<td>Potential impact of radiological progression on long-term disability</td>
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<tr>
<td>BASDAI/BASFI</td>
<td>Efficacy in patients with BASDAI &lt;40</td>
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<tr>
<td>Costs</td>
<td>Strengthen relationships used to predict costs and utilities</td>
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<td></td>
<td>Indirect costs</td>
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<td></td>
<td>Impact of ETN on early retirement/work losses</td>
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<tr>
<td>Sub group</td>
<td>Develop prognostic algorithms to identify patients who would benefit most and those who would give most efficient use of ETN</td>
</tr>
<tr>
<td>Natural course of disease</td>
<td>Quantify natural disease progression and disease progression for patients receiving anti-TNF blockers</td>
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<tr>
<td>Future economic evaluations</td>
<td>Direct comparison of costs and benefits associated with alternative anti-TNF agents and sequential use of these</td>
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**Fig. 2. Results of one-way sensitivity analyses for the 25-yr horizon summarized in a tornado diagram; dated (16 August 2006)**

**Fig. 3. Cost effectiveness plane over 2, 5, 15 and 25-yrs**
makers at the UK National Institute for Clinical Excellence we took a NHS perspective and included direct healthcare costs only. This may be considered an overly conservative approach and it is clear that if indirect costs were to be included the ICURs would be more favourable.

The EQ-5D data from the ETN RCT corroborated earlier evidence that suggested utility is driven equally by both function and disease activity. With values of 0.84 and 0.17 for BASDAI/BASFI of 0–20 and 80–100 (scale 0–100). Utilities ranging from 0.87 for BASDAI/BASFI ≤ 2 to 0.21 for BASDAI/BASFI ≥ 8 (scale 0–10); with a decrease of 0.075 for each unit increase in BASFI, have been reported for a Canadian cohort [15]. A further study on Dutch patients reports values of 0.59 and 0.76 corresponding to BASDAI measurements of ≥40 and <40 respectively again using EQ-5D data [16].

Our model estimates an incremental gain in utility of 1.59 over a 25-year period using a 3.5% discount rate. This is comparable with those estimated by Kobelt et al. [14] at 2.33 for a 30-year period using a 3% discount rate. However, our 3-year estimate is considerably higher than Boonen’s at 0.81 compared with 0.27 [16]. The authors comment that their utility gains are surprisingly small compared with the large effects on patient reported disease activity and function. They suggest the apparent anomaly could be because their utilities were derived from a cohort who had less severe disease than patients who are eligible for anti-TNF agents. It is also possible that the limited number of health states used may restrict the ability of the model to quantify the full benefits of anti-TNF treatment.

Finally, the model is based on RCT data in patients with chronic unremitting disease of relatively long disease duration. It is possible that functional ability could be improved by providing anti-TNF agents in early stages of the disease when the damage is more limited. If anti-TNF agents are shown to modify disease progression, research to identify those at risk of developing the more severe disabling disease would be beneficial. By synthesising the limited evidence currently available, this study demonstrates the potential cost-effectiveness of ETN plus NSAIDs compared with NSAIDs alone in patients with severe AS in the UK under the BSR guidelines. The findings are believed to be representative for patients with chronic unremitting disease and a research priority should be to identify patients who are most likely to benefit from anti-TNF agents and those in whom these therapies will provide the most efficient use of scarce resources. Decision makers also require evidence on both the comparative cost-effectiveness of the different anti-TNF agents and sequential treatments. The model should be updated when data become available.

### References

33. http://www.pssru.ac.uk/

