In this issue of the journal, Fautrel and colleagues present a paper that contrasts the British and French rheumatology society guidelines for eligibility for anti-TNF therapy in RA [1, 2] alongside the surveyed opinion of French rheumatologists [3]. The findings suggest that 7% of the studied RA patients were eligible according to French criteria but using the British criteria, only 0.9% representing an almost 8-fold difference in percentages that were eligible to have access to anti-TNF. In addition, separate from any specific guidelines, the French rheumatologists felt that 10% of their patients required treatment with anti-TNF, suggesting that their clinical opinion was more closely allied to their own French guidelines than to the British. How can there be such enormous differences in eligibility between two geographical neighbours? Are British patients having access to too little anti-TNF, or are the French being profligate in their eligibility criteria, and allowing too many patients onto anti-TNF?

The British and French guidelines share some features in common. They both require patients to fulfil the ACR 1987 classification criteria for RA [4], and need a demonstration of persistent disease activity with a disease activity score 28 (DAS28) being >5.1 on two occasions at least a month apart (following the EULAR classification of high levels of disease activity [5-7]). However, this is where the similarities end. The French guidelines have extended their eligibility to include patients with a DAS28 >5.1, who have ongoing signs of inflammation [defined as a DAS28 >3.2 with more than three synovitic joints, an elevated ESR (≥28 mm/h) or CRP (≥15 mg/dl)] despite >0.1 mg/kg/day of prednisolone or equivalent, or progressive radiological damage. The DAS28 as a single arbiter of eligibility to go onto anti-TNF has been criticized [8, 9], and the French guidelines acknowledge that a more sophisticated approach is required to determine who is not doing well on conventional DMARDs. A further difference between the two national guidelines relates to the failure of traditional DMARDs. Although both require a trial of MTX, the French guidelines require only 3 months at a therapeutic and tolerated dose compared with 6 months in the British guidelines. The British guidelines also require failure of a second DMARD in addition to MTX, whereas the French guidelines only require failure of MTX (or LEF or SSZ if MTX is not tolerated). Some of these differences in eligibility criteria will reflect when these guidelines were first established (the British originally in 2001, when the knowledge of the benefits of early aggressive therapy were still evolving, and the French in 2005).

However, all of these differences are trivial when consideration is taken of what happens to the guidelines once the specialist societies have produced them. It is important to remember why treatment guidelines are developed. Usually after an extensive review of the medical literature and consultations with experts in the field, treatment guidelines are developed to ensure that all patients with a specific diagnosis are given the best evidence-based therapy. However, in most countries, guidelines are seen as just that, and are not enforced in law or linked with access to the drug. This is where the British and French guidelines differ. This key difference now challenges the ability of British rheumatologists to change the eligibility criteria embedded within their national guidelines.

In the UK, the use of expensive treatment is regulated through guidance from the National Institute for Health and Clinical Excellence (NICE). Based on a review of the available clinical and economic evidence, this independent organization produces guidance that will help the UK National Health Service (NHS) decide on the best use of its finite resources. Therefore, while the UK guidelines start life in a similar fashion to the French guidelines, they are then used to determine whether their application results in cost-effective use of the drug. The final NICE guidelines may include elements from the specialist society guidelines, but only if the assessment process has determined that they are appropriate. After much negotiation with stakeholders, these guidelines are published with the full endorsement of a government body, carrying legal responsibilities for fund-holding bodies to provide the resources to support their use. Along these lines, funding bodies are also, with increasing frequency, ensuring that prescribers are adhering to the national guidelines, and therefore the availability of these drugs for patients who do not fulfil the current guidelines is extremely limited.

These differences in process appear to lead to huge differences in the proportion of French patients who would be eligible to go onto anti-TNF according to French or NICE guidelines. Is there any other evidence to suggest that British patients are receiving much less access to anti-TNF than other countries? As the authors point out, other published audits of UK patients have shown higher eligibility rates for patients in UK NHS clinics of around 6% [10, 11] (not far off the 7% of the French guidelines eligibility levels in the paper [3]). So is the figure of 0.9% much lower than would be expected for eligibility in UK practice? Or as the authors suggest, are we rendering patients victims of our success in identifying the disease earlier, and treating them with conventional DMARDs more aggressively from as close to symptom onset as possible, thus decreasing their chances of fulfilling UK eligibility criteria to go onto anti-TNF? Although conventional DMARD approaches may suppress disease activity, they are not as effective at slowing radiological damage as anti-TNF drugs, and this translates into disability in the long-term [12]. Furthermore, imagine a patient with a 1-yr history of RA being aggressively treated with high doses of MTX, SSZ and tapering doses of steroids. Our imaginary patient has a DAS28 of 4.2, is finding it difficult to reduce the steroid dose <7.5 mg/day and X-rays of hands and feet show new erosions that have developed over the year. Most clinicians (including the authors) would feel that such a person warrants access to anti-TNF, almost certainly at a time <1 yr of struggling with this disease. French guidelines would allow our imaginary patient onto anti-TNF, whereas current NICE guidelines would not.

This is not the first paper to suggest that British patients have less access to anti-TNF than other countries. A study from Scandinavia showed that patients in Denmark and Norway had approximately twice the rates of access to anti-TNF than British RA patients [13]. An international comparison of access to anti-TNF showed that those countries with the most rigorous guidelines had the lowest rates of uptake of the drug, with the UK well down in the league table [14].

What can those who come under the jurisdiction of NICE learn from these comparisons, and can the French learn anything from the British?

(i) As discussed, a DAS28 >5.1 may seem too high for certain patients, particularly in patients on aggressive DMARD
regimes with or without steroids [8]. Even though it seems intuitive that certain patients with a DAS28 < 5.1 would benefit from anti-TNF therapy, in order to change the current threshold for treatment in the UK, evidence would need to be presented to NICE that convinced them that treatment of this patient group was also cost-effective. In the next iteration of the UK guidelines, this is being explored:

(a) Data on the natural history of RA in patients with persistent DAS28 in the moderate range is required (i.e. if a patient has a DAS28 around 4.2 for >1 yr despite conventional DMARDs, what are the implications for disease progression, disability, ability to work, need for operations, etc). This data may already exist within UK databases.

(b) In the UK, there remain very few patients in routine practice who have received these drugs with moderate disease activity. However, this data does exist in other databases around the world and a combined analysis will also help to address this issue. Indeed, although as much a factor of the outcome measure itself, there is already evidence that patients with a lower baseline DAS28 are much more likely to go into remission than those starting from a much higher score [15–17].

(ii) The points raised in (i) above assume that a single hurdle for access to anti-TNF is appropriate, and as discussed, addressing eligibility for anti-TNF based solely on DAS28 score may be far from ideal. There are numerous problems with the DAS28, including some patients who do not have high levels in early disease despite aggressive synovitis [8], or patients with other conditions such as fibromyalgia that can score highly in the absence of active synovitis [18]. Can we take a lesson from the French guidelines and broaden our eligibility criteria to include a variety of patient groups for whom it would be appropriate to treat with anti-TNF?

(iii) Should we be arguing for MTX to be the only conventional DMARD to fail on before considering anti-TNF, as the French guidelines suggest? Work from BeSt suggests that following the failure of MTX, there is only a slim chance of other conventional drugs working satisfactorily [19]. On the other hand, early use of combinations of conventional DMARDs has been shown to work very effectively in RA, and at prices considerably cheaper than anti-TNF [20]. Should we be advocating the use of combinations of conventional DMARDs, failure on which should result in a prompt transfer to anti-TNF?

Although many of these suggestions seem clinically appropriate, it is not enough to simply argue this with NICE without data to show that wider use of anti-TNF would also be cost-effective. It is also important that natural history data is available on the disease of interest, so that it is possible to demonstrate the short- and long-term consequences of not intervening with expensive, but efficacious drugs. Could the existing databases have this information in sufficient detail to show that this use would also be cost-effective? On the one hand, our guidelines need to incorporate some of the complexity of decision making for eligibility for anti-TNF, whilst on the other be defensible in negotiations with NICE, and workable in clinical practice.

Finally, our international colleagues might learn from the UK experience. Although NICE has been criticized in both rheumatology and other assessments [21], the World Health Organization gave an excellent report on the processes followed by the organization [22]. Increasingly, governments are considering the use of incorporating health economic assessments into their own decision-making process on what drugs should and should not be reimbursed in their health care systems, based on cost-effectiveness and affordability [23]. The days may be limited of clinicians proposing guidelines based on clinical effectiveness, and largely ignoring health economic considerations. British rheumatologists have learned some harsh lessons since NICE was created in 1999, and international colleagues would do well to bear these in mind if their own administrations adopt a NICE approach to drug availability. Perhaps a few words of advice:

(i) It is vital that clinicians are involved in the health economic analysis to ensure that drivers of the model and its assumptions are clinically appropriate.

(ii) Head-to-head trials of comparator drugs will always be more satisfactory than indirect comparisons and grant-giving organizations will need to assist the support of such trials to address important questions on the comparative cost-effectiveness.

(iii) It is important that economic models of chronic diseases, such as RA, take into account the full socioeconomic cost of treating the condition and not solely costs to the health care system. This runs the risk of under-valuing the impact of expensive drugs on the total cost to society of diseases like RA. A recent Health Committee report criticized NICE for only considering the costs to the NHS [24], and the Department of Health are now exploring the possibility of making models more reflective of the full costs of disease, in terms of impact on the ability to work, and the cost to carers.

In conclusion, Fautrel and colleagues should be congratulated on some interesting work comparing French and NICE guidelines. The large discrepancy in percentages of patients eligible to go onto anti-TNF in the two countries could suggest either inappropriate over-use of anti-TNF in France, or that far too many UK patients are being denied access to efficacious treatments. The truth may be somewhere in between, and depends on where the balance between cost- and clinical-effectiveness is most appropriately struck. If the French government sees the rheumatology budget growing exponentially, they might become more interested in involvement in guidelines based on health economic considerations. On the other side of the channel, the British rheumatology community are working hard to ensure that the evidence base and health economic models can support extended access for patients to expensive but efficacious drugs. There are valuable lessons that French and the British colleagues can learn from each other, as we try to ensure the most appropriate access to these drugs for our patients.

Disclosure statement: C.D. has sat on an advisory board for Schering-Plough and has received honoraria for talks at symposia sponsored by Wyeth and Abbott. His department (Department of Rheumatology at Derbyshire Royal Infirmary) has received sponsorship from Wyeth, Abbott and Schering-Plough Pharmaceuticals for support of clinical meetings, and unrestricted grants to support an ultrasound machine, an anti-TNF audit clerk and research nurse. The other author has declared no conflicts of interest.

C. Deighton1, K. Hyrich2

1Department of Rheumatology, Derbyshire Royal Infirmary, Derby and 2Arthritis Research Campaign Epidemiology Unit, University of Manchester, Manchester, UK

Accepted 25 July 2008

Correspondence to: C. Deighton, Department of Rheumatology, Derbyshire Royal Infirmary, London Road, Derby DE1 2QY, UK. E-mail: chris.deighton@derbyhospitals.nhs.uk

References
