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MS TREATMENTS & NICE

Recent publicity about whether disease modifying drugs to treat multiple sclerosis (MS) should be available on the NHS has focused attention on the role of NICE (the National Institute for Clinical Excellence). NICE provides evidence-based guidance for the NHS, to ensure doctors use the most effective and affordable treatments. This briefing outlines how NICE evaluates clinical- and cost-effectiveness and examines the wider issues raised by health technology appraisal.

Background

NICE was established on April 1st 1999 as part of the NHS in England and Wales to address:

- the increasing pace of medical research and discovery;
- mounting pressure on healthcare budgets;
- variations in availability ('postcode prescribing') and quality of care.

It commissions, approves and disseminates evidence-based guidance to help doctors keep up with new developments, use resources more efficiently and even out local variations by setting national standards. The main thrust of NICE's work to date[1] has been appraising individual health technologies: drugs, medical devices, diagnostics, surgical procedures, etc. It also develops clinical guidelines for managing specific conditions[2] and develops and promotes clinical audit. This Postnote focuses on the appraisal of two drugs – β-interferons and glatiramer - for treating MS as an illustration of some of the wider issues raised by such evaluations.

Appraisal of new MS treatments

The Department of Health (DH) and National Assembly for Wales (NAW) first asked NICE to appraise the new MS treatments in August 1999 (see table opposite for details of NICE's current appraisal process). By July 2000, the appraisal committee had held its second meeting and circulated a final appraisal determination (FAD) to consultees recommending β-interferons **not** be prescribed on the NHS (appraisal of the second drug, glatiramer, had been put on hold pending its marketing approval). Eight consultees[3] appealed against various aspects of the FAD; an appeals panel announced in November 2000 upheld some of the appeals and rejected others. The main problem was assessment of

NICE's appraisal process

Step	Action
Scoping (week 0-8)	NICE initiates appraisal, identifies stakeholders (patients, professionals & manufacturers), conducts a literature search & prepares a draft scope. This scope & list of stakeholders is sent for consultation (2 weeks), finalised & published on the NICE website.
Assessment (week 7-38)	Stakeholders are invited to make submissions to NICE & to nominate clinical & patient experts who are invited to submit a written perspective. An assessment report – a review of the literature on the technology - is commissioned from an assessment group (an academic or other expert centre). This is sent to stakeholders for comment. All the submissions, the assessment report and comments on it form the basis of an evaluation report that is provided to the appraisal committee as evidence.
Appraisal (week 38-49)	First meeting of the appraisal committee (consisting of health professionals, NHS managers, health economists, representatives from patient groups & nominated experts) to consider the evaluation report & other evidence. The upshot of this meeting is an **appraisal consultation document** setting out the initial views of the appraisal committee. This is sent to stakeholders for consultation & published on NICE's website. The appraisal committee meets again to consider consultees' comments. A **final appraisal determination** (FAD) is prepared outlining the committee's final advice, sent to all stakeholders to consider if they wish to appeal, & published on the NICE website.
Appeal (week 52-)	Consultees have 15 working days to lodge an appeal. There are 3 grounds for appeal: failure to follow process; the decision is perverse in the light of the evidence submitted; and NICE exceeded its powers. If necessary NICE convenes an appeals panel to consider the appeal(s). If appeals are not upheld, the FAD becomes guidance - if they are upheld, NICE must reconsider the evidence.
Publication	NICE publishes guidance to the NHS in England and Wales based on the FAD. It also issues media briefings and guidance to patients (all information is available on www.nice.org.uk).

Source: 'Guide to the technology appraisal process', NICE, 2001.

cost-effectiveness. NICE decided to commission new economic models for both new drugs (glatiramer having received its marketing approval) in December 2000. Having considered the new models the appraisal committee held a further round of consultation, distributing a second FAD in October 2001. Once again this cast doubts about the cost-effectiveness of the drugs (see below). A number of consultees appealed against this second FAD, and an appeal hearing was held in November 2001. NICE announced in January 2002 that the appeals had **not** been upheld and issued its final guidance in February 2002, reiterating its previous advice **not** to prescribe the new MS treatments on the NHS. The following sections outline the available evidence on clinical-/cost-effectiveness of these drugs.

Assessing clinical effectiveness

MS is a disabling condition affecting some 63,000 people in England and Wales. As outlined in the box opposite, most MS patients initially experience a relapsing/remitting form (RRMS) with symptoms that come and go. Around half go on to develop a secondary/ progressive (SPMS) form, where symptoms gradually worsen. In assessing the clinical effectiveness of the two drugs (see box opposite) NICE considered evidence from randomised, double-blind, placebo-controlled clinical trials. Its most recent appraisal found:

- Each of the new drugs reduces the frequency of relapses in patients with RRMS by around 30% over 2 to 3 years (equivalent to a patient with RRMS avoiding one relapse every 2.5 years).
- One of the β-interferons (Betaferon) also reduces the frequency of relapses in SPMS.
- The new drugs may also have longer-term benefits by delaying the progression of disability. But the evidence here is less clear-cut since MS evolves over decades whereas clinical trials last 2-3 years. Longer-term studies suggest that patients taking β-interferons for 4-5 years or glatiramer for 8 years have lower levels of disability than might be expected, but the absence of control groups makes it difficult to establish a baseline for comparison. NICE concluded that the extent of long-term effects on disability cannot be predicted accurately from such evidence.

Not all MS patients benefit from the treatments. The Association of British Neurologists (ABN) has drawn up guidelines (see box below) for use of the drugs. Where these have been applied without financial constraints, ~10% of the MS population receive the drugs.

ABN guidelines for MS treatment

β-interferons or glatiramer for all RRMS patients who:

- can walk independently (β-interferons) or at least 100 meters without assistance (glatiramer);
- have had at least 2 clinically significant relapses in the last 2 years;
- are over 18 (no trials data are available for under 18s);

ABN recommends the drugs for SPMS patients who:

- can walk at least 10 metres with or without assistance;
- have had 2 or more disabling relapses in the last 2 yrs;
- have had minimal increase in disability due to gradual progression in the last 2 years;
- are over 18.

MS – the condition and the treatments

The condition - MS is caused by damage to the protective sheath that surrounds nerves in the brain and spinal column. This damage can be seen using magnetic resonance imaging (MRI), although the exact relationship between damage assessed in this way and observed clinical symptoms is not fully understood. Such symptoms include impaired vision, pain, numbness, fatigue, impaired cognition and/or muscle control, anxiety and depression. Most (~85%) patients initially experience a relapsing/remitting (RRMS) form of the disease with symptoms intensifying over hours or days, getting progressively worse for some weeks and gradually resolving. Around half of these go on to experience secondary progressive (SP) MS, with a gradual progression of disability. The remaining (~15%) of patients suffer from progressive MS from the outset.

Disease-modifying treatments - three forms of β interferons are currently licensed for use in the UK. Serono's Rebif and Biogen's Avonex are licensed for treatment of RRMS and Schering's Betaferon for treating SPMS and RRMS. Patients administer the drugs themselves through injections on a regular basis. The drugs reduce inflammation by an unknown mechanism. They can cause 'flu-like side-effects and adverse reactions at the site of injection. Glatiramer is licensed for treating patients with RRMS – it too reduces inflammation by an unknown mechanism. Patients inject themselves with the drug; side-effects may include flushing, chest tightness, anxiety, breathlessness and injection site reactions.

Assessing cost-effectiveness

Because the new MS drugs are relatively expensive (see box page 3), evaluating cost-effectiveness is an important aspect of the appraisal. All the models for MS treatment considered by NICE calculated cost-utilities – i.e. the cost required to achieve a specific increase in the quality and length of patients' lives (one measure is quality adjusted life year or QALY, another is cost per life year gained).

Since MS evolves over decades, it is reasonable to attempt to evaluate costs and benefits over 10-20 years. Clinical trials however, can only deliver evidence on how MS responds to treatment over a period of a few years. Modellers thus have to make assumptions about how benefits will accrue in the future. For instance, they don't know whether prolonged treatment will continue to prevent relapses, whether early treatment changes the course of the disease for good or delays progression, nor whether people who drop out of treatment maintain any benefits they have gained. The assumptions made about these and other factors have a profound effect on estimates of cost-effectiveness. In general, the shorter the time horizon over which clinical benefits and costs are evaluated, the less cost effective the drugs appear, because possible long-term benefits have to be ignored. As the time horizon increases, the drugs appear more cost-effective, but more assumptions have to be made in extrapolating from the trials data. Estimates provided during the appraisal varied widely with the assumptions made and the drugs assessed, but suggest costs of:

- £248,000-£810,000 per QALY gained over 5 years;
- £120,000-£339,000 per QALY gained over 10 years;
- £35,000-£104,000 per QALY gained over 20 years.

NICE's appraisal

In making its appraisals, NICE is required to consider the broad balance between costs and benefits, taking into account the efficient use of NHS resources. Of the estimates outlined above, the appraisal committee had most faith in those covering the shorter-term (5-10 years); it decided that it could not base its conclusion on cost-effectiveness solely on estimates calculated over 20 years. Its most recent determination thus recommended:

- On the basis of their clinical and cost effectiveness neither β-interferon nor glatiramer is recommended for the treatment of MS on the NHS;
- People currently receiving these treatments (1,750 in England and Wales) may continue to be prescribed the drugs because they could "*suffer loss of well being if their treatment is discontinued*" unexpectedly;
- DH, NAW and manufacturers could consider what joint action can be taken to allow the drugs to be secured more cost effectively.

MS treatments - what happens next?

While all agree there is good evidence that MS treatments offer short-term clinical benefits for some patients, NICE consider them not to be cost-effective. NICE thus invited the DH, NAW and manufacturers to consider ways in which the treatments could be secured more cost-effectively. Cost-effectiveness could be improved by decreasing costs and/or providing increased evidence of benefit. In the past few months, DH has been negotiating with the drug manufacturers, MS patient groups, ABN and other interested parties to:

- allow MS patients access to the drugs on the NHS in a cost-effective manner;
- monitor the progress of these patients long enough to obtain better evidence of the long-term impact of the treatments.

The new risk sharing scheme for MS treatments

In February 2002, DH announced a new risk-sharing scheme had been agreed. Under this scheme, all UK patients meeting the ABN criteria for RRMS or SPMS (see box page 2) will be eligible to receive MS treatments on the NHS. On entering the scheme, each patient will be assessed using a scheme to classify progression of disability (expanded disability status scores - EDSS) to establish a baseline for comparison. Each patient's EDSS will be monitored annually to allow DH to monitor the cost-effectiveness of each of the drugs entered into the scheme (manufacturers of each of the 4 drugs in question have been invited to participate in the scheme).

The scheme allows the price the NHS pays for each drug to be adjusted depending on the drug's performance. As outlined in the box opposite, the price can be adjusted to keep the cost-effectiveness of each treatment at an agreed threshold, thus guaranteeing that the NHS acquires the drugs cost-effectively. Designated neurologists will start to enrol patients in the scheme in May 2002; DH estimates it may take 18 months to enrol the 'backlog' of MS patients currently not receiving the drugs. In total, some 7,500-9,000 MS patients in England and Wales are expected to be enrolled; this may involve assessing as many as 20,000-30,000 MS patients. Monitoring and potential price adjustments are expected to continue for 10 years. Interested parties such as the Association of the British Pharmaceutical Industry (ABPI), ABN, MS Society, MS Trust and NICE have welcomed the new scheme.

Cost-effective provision of MS treatments

The costs per patient per year for each of the drugs supplied to the NHS at the start of the scheme are:

- Avonex £8,502
- Betaferon £7,259
- Glatiramer £5,823
- Rebif £7,513 (low dose) or £8,942 (higher dose)

At the start of the scheme, manufacturers will agree target outcomes with the DH for each of the drugs. These are effectively predictions of how well the drugs will perform over a 20 year period. The NHS will start off paying the costs of the drugs outlined above. If the target outcomes are met in full, then the long-term benefits experienced by patients mean that the drugs will have been cost-effective and no price adjustment will be necessary. But if monitoring shows that the drugs have failed to deliver the agreed outcomes, the price will be adjusted accordingly to keep cost-effectiveness of the treatments to an agreed threshold. For the purposes of this scheme, the threshold agreed is £36,000 per QALY. NICE does not have a threshold, although retrospective analysis of its first year of appraisals suggests that positive recommendations were generally associated with costs per QALY (or similar measures) of £30,000 or less. In setting the threshold at £36,000 per QALY the DH took NICE's experience and other factors (such as potential savings in Social Services costs from avoidance of severe disability) into account. DH estimates that costs of treatment in a full year could be around £50M, although this figure is likely to be considerably lower for 2002-03.
Source: DH Health Service Circular 2002/004.

Wider implications

Drug manufacturers and patient groups have identified a number of more general issues concerning the appraisal process. They argue that appraisal delays the introduction of new technologies to the NHS, preserves the inequalities of postcode prescribing and that the recommendations place undue emphasis on cost-effectiveness. Patient groups also question the emphasis on short-term cost-effectiveness, arguing that short-term clinical trials are not the best means of assessing treatments for long-term, complex, conditions like MS. These issues are discussed in more detail below.

Uptake of new technology and timing of appraisal

One of the reasons for establishing NICE was to improve NHS patient's access to proven new technologies. But the MS Society and the MS Trust suggest that appraisal of MS treatments has significantly delayed their introduction (the process took longer than the usual 12 months). ABPI also points to other examples where it considers that appraisal by NICE has delayed the use of a new drug. It has suggested that such problems could be avoided by appraising new drugs **after** they have been used in the NHS for some time to allow data on longer-term costs and benefits to be collected prior to appraisal.

It argues that such an approach would lead to more reliable appraisals because a drug would be used extensively in a broad population.

However, other NICE guidance has been timed to coincide with the introduction of new technologies to ensure that (where appropriate) they can be taken up by the NHS without delay. NICE has indicated that it would like more technologies to be referred to it at an earlier stage in their development. It argues that the data required for appraisal can be collected in the clinical trials conducted for regulatory purposes (to assess safety, efficacy and quality) **before** marketing. While acknowledging the appraisal of MS treatments took longer than usual, NICE sees these treatments as something of a special case, partly because of their high cost and partly due to the long-term and complex nature of MS.

'Postcode prescribing'

Postcode prescribing raises two main issues. First is that the appraisal process itself may preserve regional variations in availability for the duration of the appraisal if health authorities delay decisions on funding until NICE guidance is published. The risk-sharing proposal for MS treatments should even out such variations provided it is implemented fully throughout the UK. This raises the question as to whether further arrangements are needed to allow NHS patients throughout the country access to certain new technologies pending NICE appraisal. One option would be to use the risk-sharing scheme agreed for MS treatments as a model for other new technologies that are difficult to appraise. Another option, preferred by NICE, would be for technologies to be referred for appraisal at an earlier stage in their development.

Second, is the need to ensure that doctors act on NICE guidance. ABPI submitted evidence to the Health Select Committee's inquiry into NICE in January 2002 suggesting that doctors were slow to comply with NICE guidance. For instance, prescribing patterns of two drugs (taxanes) used to treat breast and ovarian cancers have changed little since NICE recommended their use in appropriate circumstances. The ABPI figures also showed wide variations in prescriptions of these drugs from one health authority to another. In a survey commissioned by CancerBACUP carried out in November 2001, fewer than half of all health authorities in England and Wales had a policy for monitoring compliance with NICE guidance, although 85% did have policies to ensure taxanes would be available to women with breast or ovarian cancers. The Government recently announced the requirement for health authorities and primary care organisations to implement NICE guidance was to be made obligatory; up to £250 million of Government funds are available to support this obligation.

NICE is consulting on how to improve dissemination of its guidance, and is also integrating it with other clinical support systems such as computer systems for GPs, which contain evidence-based recommendations for the management of specific conditions.

NHS resources

NICE appraisals may have significant resource implications for the NHS. The ABPI has expressed concern that the appraisal process places too much emphasis on cost savings, while others[4] suggest that NICE is under pressure from ministers not to approve technologies with significant resource implications for the NHS. NICE however insists that this is not the case. While ministers may give NICE guidance on available resources, this has **not** happened in any appraisals to date. Such guidance covers the possibility that, at some point in the future, NICE might appraise a technology that meets its other criteria but which is unaffordable in terms of the resources available to the NHS. Under these circumstances, NICE would publish any guidance it received from ministers; it would be for ministers to decide whether to up the resources available to the NHS.

Assessing quality of life

MS patient groups have also questioned the methods used to evaluate the drugs' impact on quality of life. They argue that appraisal based on short-term clinical trials using measures such as QALYs may overstate the costs without embracing all of the longer-term benefits. While the limitations of these methods have been widely debated, one option suggested by CancerBACUP and others is to require clinical trials to be designed to take quality of life data into account.

Other issues

Submissions to the Health Committee's inquiry have also highlighted a number of other issues. Patient groups have indicated that improvements could be made in the selection of technologies for appraisal, selection of expert advisers and the criteria used to assess cost-effectiveness (as outlined in the box on page 3, NICE has never set a formal threshold for cost-effectiveness). There is also the question of NICE's independence. A number of contributors to a recent debate in the House of Lords[5] suggested that NICE should be free to select technologies for appraisal, rather than being directed towards subjects by the DH/NAW. Finally, ABPI has suggested that NICE should focus more of its resources on developing clinical guidelines for the management of disease rather than appraising individual technologies. However, NICE points out that it already spends a significant proportion of its resources in this way, and that the NHS currently has more clinical guidelines in development than any other programme in the world.

Endnotes

1 NICE has completed some 30 such appraisals to date.
2 NICE had published 4 clinical guidelines by January 2002.
3 Biogen, Schering, ABN, Royal College of Nursing, MS Society, MS Research Group, MS Research Trust and Neurological Alliance.
4 See "The Failings of NICE", BMJ, 2/12/2000
5 House of Lords Hansard, vol 630, 23 Jan 2002.

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