How NICE may be outflanked

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were upheld, five resulted in relatively minor changes in the wording of the guidance. But five decisions (interferon beta in multiple sclerosis, drugs for colorectal cancer, flu antivirals, growth hormone in adults, and renal immunosuppression in adults) were referred back to the appraisal committee for further appraisal. The appeals process has required NICE to show that it has been comprehensive in its examination of the evidence and consistent in its treatment of each topic.

Discussion

At its current rate of appraisal—around 20 a year—NICE can cover only a minority of new and existing treatments. This led to announcements in late 2005 of a more rapid review process. However, a more rapid process is likely to be considerably less intensive. The appraisal of drug treatments for multiple sclerosis, for example, took much of NICE’s first two years, with 338 documents listed on its website. It eventually recommended against use of interferon beta and glatiramer acetate because of their high cost per QALY. Despite considerable effort, including additional research, NICE was unable to identify a subgroup of patients in whom these drugs might have a more acceptable level of cost effectiveness. The fact that the government then intervened with a special purchase scheme based on a cost per QALY gained of £36 000 indicated that the government thought this was an acceptable level, at least for these drugs.

Overall NICE must be judged to have succeeded in surviving some controversial decisions. Its appeal system has imposed consistency and has so far prevented appellants proceeding to legal challenge. Although clinicians have understandably feared blanket restrictions, these have been fairly rare. NICE continues to be best characterised not by saying no, but by saying yes but . . .

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How NICE may be outflanked

R E Ferner, Sarah E McDowell

We argued a decade ago that the NHS should not have to pay for new drugs unless they are at least as good as older ones, nor for expensive drugs whose benefits are uncertain. Since then, the National Institute for Health and Clinical Excellence (NICE) has been created. NICE appraises technologies that are available to the NHS and recommends whether they should be used unreservedly, with restrictions, or not at all. Part of its remit is to ensure equity, but equity is not in everyone’s interests. Here, we consider how individuals or groups with specific interests may seek to outflank NICE.

Individual benefit or common good?

When many people share common resources, it is rational for each individual to increase personal use of the resources. But if all individuals do this, the

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References 1-26 are on bmj.com
Appraisal process

NICE examines the value of drugs only when it is invited to do so by the Department of Health and Welsh Assembly, so it may never review some important aspects of therapeutics. The process is complex, involves many interested parties (stakeholders), and takes around two years to complete. The delays between the initial suggestion and the final determination can allow patterns of treatment of uncertain cost effectiveness to become established. The longer the patterns persist, the harder they become to reverse. The use of verteporfin in treating age related macular degeneration is a case in point. Further treatments were licensed during the time NICE took to appraise the evidence and rendered its guidance outdated.

NICE clearly appreciates the need to provide thorough analysis in good time. It now aims to appraise a drug for a specific indication in about 40 weeks. Appraisal may begin before regulatory approval has been granted, so that NICE's views are known within a few months of the drug being licensed. Advice is expected soon on the use of trastuzumab in early breast cancer, for example, even though the manufacturer did not apply for a licence until February 2006.

Role of big pharma

Pharmaceutical companies spend over $800m to develop and license a new drug, so they are understandably interested in the financial returns. An obvious insurance against loss is to produce a drug that is clearly beneficial and whose costs are proportionate. Even if a new drug offers only slight benefits at an inflated cost, a company may be able to persuade doctors or patients of its value by marketing. It can then hope for sales independent of guidance from NICE or other expert bodies. Companies can also sell drugs by relabelling normal phenomena such as male pattern baldness and social phobia as diseases that then merit drug treatment.

The promotion of trastuzumab (Herceptin) shows how companies raise awareness of new drugs. Marketing was muted at first, as specialists learnt of pilot studies in patients with advanced disease. A paper reporting an early trial in a wide circulation general medical journal amplified the signal. The paper was accompanied by an enthusiastic press release, encouraging medical correspondents to spread the word to the wider public. These strategies mean people become attuned to the company message long before licensing.

The manufacturer or sponsor of a product has a key role in the appraisal process through the submission of data to NICE's evidence review group. The review group no doubt critically assesses the industry submissions. However, published company data contain inherent biases. Industry funded randomised trials are more likely to favour the treatment under test, and authors are more likely to be positive in their conclusions if a randomised trial is funded by a for-profit organisation. Published economic evaluations of cancer drugs sponsored by drug companies are also less likely to report unfavourable qualitative conclusions.

One reason for this bias could be that companies fund the trials that they think are most likely to give positive results, but other explanations are possible. Conscious or unconscious optimism of those most interested in a treatment's success could colour the judgment of study authors. Certainly, expected cost-utility can vary greatly from one study to another. In the case of photodynamic therapy, industry estimated the cost of averting two years of blindness as £70 000, whereas academic analysis suggested costs between £150 000 and £390 000.

Companies also harness the media to support their views in battles with NICE. If NICE gives restrictive guidance, drug companies issue press releases decrying the judgment. Pfizer described the recent decision not to recommend inhaled insulin as "perverse," and Link Pharmaceuticals claimed NICE was denying "potentially life-prolonging treatments" to patients with brain tumours.

Patients and patient groups

Patients may wish to have treatments that NICE has yet to pronounce on or has recommended against. Patient groups share a common interest with drug companies in promoting access to specific treatments that others will pay for, and so they provide a route for companies to influence the perceptions of their drugs at a distance. As Jo Spink, a public relations professional, explains, "Patients are a powerful force and can highlight the clinical, societal and quality of life benefits of a treatment far more passionately than any press release ever could."

Patient groups have been described as conduits for drug companies to promote their products and as "ground troops" to be used to lobby governments for increased access to new drugs. A recent survey found that 76% of patient groups based in the European Union received support from drug companies, although how much they received was unclear. Groups campaigning for NICE to approve specific drugs often have declared corporate relations with pharmaceutical companies. Financial support from a drug company may not compromise a patient group's independence, but companies are not motivated by altruism, and the House of Commons Health
Analysis and comment

Select Committee has advised that measures be taken to limit the influence of industry on patient groups. Patient groups often object strongly if NICE's preliminary recommendations are restrictive. Vocal campaigns preceded changes in advice on treatment for Alzheimer's disease and osteoporosis, and patient groups are seeking to overturn NICE's preliminary, unfavourable, view of inhaled insulin.

The influence of patients and patient groups can be seen even before a NICE appraisal has been commissioned. Trastuzumab has yet to be licensed for use in early breast cancer, its longer term efficacy is uncertain, and its propensity to cause myocardial damage in patients who have taken anthracyclines is worrying. The cost of treating a patient with trastuzumab in the United Kingdom is about the same as the average annual income. Patients have campaigned successfully to place trastuzumab at the forefront of public and political consciousness.

This has led to the feeling that the licensing and NICE approval of trastuzumab for early stage cancer is a foregone conclusion. This is a sentiment expressed by the chief executive officer for Breakthrough Cancer Care: "The fast track appraisal of drugs by NICE is to be welcomed but we need to ensure that once approved, guidance is implemented fully and that cancer patients receive the drugs recommended."

Media influence

Dying patients denied life saving drugs make compelling copy. Better still, when heartless bureaucrats are persuaded to change their minds under media pressure, the media can take the credit for saving the patient. The Manchester Evening News even received an award for its campaign over trastuzumab. Stories of wonder drugs, carefully encapsulated in press releases, can make useful copy even in the absence of human interest. And careful deployment of celebrities by patient groups can ensure media exposure for human interest. And careful deployment of celebrities releases can make useful copy even in the absence of

Practising clinicians

Published NICE guidelines may not be implemented as intended. Abacus International found that 12 of 28 NICE appraisals were underimplemented and four were overimplemented. Since many NICE decisions are based on fine and perhaps generous judgments of cost-utility, overimplementation is likely to be expensive.

Politicians

Many members of parliament are ready to espouse popular causes such as supporting patients with cancer or crippling diseases. Tabling questions in parliament is an effective way to do this. The House of Commons question book lists 84 questions on trastuzumab, 56 on donepezil, and 188 on interferon beta, but only two on ciprofloxacin, and none on penicillin or prednisolone.

Ministerial interventions may complicate matters. While he was a health minister, Stephen Ladyman commented on preliminary guidance that recommended the withdrawal of drugs for Alzheimer's disease. He stated that "they [NICE] have to look at the wider impact of this decision. It may well be that once they have looked at the extra evidence, they will come to a different decision." Even before trastuzumab has been licensed for treatment of early breast cancer, Patricia Hewitt, the secretary of state for health, has stated that primary care trusts "should not refuse to fund Herceptin [trastuzumab] solely on the grounds of its cost. She has instituted genotyping of all breast cancers, so fostering expectations of trastuzumab treatment directed at the 20% of tumours that are HER-2 positive.

Pressured decisions

Opportunities exist for distortion long before the NICE appraisal process begins. They continue after the process has begun and persist after preliminary findings are published. Even when the final NICE determination recommends abandonment of or restriction in the use of a treatment, interested parties may make determined efforts to by-pass NICE's ruling. Audits suggest that many of NICE's recommendations are not implemented completely.

It is easy to see why patients, whose illnesses provide strong motivation to obtain a share of NHS resources, wish their voices to be heard. It is also clear that companies, which have to make a profit, will seek what advantage they can. Less easily understood is the way that politicians seem to undermine NICE. The government risks undermining NICE by setting up NICE as an independent body, and so ministers should be absolutely scrupulous in allowing it to function independently. By making, or appearing to make, decisions before NICE has pronounced and for reasons of political expediency, some politicians may be subverting the process. It will be a test of NICE's resolve to see that treatments are cost effective when they analyse the data on trastuzumab in early breast cancer.

NICE should ensure that the funding available for drugs in the NHS is spent in a way that best serves patients. But in the ideal world the appraisal process would be insulated, and seen to be insulated, from external financial, political, and emotional pressures.

Competing interests: REF was senior registrar to the current chair of NICE.

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Summary points

The work of NICE is critically important to the rational distribution of NHS funds

 Patients and drug companies seek to influence the decisions both during and after appraisal

The government risks undermining NICE by making decisions before guidance is published

Appraisal of treatments needs to be insulated from external pressure
When I use a word

Nauseated/nauseous

I am often told that a patient is nauseous, only to find that he or she is actually nauseated, not nauseous at all, or at least not what I mean by nauseous.

The word nausea comes from the Greek naus or nau, which originally meant a ship (Greek nau = ship). In Latin nauseant means to make sick; nauseated (from the supine form nauseatum) therefore means made to feel sick (verb transitive) or feeling sick (adjective).

Now the suffix -osus in Latin meant full of or rich in. Unless you are sure you have that effect on others.

The word nauseous is often used in the literal sense, to mean smelling or tasting unpleasant and (figuratively) loathsome or disgusting. And that meaning persisted until about the middle of the 20th century. Webster's second (1965) showed the use of nauseated in the verbal sense and nauseous in the adjective sense.

Thus, the modern American usage was made in its original Latin sense of causing nausea, and therefore nauseous should be used in the literal sense, meaning causing nausea. When nausea came into English from the Latin it first meant to feel sick (that is, squeamish) or fastidious, but that meaning rapidly became obsolete. At the same time nauseous was used in its original sense of self-depreciation, is to ignore the point of view of the second. To call oneself nauseous, except in self-deprecation, is to ignore the point of view of the second. To call oneself nauseous, except in self-deprecation, is to ignore the point of view of the second.

For example, Wilson Follett, in his The Elements of Style (3rd edition, 1979) wrote: “Do not say ‘I feel nauseous’, unless you are sure you have that effect on others.”

Nevertheless, by 1989 Webster's Dictionary of English Usage had gathered a large amount of evidence that the widespread use of nauseous to mean nauseated: “Any handbook that tells you that nauseous cannot mean ‘nauseated’ is out of touch with the contemporary [US] language.”

Searching PubMed for examples of nauseous and nauseated in the titles and abstracts of bioscience publications, I have found only seven instances of nauseous in UK publications, compared with 51 worldwide, and 97 instances of nauseated worldwide. In one paper both were used: “The procedure had no significant effect on cardiovascular variables in control subjects or in subjects who were exposed to vestibular stimulation but who were not nauseated by it. Those subjects who felt nauseous showed a tachycardia and forearm vasodilatation” (Cardiovascular Research 1982;16:510-2). This example is interesting in that it shows the use of nauseated in the literal sense and nauseous, meaning nauseated, in the adjectival.

But I still think that, although several of my patients are or become nauseated, sometimes because of drugs that I give them, very few of them are really nauseous.

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