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Has NICE been nice to cancer?

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ABSTRACT

This article reviews the work of England's National Institute for Health and Clinical Excellence (NICE) in the area of cancer treatment since it was established in 1999. NICE provides guidance to the National Health Service (NHS) in England and Wales on the clinical- and cost-effectiveness of therapeutic interventions and aims to support uniform and evidence-based care. Its most high profile work involves making judgements on whether new drug treatments should be available to NHS patients. Over 20 appraisals of anticancer drugs have now been completed by NICE; most have endorsed the availability of the reviewed agent, which is good news for cancer patients. Unfortunately, positive guidance does not, necessarily, eradicate inequalities of access.

There are also concerns relating to access to drugs during the period when NICE guidance is being developed and for patients requiring treatments — often for less common cancers — which are not referred to NICE for appraisal.

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1. What is health technology assessment?

Health technology assessment (HTA) has been defined[1] as the structured evaluation of the properties or effects (or both) of a health technology, designed to answer such questions as:-

- Does the treatment work?
- Who does it work best for?
- At what costs do we get the results?
- How does the treatment compare with the alternatives?

Recent years have seen an upsurge in HTA activity at regional and national level in many countries.[2] Two key forces have driven this. Firstly, a growing realisation of the need for the application of medical interventions to be evidence-based so that harmful or less effective treatments are discarded and useful ones widely applied. Secondly, as the rate of technological innovation has increased and the population becomes more long-lived, the demand for health technology has begun to outstrip the willingness or ability of some healthcare providers to pay for it, stimulating interest in cost-effectiveness analysis as a means of directing budgets towards those interventions that result in the greatest health gain for the resources available.[3]

2. The background to HTA in England and Wales

Despite a small but growing private healthcare sector, most medical care in England (as in the rest of the United Kingdom) is provided free of charge at the point of delivery by the National Health Service (NHS) funded by taxation. The NHS has long struggled to match the demand for its services with its resources, with local managers attempting to maintain this balance by restricting spending on certain technologies and services. Local decision making of this sort inevitably leads to regional inequality of access to particular treatments within a supposedly national service. These inequalities became more obvious in the early 1990s when NHS reorganisation devolved much budgetary responsibility to local NHS

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Trusts (Primary Care Trusts (PCTs)) charged with purchasing specialist services, including cancer treatments, from hospitals. Since individual treatment centres usually treated patients living within the catchment area of several PCTs, different local decisions on whether to pay for specific treatments could result in patients being treated in adjacent beds having different access to treatment, a practice that has become known as 'postcode prescribing' and whose existence has been acknowledged even by government ministers responsible for the NHS.[4]

The problem of 'postcode prescribing' was nowhere more apparent than in oncology where the 1990s represented a period of rapid therapeutic advance, with a rise in the number of patients receiving active therapy and a surge in the number of new drugs available to treat them. Compared with the older alkylating agents and antimetabolites, these novel agents had a considerably higher acquisition cost. They were also clearly identifiable items within local health economies, with little or no use outside of oncology facilitating the enforcement of any decision not to use them.

Variable access to treatments within a supposedly national service rapidly became a source of great dissatisfaction amongst clinicians and patients alike and regularly featured in the news media.[4,5] This led to a number of initiatives to encourage a consistent approach to healthcare including the establishment of the National Institute for Clinical Excellence (NICE) in 1999.[4,6]

3. What is NICE?

On its website, NICE describes itself as 'the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health'.[7] It provides this guidance in three distinct forms:-

- *Health Technology Appraisals (HTAs)*. These provide guidance on the use of new and existing medicines and treatments within the NHS. Around 25 relevant to cancer treatment have been completed so far.
- *Clinical Guidelines (CGs)*. These provide more comprehensive guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS. About 10 have been published so far.
- *Interventional procedures guidance (IPG)*. This provides guidance on whether interventional procedures used for diagnosis or treatment are safe enough and work well enough for routine use. Approximately 20 pieces pertinent to oncology have appeared so far.

Within the area of cancer therapy, HTAs - most of which have dealt with new anticancer drugs -have been far more controversial than other types of guidance. There are a number of reasons for this:-

1. *HTAs are directive in their recommendations*. They always state explicitly whether or not the technology under review should be available under the NHS either as an option or as the treatment of choice. By contrast IPGs give an opinion on whether there is adequate evidence on the safety and efficacy of interventions to enable them to be recommended for routine use. In the remaining cases additional monitoring and patient education is usually recommended, but they seldom explicitly exclude an intervention from NHS provision.
2. *HTAs usually cover well-tried treatments*. Unlike most of the interventions considered in IPGs and many of the topics covered by CGs, drugs reviewed in HTAs have already been the subject of a review of their safety and efficacy for licensing purposes leading to the criticism that NICE review is duplicating work already done and thus unnecessarily delaying patient access.
3. *Cost-effectiveness is an explicit part of HTAs*. Assessment of cost-effectiveness is not part of the preparation of IPGs and although CGs may make reference to the cost and cost-effectiveness of treatments they do not include a rigorous cost-effectiveness analysis of all recommendations made. However, all HTAs involve a rigorous appraisal of cost-effectiveness. The preferred currency for appraisal of cost-effectiveness is the cost per quality-adjusted life year (QALY). If the cost per QALY of an appraised technology is too high, NICE will direct that it should not be made available under the NHS even if it is clinically effective. NICE states that at a cost per QALY gained of below £20,000 cost-effectiveness is unlikely to be a barrier to positive guidance from NICE, whereas above £30,000 per QALY very compelling arguments will need to be made with regard to the certainty of the benefits associated with a new treatment and the needs of the patient population who are expected to receive it. In the first HTA of oxaliplatin and irinotecan as treatments for previously untreated metastatic colorectal cancer, NICE issued guidance that acknowledged the clinical effectiveness of these agents used together with fluoropyrimidines, but stated that they should not be used for most patients treated within the NHS because of their poor cost effectiveness. This guidance was based on an independent review of the cost-effectiveness of the two agents that estimated that they would result in an incremental cost per progression-free life year gained of £41,000 in the the case of irinotecan and £23,800–£67,900 in the case of oxaliplatin.[8]
4. *Audit of compliance with HTA guidance is simple*. Most cancer related HTAs concern the use of specific drugs for restricted patient populations. By monitoring sales of these agents it is possible to estimate the impact of guidance and the degree of adherence to it in a way that is impossible with other types of guidance. Over the last few years such tracking exercises have suggested extremely variable compliance with guidance which has sometimes been contested by healthcare providers (see below).
5. *Funding of HTA recommendations is mandatory*. The Secretary of State for Health has directed that the NHS (via local NHS Trusts) make available adequate funding and resources to permit the implementation of any treatments recommended by NICE as a result of HTAs.[9] Normally funding has to be made available within 3 months of the publication of the relevant HTA guidance, though this period can be extended at the discretion of the Secretary of State, where there are specific problems with rapid implementa-

tion such as the availability of specialist staff trained in delivering the treatment in question. By contrast there is no general mandatory requirement on the part of the NHS to make funding available to support the recommendations made in CGs and IPGs. Without funding many changes in practice are impossible and in a climate where budgets are already overstretched there is often reluctance on the part of PCTs to make funds available for service developments if they have any discretion in the matter.

4. Has the guidance that NICE produced been in the interests of oncology patients?

Since Clinical Guidelines and Interventional Procedures Guidance are, essentially, consensus guidelines on best practice produced by synthesis of the available evidence by professionals working within oncology, they are, for the most part, uncontroversial and accepted as providing sound evidence-based guidance which, if followed, will benefit patients.

With HTAs there is, as has already been explained, the possibility that guidance may deny patients access to a treatment that clinical experts agree is clinically effective but which economists deem to be poor value for money. Oncologists and cancer patients are unlikely to consider such guidance to be in the interests of cancer patients. In fact, of 22 HTAs completed by NICE on new anticancer drugs, only three (Technology Appraisals 23, 33 and 37) have resulted in recommendations that the NHS restrict usage more narrowly than was indicated by the Marketing Authorisation of the products in question at the time of the appraisal.[7] The restrictions placed on the use of irinotecan and oxaliplatin for the first-line treatment of advanced colorectal cancer in Appraisal 33 were removed on subsequent review of the guidance, published this year as Appraisal 93.

5. Has NICE guidance had any impact on clinical practice?

However clear guidance is, it only influences practice if followed. Clinical Guidelines and Interventional Procedures Guidance documents do not seem to have attracted the attention of healthcare researchers or the media, and it is difficult to determine the extent to which they have been followed and their impact on clinical outcomes for cancer patients. In any case it is probably too soon to determine the impact of some of the organisational changes recommended in the CGs.

However, there is limited but good evidence that NICE HTA guidance on anticancer drugs *does* alter prescribing practice.

Pharmaceutical products marketed by Roche have been the subject of many HTAs, including five completed appraisals in the area of oncology. Therefore, Roche developed an interest in the influence of NICE guidance on the sales of its products.

A positive recommendation from NICE concerning a Roche oncology product has always been met with an upturn in sales growth implying that the guidance has driven a change towards increased prescribing. This is well illustrated in Fig. 1 which tracks sales of trastuzumab (Herceptin®). From its launch in April 1999 sales showed slow steady growth. How-

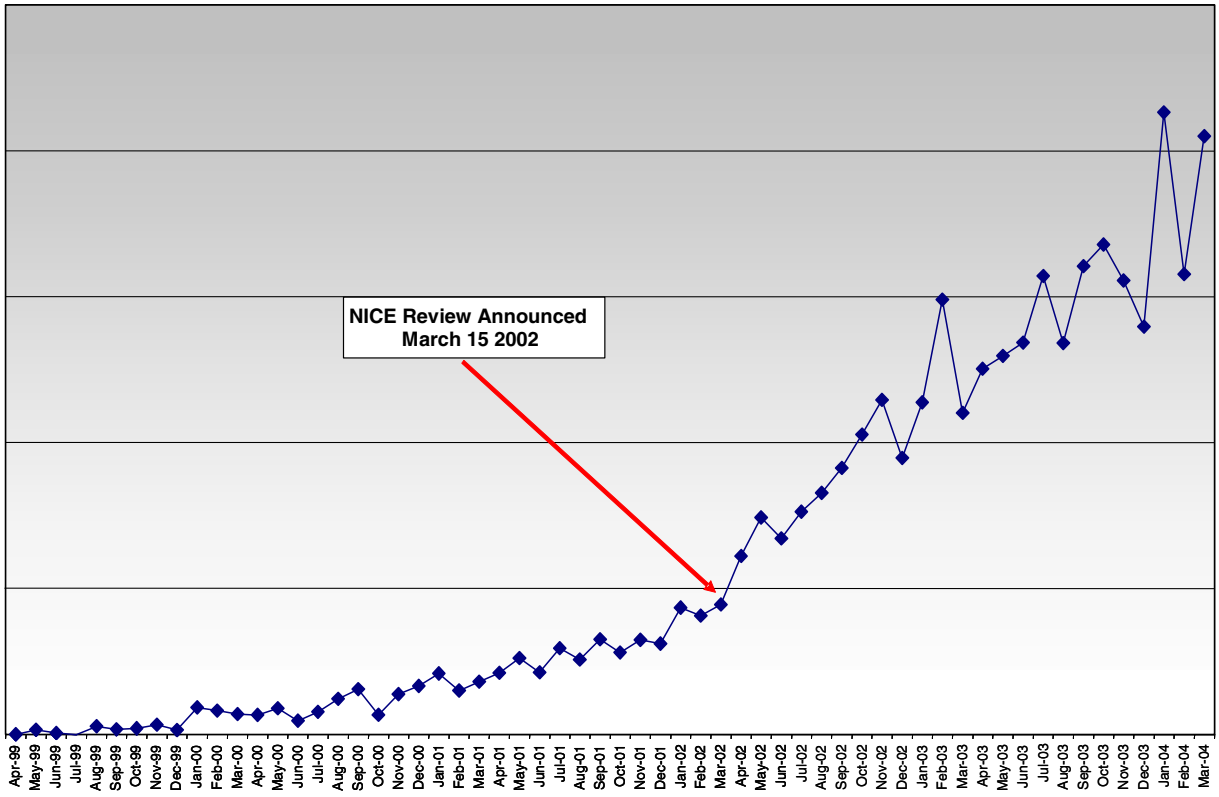

Fig. 1 – Monthly sales of trastuzumab from UK launch.

ever, growth accelerated rapidly following the publication by NICE, in March 2002, of guidance that trastuzumab should be added to standard chemotherapy in women with HER2 overexpressing metastatic breast cancer. During 2002, no significant new clinical data on trastuzumab emerged, no change was made to its licensed indication and there was no alteration in the commercial terms on which Herceptin was supplied. Therefore, it is hard to escape the conclusion that NICE guidance alone drove the sales growth observed in the months following March 2002.

6. Has NICE guidance produced the desired change in clinical practice?

Although the previous example suggests that NICE guidance is achieving the desired result by effecting a rapid change in practice, this is not the whole story. By providing national guidance, NICE intended to reduce inequality of access to new treatments. Data on the national consumption of a drug do not tell us whether it has been successful in this regard.

Roche therefore embarked upon a more sophisticated analysis of its sales data.

Firstly, epidemiological and census evidence was used to calculate the number of patients eligible for NICE-recommended Roche oncology products in each of 34 Cancer Network areas of England plus three each in Wales and Scotland.

Cancer Networks are non-statutory, administrative bodies whose role is to work with budget holders and healthcare providers to ensure that the best outcomes are achieved for cancer patients in their area. Cancer Networks would be expected to take responsibility for ensuring the implementation of NICE guidance within their geographic area.

Once the patient population per network had been estimated, the amount of a drug required to treat these patients was calculated and compared with purchases of the drug by hospitals within the network, allowing penetration of NICE guidance to be assessed – a network where drug purchased by hospitals was equivalent to the estimated requirement for treating all eligible patients for whom NICE recommended it would be considered to have 100% penetration.

This methodology has a number of limitations:-

- Some patients resident in one network area may be treated in a hospital in an adjacent network, though cross boundary flows are likely in both directions and should, largely, cancel out.
- Estimates of patient numbers did not reflect local geographical variations in incidence/prevalence.
- Treatment of private patients within NHS hospitals might have given a spuriously high level of penetration in one or two hospitals, with large private facilities on site.

However, these limitations could not have accounted for the differences in penetration seen across all products and persisting for years after the publication of NICE guidance.

Again this is well illustrated with respect to Herceptin. As shown in Fig. 2 the percentage of eligible women receiving Herceptin during a 6 month period 18–24 months after NICE guidance, varied from less than 10% to more than 120% according to network.

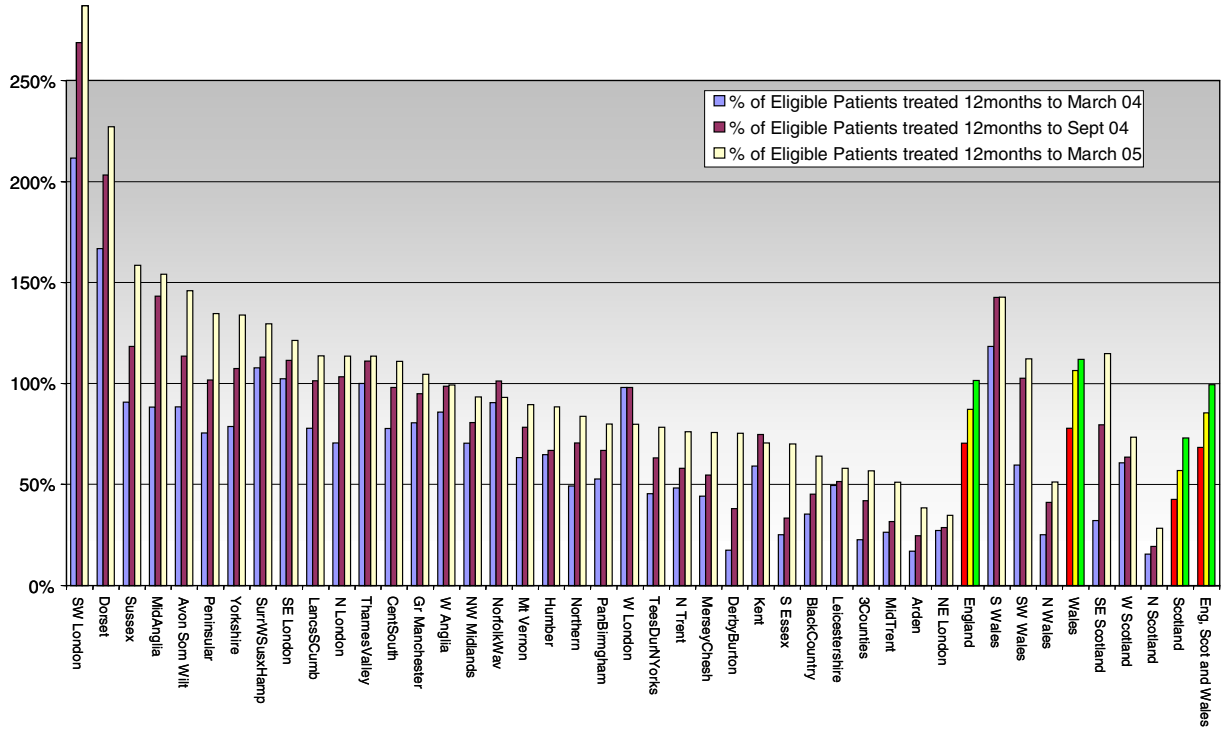

Fig. 2 – Uptake of trastuzumab in successive 12 month periods by UK cancer network. Percentage of patients eligible for treatment according to NICE guidance actually treated estimated from drug purchases.

If one accepts that a large part of this variation is due not to the methodological limitations above, but to an uneven application of NICE guidance, then this analysis would suggest that NICE guidance has, at least in part, failed to eliminate inequality of access to new treatments based on place of residence.

7. Why do inequalities of access to NICE recommended treatments persist?

Concerns about evidence of variation in the usage of NICE endorsed anticancer treatments between Cancer Networks, such as that presented above, led the Secretary of State for Health to commission an investigation into variations in the usage of cancer drugs across the country. This confirmed that variations in the usage of NICE approved drugs varied by between 2.6-fold and 11.6-fold between networks, depending on the drug under consideration. The report of this investigation,[10] which appeared in June 2004, concluded that 'legitimate' reasons for variation in drug usage, such as cross-boundary movement of patients, could not account for all of the variation seen and that other factors were probably important, including:-

- Capacity issues (staff shortages and lack of physical capacity to deliver treatments)
- Personal preferences of some clinicians
- Variations in the effectiveness of NHS leadership, including variations in the extent to which cancer networks, PCTs and NHS trusts plan ahead collectively and proactively for the likely impact of guidance still in preparation

The report makes a series of seven recommendations to reduce these variations, though an imminent reaudit of prescribing practice is awaited in order to determine the extent to which these recommendations have been taken up and whether inequalities have been reduced.

8. What are the limitations of the current system?

From what has already been said it would seem that NICE guidance on new cancer drugs has generally been favourable and has caused, or at least permitted, an increase in their use, though implementation has been uneven, with the result that inequality of access to treatment remains. This would suggest that if compliance with issued guidance could be improved, all would be well. Although application of guidance is clearly vital if it is to be effective, a factor recognised by NICE in their appointment of an Implementation Systems Director, concerns in this area are not the only ones that have arisen for cancer patients as a result of the existence of NICE.

8.1. *Delays*

The NICE process is thorough, but it is not swift. Each appraisal follows a set timetable extending over 1 year (longer if an appeal is made against the final guidance) from the point where stakeholders are invited to make submissions, signalling the start of the process.

However, this does not mean that NICE guidance is available on all new cancer treatments 1 year post-launch. Treatments are not automatically appraised and the NICE work programme consists of topics emerging from a defined topic selection process.[11] Ultimately, the NICE work programme consists of treatments referred to the organisation by central government, specifically, the Secretary of State for Health and the National Assembly for Wales whose choice may be based on suggestions from:-

- National Clinical Directors (government appointed officials responsible for improving national provision for a variety of diseases including cancer)
- Healthcare professionals or members of the public posting topic suggestions on the NICE website
- The National Horizon Scanning Centre working in conjunction with the National Coordinating Centre for Health Technology Assessments

The latter is probably the most significant source of topics and the Department of Health's Advisory Committee on Topic Selection has set criteria for topic selection including whether the proposed intervention lies in a clinical priority area for the NHS, whether it will have a major budget impact and whether guidance is likely to alter current practice.

Naturally the topic selection process takes time and may fail to identify some treatments as worthy of review. For example, a new treatment for a rare condition might be rejected if it fell outside of a priority area as it might be expected to have a low impact.

Once a topic has been selected and referred, NICE embark on a process of 'scoping' to determine exactly what questions should be asked during the appraisal. Key to this part of the process is specification of the comparator interventions which should reflect current practice. Inevitably, 'scoping' takes time and introduces further delays into the process.

Thus, assuming a topic is selected for NICE appraisal, publication of guidance to the NHS can take a considerable time. For example, although erlotinib (Tarceva) which received regulatory approval in September 2005 is already on the NICE work programme, guidance to the NHS is not scheduled to be published until December 2006.

8.2. *'NICE blight'*

The slowness of the appraisal process has led to a condition that has been termed 'NICE blight', whereby there is a *de facto* block on prescribing products that have not yet been the subject of a NICE review with NHS budget holders reserving their limited development funds for items positively reviewed by NICE and where they have no choice but to make money available. When NICE was established, the Department of Health made it clear that the absence of NICE guidance is not a reason to withhold funding for a treatment and that in such cases decisions must be made at local level using the evidence currently available.[12] Unfortunately, in many cases the outcome of such local data review is that the treatment will not be funded. Such verdicts are difficult to challenge since there is no guidance available on the

circumstances in which it is reasonable for a budget holder to refuse to fund a treatment.

It is hard to prove the existence of 'NICE blight' – it is unlikely that any healthcare funding body will admit that they are using the absence of compulsion to avoid funding a new treatment. However, it can be inferred by the rapid increase in uptake that often follows the recommendation of an intervention by NICE (see above). Given that, to date, NICE guidance has followed a considerable time after product licensing, and even longer after the availability to clinicians of the data from key clinical studies, it seem unlikely that clinicians suddenly decide that they want to use products just because NICE have recommended them. It seems more plausible that NICE facilitates clinicians' wishes by removing a restriction on their ability to prescribe.

8.3. *Histological bias*

The pharmaceutical industry inevitably concentrates its efforts on obtaining product registrations that permit it to actively market its products for treatment of the most common tumour types. However, whilst the key registration trials are being conducted by drug companies, a wealth of information on the utility of the drug in less common cancers is often accruing simultaneously as a result of clinician-led studies. This information is often quite sufficient to persuade clinicians on the value of a new agent in a situation where it does not, and may never have, a Marketing Authorisation. Without this regulatory approval a product will not be reviewed by NICE and the lack of NICE endorsement may be used as a reason not to make it available under the NHS. The result of this sequence of events is that patients with less common tumours may have very limited access to newer anti cancer agents.

9. Conclusion

NICE has done a good job with the resources available to it. They have established a rigorous system of HTA appraisal that has resulted in most of the anticancer treatments reviewed by the organisation becoming more widely available to NHS patients. Recommendation of a treatment by NICE does have an impact on treatment uptake, though it does not result in equal access for all NHS patients, though the organisation itself cannot be held responsible for the uneven implementation of its guidance. The problems with NICE are mostly related to the time that it takes to complete its appraisals. These delays are in turn a consequence of its inability to determine its own work programme and inadequate resourcing to carry out the number of appraisals required to keep pace with the rate of medical innovation, though changes in the appraisal system that have recently come into effect may, in future, reduce the time between product licensing and NHS guidance.

Conflict of interest statement

Both authors are employed by Roche Products Ltd, a company which produces a number of anticancer drugs that have been the subject of completed and ongoing NICE appraisals.

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