The National Institute for Health and Clinical Excellence and Its Role in Assessing the Value of New Cancer Treatments in England and Wales

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Abstract

The boundaries of medical science in the treatment of cancer are constantly extending. Developments of existing treatments, innovative approaches, new discoveries, and more targeted therapeutic options are translating into practice. With advances come increasing costs, often of a magnitude that stretches finite financial resources. When decisions about funding are made on behalf of a population, standardized processes and methods are needed in order to produce robust guidance in a fair, consistent, and transparent way. The challenges of making these difficult decisions are brought into particularly stark relief when potentially life-extending treatments for patients with a short life expectancy are appraised. The National Institute for Health and Clinical Excellence (NICE) produces guidance on the clinical- and cost-effectiveness of medicines compared with current standard practice. Approximately 40% of the technologies appraised by NICE are indicated for cancer, and the majority of these are pharmaceuticals, mostly biological agents. This article provides an overview of the current role of NICE in making new technologies for cancer available in England and Wales. This includes a summary of experiences with end-of-life treatments and the supplementary advice regarding such treatments that was issued by NICE to its decision-making committees in 2009.

Why Does NICE Exist?

The National Health Service (NHS) was established in 1948 to provide free health care at the point of delivery for all patients. The NHS is funded by public taxation and has a fixed central annual budget of approximately £106 billion ($160 billion), accounting for 18% of current government expenditures. The NHS (like all health care systems) cannot afford every health care intervention for everyone, and decisions about allocating health care resources must be made (1).

In England and Wales, local health care is currently commissioned by 152 Primary Care Trusts (PCT). Services can vary between PCTs because of local needs, but also because of local leadership or funding policies. In the late 1990s, postcode prescribing (i.e., variation in prescribing across PCTs) became an increasingly sensitive political and health care issue. The National Institute for Health and Clinical Excellence (NICE) was established in 1999 primarily to ensure that everyone has equal access to medical treatments and high-quality care from the NHS, regardless of where they live in England and Wales. NICE is a Special Health Authority of the NHS with a remit to make its recommendations independently of government (central and local), industry, and all other stakeholders.

What Does NICE Do?

NICE is a guidance-producing organization that is dedicated to promoting good health and preventing and treating ill health. It produces several types of guidance, including technology appraisals, clinical guidelines, and public health guidance. All guidance aims to resolve uncertainty and promote equity of access and care throughout England and Wales. The Technology Appraisals program produces guidance on the use of new and existing technologies (i.e., pharmaceuticals, devices, and diagnostics) within the NHS. The majority of appraisals are of pharmaceuticals. NICE can only consider the clinical- and cost-effectiveness of a technology in line with its marketing authorization or Conformité Européenne marking.

Recommendations are developed by independent committees whose members do not work for NICE and have expertise in various areas, including clinical (e.g., medical, nursing, and pharmacy) and academic (e.g., health economics and statistics) fields, NHS management, and industry. These committees may also include patients and other members of the public. The appraisal process (2, 3) is underpinned by the need for transparency, robust assessment of evidence, and the involvement of stakeholders (i.e., the manufacturer of the technology, manufacturers of competing technologies, clinical and patient groups, NHS commissioners, and the public).
Technology appraisals result in guidance regarding treatments for use in line with clinical practice or the marketing authorization, optimized use in specific circumstances, use only in the context of research, or not recommended. The Secretary of State has directed the NHS to fund technologies that are recommended by the Technology Appraisal program. Other planned health care interventions may have to be displaced (reduced, cut, or delayed) so that funds can be made available for the implementation of NICE technology guidance within 3 months of being issued. Guidance can also be issued with recommendations for future research; however, no funding is routinely available to conduct research recommended by the appraisal committee. All recommendations are issued with a date by which they will be considered for review, which is typically 3 years from the date of publication.

How Are Health Technologies Assessed and Appraised?

The aim of an assessment is to produce estimates, taking into account any uncertainty, of a technology’s clinical- and cost-effectiveness for a specific indication. An assessment usually has 2 components: a systematic review of the clinical evidence and an economic evaluation (4). These components address the following questions:

- How well does the technology work compared with current NHS practice?
- How well does the technology work in relation to how much it costs compared with current NHS practice (i.e., does it represent value for money)?

The technologies are appraised by an independent appraisal committee. The committee considers submissions from key stakeholders, an independent academic critique of the manufacturer’s submission, and views expressed by patients and clinical and commissioning experts. The committee meetings are conducted in 2 parts: a public session and a private session. The manufacturer’s representatives are present at committee meetings to answer questions of a factual nature.

The committee will consider the nature and quality of the evidence submitted and use the best available evidence to inform decision making (for example, randomized controlled trials are considered preferable to single-arm studies). In addition, the adverse events associated with a technology, the alternative treatments that are available, and whether there are any subgroups of patients in whom the technology may have differential effects are also considered. The cost-effectiveness of the technology (i.e., the value for money represented by the new technology compared with technologies already used by the NHS) is measured in terms of the incremental cost per quality-adjusted life year (QALY) gained, or incremental cost-effectiveness ratio (ICER):

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\text{ICER} = \frac{\text{Total cost of intervention} - \text{Total cost of comparator}}{\text{QALYs with intervention} - \text{QALYs with comparator}}
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Above a most plausible ICER of £20,000 ($32,000) per QALY gained, judgments about the acceptability of the technology as an effective use of NHS resources will take into account (i) the degree of certainty around the ICER (the committee will be more cautious about recommending a technology when it is less certain about the ICERs); (ii) reasons indicating that the health-related benefits have not been fully captured by the QALY (such as severity of disease); and (iii) the innovative nature of the technology. As the ICER increases, the committee will have to identify an increasingly strong case for supporting the technology as an effective use of NHS resources. In addition, the committee can take into account special considerations when appraising treatments that are potentially life-extending and given at the end of life. Of importance, in all circumstances, there is no fixed threshold under which a technology will be recommended for use.

Cancer Technologies and NICE

The Cancer Reform Strategy, building on the NHS Cancer Plan, was published in 2007 (5). This strategy outlined actions for improving cancer outcomes, and to that end NICE was given 2 key objectives. First, NICE should issue guidance as close as possible to the date when a drug is licensed, ideally within 6 months of product launch. Second, all new cancer drugs and indications will be referred to NICE and appraised (provided there is a sufficient patient population and evidence base to do so). To date, NICE has published 222 technology appraisals, 78 of which (containing 115 individual recommendations) involved cancer drugs. Overall, 71% of all cancer drugs that have been appraised have been recommended (fully or optimized) for use in the NHS. In line with this, expenditures for anticancer drugs have increased.

When appraising cancer drugs, it is critical to obtain sound measurements of benefits (i.e., improvement in potential cure rate, overall survival, progression-free survival, response rate, and health-related quality of life) and adverse consequences (i.e., toxicity of treatment and health-related quality of life). Key parameters in the economic model include the cost of the drug (which may depend on factors that need to be estimated, such as time to progression), cost of administration, cost of other drugs (especially comparators, but also drugs given after progression or in addition to the intervention), cost of treating adverse effects (of the intervention and the comparator), and generalizability of the trial population to the likely patient population in clinical practice in England and Wales. Often the data surrounding these key inputs are missing, incomplete, or short-term, and assumptions and extrapolations are required.

Issues in Appraising Cancer Technologies

Correct comparator

In all appraisals, the correct comparator is a crucial consideration for the committee. There are many reasons...
why the comparator in the pivotal trial may not be the same as the comparator of interest in the appraisal.

Often the comparator in a clinical trial, particularly in oncology, is not what would be considered routine and best practice at the time a technology is appraised. Some studies are also placebo-controlled. Although this may be appropriate for regulatory authorities, placebo-controlled trials are often insufficient to demonstrate the value of a new technology over current NHS practice by the time a technology has received a marketing authorization. Additionally, the comparator that was chosen when the trial was designed may be outdated by the time a technology has received marketing authorization and is being appraised. For example, in the appraisal of paclitaxel for early breast cancer (TA108; ref. 6), the comparator in the evidence base of doxorubicin and cyclophosphamide was not considered relevant to current practice. The committee concluded that there was a lack of comparative evidence with the comparator most used within the NHS in England and Wales [i.e., 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) or epirubicin followed by cyclophosphamide, methotrexate, and 5-fluorouracil (E-CMF)], and paclitaxel was not recommended as a cost-effective use of NHS resources.

In the absence of direct evidence of a comparison with standard care in the NHS (e.g., because the comparator in the trial is standard practice in other countries but not in the United Kingdom), it is often necessary to conduct indirect or mixed treatment comparisons. However, these methods are evolving and they are associated with increased uncertainty, a factor that the appraisal committee considers when judging the true added value of a new technology. For example, in the appraisal of lenalidomide for multiple myeloma (TA171; ref. 7), the evidence for the effectiveness of lenalidomide (plus dexamethasone) compared with bortezomib monotherapy in people who had received only one prior therapy was derived from an indirect comparison via the common comparator of high-dose dexamethasone. The committee considered that this indirect comparison increased the uncertainty in the clinical- and cost-effectiveness estimates because it included a heterogeneous range of studies. Overall, lenalidomide could not be recommended as a cost-effective use of NHS resources for the treatment of multiple myeloma in people who had received only one prior therapy. However, in people who received 2 or more prior therapies, no indirect comparison was required, and lenalidomide was recommended (under certain circumstances) as a cost-effective use of NHS resources.

Occasionally, trials may include no comparison at all (single-arm trials), or the intervention will be given in both treatment arms at different dosages (for example, because of ethical considerations or accelerated/early marketing). This makes estimating comparative effectiveness more challenging. To account for this, historical controls or data from treatment arms of other trials can be modeled, or nonresponder data in a single-arm trial can be used as a proxy for people who did not receive active treatment. However, such approaches greatly increase uncertainty. One such example is the appraisal of ofatumumab for chronic lymphocytic leukemia (TA202; ref. 8). In this appraisal, the committee considered that the effect of using data from the nonresponders in the single-arm trial as a proxy for best supportive care was highly uncertain. The evidence base was not considered robust, and the technology could not be recommended as a cost-effective use of NHS resources.

**Immature/short-term data**

In a health technology assessment, it is important to capture all relevant differences in health outcomes and costs between the intervention and the comparator. In order to do so, analyses need to use an appropriate time horizon, and for cancer technologies this is usually a lifetime horizon. Therefore, the available trial data must be projected into the longer term, which is often challenging when trial data are obtained from short-term studies or from interim analyses. In these cases, the uncertainty surrounding the effectiveness of a technology can be too great to allow the committee to recommend use in the NHS. For example, in the appraisal of adjuvant imatinib after surgery for gastrointestinal stromal tumors (TA196; ref. 9), only 1-year data were available, which the committee considered too immature to form any conclusions on the longer-term effectiveness of imatinib. Therefore, the committee could not recommend imatinib as a cost-effective use of NHS resources, but considered that an early review date, coinciding with the end of a pivotal trial with longer treatment duration and follow-up, was appropriate.

The use of surrogate outcomes as a proxy for longer-term endpoints, or the extrapolation of short-term data into the long-term, can also be challenging. For example, the choice of modeling techniques and curve fitting to extrapolate data can influence the level of uncertainty in the results of the analysis. A number of fits and techniques may appear to be appropriate for short-term observed data but may diverge widely in the longer term. An example of this occurred in the appraisal of sorafenib for hepatocellular carcinoma (TA189; ref. 10). In this appraisal, the original curve fitted to the data resulted in an ICER of £53,000 (£86,000) per QALY gained, but another curve (which also fit well with the empirical data) resulted in a substantially higher ICER. Therefore, the committee agreed that the true ICER lies within a range between these estimates, and because the ICERs were high and there was uncertainty about the estimates, sorafenib was not recommended as a cost-effective use of NHS resources.

Another factor that decision-makers need to consider is whether the trial participants received only the treatments they were randomized to in the study or they switched or crossed over to another treatment in the trial. This is the case in many oncology trials, and it is frequently observed when a technology is likely to be beneficial and thus crossover after disease progression is allowed. Traditionally, to account for this, patients who have switched treatments are censored from the analysis. Although this

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*Clinical Cancer Research*
technique is relatively straightforward, valuable information can be lost, and the results may not be reliable if the proportion of patients who crossed over is high. Novel statistical techniques that attempt to control for confounding caused by crossover, such as the rank preserving structural failure time (RPSFT) model, are becoming increasingly common. In the appraisal of sunitinib for gastrointestinal stromal tumors (TA179; ref. 11), more than 70% of patients who were randomized to placebo received sunitinib after disease progression. Censoring was not considered reliable due to the high proportion of patients in the control arm who received the active intervention, and the committee accepted the use of the RPSFT method. This was after careful consideration of the results derived from the analysis of progression-free data (which were not confounded by crossover) and exploration of the face validity of the economic model (examination of whether the improvement in overall survival with sunitinib treatment derived using the RPSFT method was corroborated by the increase in progression-free survival with sunitinib treatment seen in the trial). The committee was able to recommend sunitinib as a cost-effective use of NHS resources.

Costs. Clearly, in a cost-effectiveness analysis, estimating costs and resource use is key. People often think that these elements can be calculated with certainty. However, sometimes the cost paid by the NHS for a drug is unclear. Factors such as dose intensity, treatment "vacations," cost of administration, costs of treating adverse events, and patient access schemes may need to be considered. Also, the costs of any additional treatments given either in combination with the technologies or after the study treatment period has ended (usually coinciding with disease progression) are considered by the committee. For example, in the appraisal of sunitinib for gastrointestinal stromal tumors (TA179; ref. 11), some patients continued to receive sunitinib after the stated end of the study. The submitted economic model did not include these costs of sunitinib (the costs were assumed to end as per the stated study protocol). The committee concluded that although it was likely that additional benefits were associated with the additional sunitinib given, the costs should have been incorporated into the model. In this instance, even after these costs were incorporated, the committee was able to recommend sunitinib as a cost-effective use of NHS resources.

Quantifying the duration of a cancer treatment (and therefore the total drug costs) can also be challenging, and this is particularly so for monoclonal antibodies and targeted drugs that are given until disease progression occurs. Estimates of median disease progression can be subject to uncertainties for reasons previously described (such as extrapolating clinical benefit over the longer term). The committee always recognizes the value of additional progression-free survival but must also consider the opportunity cost. Recommending a treatment could actually reduce the net health in the NHS if it displaces other health care resources that provide greater health benefit. Therefore, it is often necessary to consider subgroups and/or specific circumstances for which there is greater evidence of cost-effectiveness. For example, in the appraisal of cetuximab for colorectal cancer (TA176; ref. 12), after much consideration and additional analyses from the manufacturer, the committee concluded that cetuximab represented a cost-effective use of NHS resources only if it was given for up to 16 weeks to patients with currently unresectable liver metastases that could become potentially resectable if there was a significant response to therapy. This recommendation resulted in treatment being given to those who were most likely to benefit, thus maximizing the use of NHS resources.

Estimating health-related quality of life

The impact of an intervention on health-related quality of life is of great importance and is particularly relevant in appraisals of palliative cancer technologies, where the aim of treatment is to maximize quality of life for as long as possible. However, quality of life is difficult to quantify, and what matters to one person may matter less to another, varying, for example, by age, severity of disease, length of time living with a disease, and life expectancy. It may also be difficult to ascertain how a person’s quality of life actually changes over the course of treatment and disease. Commonly, robust measurements of health-related quality of life that can be used for health economic analyses are not captured in clinical trials.

In addition, because NICE appraises technologies across all disease areas, there is a need for consistency in measuring the effects of technologies on health-related quality of life. Therefore, there is a preference for the use of the health status instrument known as the EQ-5D. The EQ-5D is based on the following factors: mobility, ability for self-care, ability to undertake usual activities, pain/discomfort, and anxiety/depression. The health states described with this instrument can then be valued and expressed in numerical terms as utility values. In NICE appraisals, the value placed on states of health described using the EQ-5D should reflect preferences of the general public (as opposed, for example, to people with one particular disease, or their physicians). If so, we would be happy for it to be changed.

When quality-of-life measures such as those described above are not available, assumptions must be used and alternative methods to generate the data must be explored. Options such as mapping (e.g., from a disease-specific measure to the EQ-5D instrument), expert surveys, or alternative values based on other treatments in a similar disease area are often used. However, these methods can lead to increased uncertainty. For example, in the appraisal of bevacizumab for renal cell carcinoma (TA178; ref. 13), quality-of-life data had not been collected from patients being treated with bevacizumab. Proxy values were taken from studies of sunitinib for the same condition at the same line of treatment. However, the committee believed that values associated with sunitinib treatment would not be the same as those associated with bevacizumab treatment, due to the different modes of administration (sunitinib is given orally, generally at home, whereas...
bevacizumab is given as infusions) and different side-effect profiles observed in the trials. The committee concluded that the cost-effectiveness estimates of bevacizumab that had been presented were underestimated, and bevacizumab was not recommended as a cost-effective use of NHS resources.

**Life-Extending, End-of-Life Treatments**

In January 2009, NICE issued supplementary advice for appraising treatments that are potentially life-extending for patients with a short life expectancy and are licensed for indications affecting small numbers of patients (14). This advice applies when the data are considered robust and the assumptions used in the economic evaluation are considered plausible, objective, and robust. When all of the criteria are met, the appraisal committee must consider the impact and magnitude of additional weight that would have to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the technology to fall within the currently applied ICER threshold range.

These criteria were first applied in the appraisal of lenalidomide for multiple myeloma (TA171; ref. 7). The appraisal committee concluded that the relevant ICERS upon which to base a decision were £43,800 ($71,000) per QALY gained for the subgroup of patients who had received 2 or more prior therapies, and £41,300 ($67,000) per QALY gained for the subgroup of patients who had received 2 or more prior therapies including thalidomide. These ICERS already incorporated a patient access scheme, without which the corresponding ICERS were £47,100 ($76,000) and £43,600 ($70,000) per QALY gained. With life expectancy without lenalidomide estimated to be less than 24 months (and potentially as low as 9 months), robust evidence suggesting that lenalidomide increased survival by more than 3 months compared with dexamethasone, and the eligible population estimated to be 2,100, the criteria were met. The committee went on to consider that the magnitude of the additional weight that would have to be assigned to the original QALY benefit for the cost-effectiveness of lenalidomide to fall within the currently applied ICER threshold range was acceptable.

Since these end-of-life criteria were first introduced, NICE has published 57 technology appraisals of 70 individual technologies (including 31 appraisals of 33 technologies of cancer indications). Twenty of these appraisals (23 technologies) were considered under the end-of-life
criteria (i.e., they were associated with a short life expectancy of normally <24 months).

Of the 23 technologies that were considered in light of the criteria, 13 were considered to fulfill them. Eight of these were then recommended as treatment options and were recommended for use in the NHS (Table 1).

The Future of NICE

NICE has existed for more than 10 years and has produced well over 200 pieces of technology appraisal guidance to the NHS. During this time, NICE has grown and worked to improve the quality of patient care and equality of access to that care. NICE recently established NICE International to provide advice on the use of evidence and social values in decision making and a scientific advice program to provide product-specific advice to manufacturers about products in development that may be referred for a technology appraisal. Worldwide, there is increasing acceptance of the importance of considering both clinical and cost-effectiveness (value for money) in allocating health care resources.

Because the NHS is funded by taxation and contributes to 18% of government expenditures, the provision of health care is subject to intense political scrutiny. The new coalition government (elected in 2010) has presented a number of proposals, including establishing NICE under primary legislation, and more are to come. In 2010, the government set out its plans to establish a Cancer Drugs Fund in April 2011 and made an initial £50 million ($81 million) available for this purpose (15). The fund will provide a means to fund treatments that have not been recommended or have not yet been appraised by NICE. Decisions about the allocation of the Cancer Drugs Fund will be led by clinicians and cancer specialists. A new value-based approach to pricing of branded medicines has been proposed to replace existing arrangements in 2014 (16). The exact impact of these developments on the role of NICE technology appraisals is currently uncertain.

Recent government consultation papers put NICE at the center of the new NHS, with the responsibility for developing clinical quality standards that will underpin clinical outcomes (17). These standards will be the new basis for assessing the performance of the NHS. Currently, standards for the treatment of breast, ovarian, prostate, and lung cancer are in development.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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