



Saying No Isn't NICE — The Travails of Britain's National Institute for Health and Clinical Excellence

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Britain's National Institute for Health and Clinical Excellence, known as NICE, is an independent, government-funded organization that advises the British National Health Service (NHS).¹ Established

in 1999, the institute has recommended coverage for hundreds of medicines. Since 2002, NHS organizations in England and Wales have been required to pay for medicines and treatments recommended in NICE "technology appraisals." The NHS usually does not provide medicines or treatments that are not recommended by NICE — although exceptions are possible.

NICE (www.nice.org.uk), however, has been criticized for the slow release of its appraisals, which has delayed the availability of some treatments that it eventually views favorably.² Some of its decisions seem unfair, and

the institute has been vilified for recommendations to limit or deny coverage for some high-profile medicines for cancer and other life-threatening diseases. Its decisions are often appealed (see table), usually by manufacturers, and one decision — that coverage of donepezil and other drugs for Alzheimer's disease should be restricted to patients with at least "moderate" (rather than "mild") disease — has been challenged in court.

NICE is often challenged for its decisions on cancer drugs that are very costly but extend life, on average, by only several months. In August 2008, oncologists, patients, and drug manufacturers

attacked NICE's preliminary recommendation against coverage of four expensive drugs for advanced renal-cell cancer — bevacizumab, sorafenib, sunitinib, and temsirolimus. Although the institute considered the drugs clinically beneficial in specific situations, it concluded that they "were not cost-effective within their licensed indications." At a NICE board meeting in Plymouth, England, in September, a 57-year-old man with metastatic renal cancer described how sunitinib had stabilized his disease for more than 2 years, during which he had continued to work full-time. Although he had some pain and limited mobility, he said, "the quality of life this drug gives me is priceless."

In another recent appraisal, NICE recommended restrictions on coverage of drugs other than

Appeals of NICE Technology Appraisals, January 2000–September 2008.*					
Year	No. of Technology Appraisals Published	No. of Appeals Submitted	No. of Appeals Allowed (No. Withdrawn or Dismissed without Hearing)	No. of Appeals Upheld after Hearing	No. of Appeals Dismissed after Hearing
2000	17	8	8 (0)	2	6
2001	14	5	4 (1)	1	3
2002	24	11	10 (1)	7	3
2003	19	4	4 (0)	1	3
2004	13	5	2 (3)	1	1
2005	6	3	3 (0)	0	3
2006	20	6	6 (0)	3	3
2007	21	5	5 (0)	4	1
2008	25	10	8 (2)	0	6
Total	159	57	50 (7)	19	29

* Data are from the House of Commons Health Committee² and NICE. Groups such as manufacturers and patient or professional organizations may appeal decisions through an internal process that NICE has established. When an appeal is upheld, the decision is sent back to the appraisal committee for further consideration. The resulting changes may be minor, such as changes in wording, or major and can take into account additional information that has become available since the appraisal was initially prepared. As of September 2008, two appeals were pending.

generic alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. After rejecting an appeal, NICE released the final guidance in late October. After NICE issued a preliminary recommendation against the use of lapatinib plus capecitabine for previously treated HER2-positive advanced breast cancer, the maker of lapatinib offered to pay the cost of this drug for up to 12 weeks of therapy. The NHS would pay after 12 weeks. This offer is still under consideration.

For coronary artery disease, NICE recommended the use of drug-eluting coronary stents only if the price difference between drug-eluting and bare-metal stents was no more than £300 (\$516, at \$1.72 per £1). For patients with neovascular age-related macular degeneration, NICE recommended covering ranibizumab but not

pegaptanib; during the institute's review, ranibizumab's manufacturer agreed to cover the cost of the drug for people who need more than 14 injections per eye, starting with the 15th injection.

NICE can be viewed as either a heartless rationing agency or an intrepid and impartial messenger for the need to set priorities in health care. Insofar as it is the latter, its experiences may be instructive for many countries, including the United States, regardless of the differences in their health care systems. The U.S. Centers for Medicare and Medicaid Services may eventually gain the ability to negotiate drug prices, and Congress is considering the creation of a health care comparative effectiveness research institute, as proposed in a 2008 bill (S.3408). This institute would have a more limited scope than NICE has: it would develop evi-

dence about what does and does not work in health care and would fund research but would not consider cost or factors of health plan design. Nonetheless, such an institute could help to improve quality and slow escalating costs only if it were able to make tough calls and remain independent of political and financial interests.

In the United Kingdom, the NHS funds and delivers about 95% of medical care. And although its budget has increased substantially in recent years, it is a tax-funded system with a finite amount to spend. During a recent visit to NICE, I was told by Michael Rawlins, the physician who has chaired the institute since its inception, that it has "to be fair to all the patients in the National Health Service, not just the patients with macular degeneration or breast cancer or

renal cancer. If we spend a lot of money on a few patients, we have less money to spend on everyone else. We are not trying to be unkind or cruel. We are trying to look after everybody.”

NICE has about 270 full- and part-time staff members and an annual budget of about £32 million (\$55 million). It calls on about 2000 outside experts to help develop guidance. There is a comprehensive practice code regarding conflicts of interest; the directors of NICE, the chairs of its advisory bodies, and employees of the institute and its collaborating centers can have essentially no financial relationships with industry. Members of advisory bodies must declare their interests, and when a conflict is identified, they cannot take part in decisions.

In addition to technology appraisals, NICE offers public health guidance, clinical guidelines, and guidance about diagnostic and therapeutic procedures. The institute recently began to open part of the meetings of its advisory committees to the public; the committees, however, consider confidential commercial, patient, and academic data in private and deliberate in closed sessions. NICE's technology appraisals are prepared by three committees that the institute appoints but are otherwise independent. Although the NICE board may reject a committee's recommendation, it has never done so.

NICE formally appraises about 40% of new drugs and new license indications for existing medications, as well as some medical devices, diagnostic techniques, and surgical procedures. It does not license drugs, nor

does it appraise unlicensed products or off-label uses; the Medicines and Healthcare Products Regulatory Agency is responsible for licensing drugs and devices and ensuring their safety and ef-

fectiveness. NICE reaches conclusions about whether treatments are clinically effective, as compared with relevant alternatives, and determines whether they are cost-effective by using economic analysis to compare their value-for-money with that of other treatments.³

NICE does not set or negotiate drug prices. However, some of the institute's initial evaluations, such as those of ranibizumab for macular degeneration and bortezomib for multiple myeloma, have led manufacturers to offer the NHS better deals, resulting in favorable recommendations. For example, if patients with multiple myeloma have a full or partial response to bortezomib, the NHS pays and treatment continues; otherwise, treatment is discontinued, and the manufacturer refunds the drug's cost.

Assessing cost-effectiveness is the most controversial aspect of NICE's work. The institute estimates an incremental cost-effectiveness ratio, or the cost per quality-adjusted life-year (QALY), gained through a treatment's use, which, despite its imperfections, is widely considered the best available method for assessing value for money in health care. This

ratio provides a means for considering costs in the context of both the quantity and quality of additional life by assigning a value ranging from 0 (death) to 1 (perfect health) to the quality of life for a given period. However, the method is complex; the cost-effectiveness ratio applies to groups of patients, not individuals, and is commonly confused with the cost of the medication, which is only one of many costs that are considered — others include, for example, the cost of medical care related to the treatment. Of course, if pharmaceutical manufacturers charged less for their products, NICE would find more medications cost-effective. The analyses are also susceptible to bias, and the cost-effectiveness ratio can vary widely depending on assumptions made about clinical benefit and harmful effects or other factors. Although resource use is most inefficient when an expensive intervention provides little or no benefit, resources can also be squandered through wide use of less expensive but relatively ineffective medicines.⁴

In the United States, a figure of \$50,000 per QALY is often used as a threshold to assess the cost-effectiveness of an intervention. This threshold was recently criticized as “an arbitrary decision rule that lacks theoretical or empirical justification and is in any case outdated.”⁵ Scott Grosse of the Centers for Disease Con-

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— Sir Michael Rawlins, chairman, NICE

trol and Prevention noted that although treatments that cost up to \$200,000 per QALY are often adopted, it would “be very expensive if all interventions with a [cost-effectiveness] ratio at this level were regarded as providing good value for money.”⁵

In general, NICE considers treatments cost-effective if their incremental cost-effectiveness ratio is £20,000 (\$34,400) or less per QALY. This ratio, however, is not a rigid cutoff. On occasion, NICE accepts values between £20,000 and £30,000 (\$51,600). On rare occasions, it accepts values beyond £30,000. This approach allows the appraisal committees to consider other evidence, to recognize that all cost-effectiveness ratios have uncertainty intervals, and to exercise their judgment in making decisions.

For example, in 2002 NICE was criticized for not recommending coverage of beta interferon and glatiramer acetate for treating multiple sclerosis. Subsequently, Britain's Department of Health decided to make the drugs available in the NHS as part of a 10-year trial. If the medications turned out to be less cost-effective than £36,000 (\$66,600) per QALY, the manufacturers agreed to reimburse the NHS for their cost. However, an interim report has yet to be released; it is uncertain whether the study will yield reliable information or whether the NHS will ever receive any reimbursement.²

The highest incremental cost per QALY that NICE has accepted is about £49,000 (\$84,000), for imatinib mesylate, when used in the blast-cell phase of chronic myeloid leukemia. By comparison, NICE calculated that the four

treatments for advanced renal cancer that it evaluated had incremental costs per QALY of £71,462 (\$122,915) for sunitinib, £94,385 (\$162,342) for temsirolimus, £102,498 (\$176,297) for sorafenib, and £171,301 (\$294,638) for bevacizumab. A final recommendation on coverage is pending.

According to Rawlins, “The big problem is why we have chosen £20,000 to £30,000 per quality-adjusted life-year. I have always been very honest about this. There is really no empirical research that tells us where the boundaries ought to be. It is really a judgment of the economic community that has provided that sort of number.”

In the months ahead, NICE has a full agenda. The institute is continuing to study its threshold ranges for QALYs and other aspects of its assessment methods. It has committed to publishing its appraisals of new drugs and other treatments as quickly as possible — ideally, within 4 months of their becoming available for general use. Fully achieving this goal will take several years and require the institute to begin its evaluations about 15 months before new medicines are approved for marketing. And as part of broader changes in the system for pricing drugs that are purchased by the NHS, the Department of Health may give NICE a formal advisory role.

NICE is also seeking permission from the House of Lords to appeal the April 2008 decision of the Court of Appeal in the Alzheimer's disease case. If the current decision stands, NICE will have to make public “fully executable versions” of its economic models, which would make it eas-

ier for manufacturers to challenge the underlying assumptions. The appellate decision could also make it difficult, if not impossible, for NICE to protect confidential information, such as unpublished research reports or the likely price of drugs not yet on the market. NICE is also facing three additional judicial reviews, one about its appraisal of osteoporosis treatments, another about a clinical guideline on chronic fatigue syndrome, and a third about the use of abatacept, which it did not recommend covering for rheumatoid arthritis.

According to Andrew Dillon, NICE's chief executive, when it appears that the institute cannot support coverage of a treatment given its current price, “we encourage companies to think about what they might do [to make their product cost-effective]. . . . We push the envelope just as much as we possibly can.” Although the United Kingdom represents only a small percentage of the overall drug market, the institute's work has focused global attention on the importance of evaluating the comparative effectiveness and the cost-effectiveness of medical treatments. It remains to be seen, however, how many other countries will follow its lead. After all, saying no takes courage — and inevitably provokes outrage.

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Drug Development for Neglected Diseases — The Trouble with FDA Review Vouchers

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September 2008 marked the beginning of a new federal program intended to promote the development of pharmaceutical products for so-called neglected diseases — infectious diseases that disproportionately affect poor populations in developing countries. Implemented by the Food and Drug Administration (FDA) Amendments Act of 2007, this program will give the sponsor of a drug for a tropical disease a “voucher” entitling the company to expedited FDA review of a new drug application for any other product it makes.¹

The need to encourage additional research in this field is clear. Diseases such as tuberculosis, malaria, leishmaniasis, and trypanosomiasis affect millions of people each year, but these people live primarily in resource-poor settings with underdeveloped health care systems. As a result, the for-profit pharmaceutical industry has invested little in treatments for these conditions. One study found that of the 1393 new chemical entities marketed between 1975 and 1999, only 16 were for such diseases.²

The new program links the development of drugs targeting tropical diseases to accelerated approval of a company's other,

more profitable drugs for conditions prevalent in wealthier countries. A voucher obtained after the approval of a drug for a tropical disease can be used to require accelerated regulatory review (in 6 months or less) of a cholesterol-lowering drug or an antidepressant, for example, that the sponsor might sell in the United States for thousands of dollars per year of treatment. According to the arrangement's proponents, vouchers could speed up FDA evaluation time by an average of 12 months, providing domestic patients with more rapid access to the latter types of drugs.³ A voucher could be worth more than \$300 million, thanks to the earlier period of market exclusivity afforded by decreasing the time a drug spends in FDA review.

As enacted, however, priority-review vouchers represent an inefficient and potentially dangerous way of encouraging research into tropical diseases. It is inefficient because the program does not directly connect the incentive with the innovation. Large pharmaceutical companies traditionally have not conducted effective research programs on tropical diseases. These manufacturers will be unlikely to start such a

program merely because of the prospect of earning a voucher some years in the future, since the voucher's value depends on the success of potential “blockbuster” drugs that are currently in their pipelines, which is far from assured. In fact, tropical-disease research is predominantly conducted by small pharmaceutical companies with limited drug portfolios. Such companies will often be unable to use their vouchers, although the law permits voucher rights to be sold to a large manufacturer. Relying on these sorts of transactions to spur innovation is speculative as well, and the deals between small and large pharmaceutical companies affecting agents of great importance to global health will lack transparency. Such deals may include other payments or exchanges of intellectual property that raise the cost or restrict the future availability of the products.

Another source of inefficiency is that a voucher's value will bear no relation to the usefulness of the drug whose development it is intended to reward. For example, the law stipulates that no voucher will be earned for a product whose “active ingredient” was previously approved. As a result, an effective novel antimalarial