WICKENSTONES
PARTNERS IN BUILDING VALUE

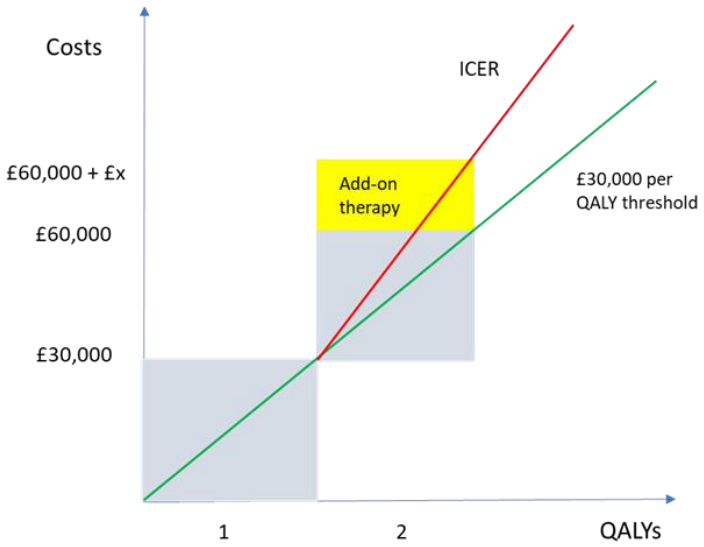
Health technology assessment

Can't give it away? HTA for add-on therapies

The development of new life extending therapies has coincided with an ongoing debate around society's maximum willingness to pay for health gains, typically expressed in the form of quality adjusted life years (QALY). This is sometimes termed the cost-effectiveness 'threshold'.

In the case of NICE, a threshold of around £20,000-30,000 per QALY gained is applied. If the price of a new therapy gives an incremental cost-effectiveness ratio (ICER) above this range, a reduction in its price is normally required for the therapy to be approved, frequently achieved using a patient access scheme (typically a confidential discount).

Figure 1: A technology which is not cost-effective at zero price



However, things start to become more complicated in the case of new therapies which are added to existing treatment, when the ICER will include the costs of both the new and existing treatments over the life years gained. In the extreme case, the cost of existing treatment is sufficient by itself to raise the ICER to the level of the threshold. According to the usual calculations, the new therapy

cannot therefore be cost-effective at any price. This is despite the add-on product generating health gain not achievable with existing therapy alone. In Figure 1, the costs of existing care use up the threshold, with any additional add-on cost (£x) raising the ICER to an unacceptably high level.

Illustrative examples

In the NICE appraisal of pertuzumab in combination with trastuzumab and docetaxel in breast cancer, an increase in progression free survival (PFS) was achieved at a cost of over £27,000 per year with a zero price for pertuzumab. Given the QALYs associated with PFS, the implication was that pertuzumab had no probability of being cost-effective at a threshold of £30,000 per QALY gained. At this point the appraisal was suspended and the issue referred to the Decision Support Unit (DSU) for further consideration. A number of other appraisals, including cetuximab and bevacizumab (Table 1), were also examined[1].

Table 1: Example NICE appraisals of technologies which were not cost-effective at zero price

Technology evaluated	Indication	NICE guidance
Pertuzumab, trastuzumab and docetaxel vs trastuzumab and docetaxel	HER2-positive metastatic or locally recurrent unresectable breast cancer	Recommended
Cetuximab plus platinum-based chemotherapy vs platinum-based chemotherapy alone	Recurrent or metastatic squamous cell cancer of the head and neck	Recommended
Bevacizumab plus FOLFOX or XELOX vs FOLFOX or XELOX alone	Metastatic colorectal cancer	Not recommended

Can HTA processes accommodate these cases?

Although these examples suggest that no price discounting for the new product would be sufficient to meet the cost-effectiveness criterion, two of the drugs (pertuzumab and cetuximab) were ultimately approved by NICE (albeit with commercial agreements) after an initial negative decision. Evidently some additional flexibility beyond the price of the drug under consideration is possible in the HTA process. The aim of this discussion paper is to suggest areas where HTA processes might have the flexibility to capture these benefits, either through the threshold or the component costs and/or QALYs of the ICER.

Adjusting the threshold ICER

Superficially making the case for an adjusted threshold appears to be a fruitful avenue to explore. After all, there has been an extensive debate around the application of different cost-effectiveness criteria to, for example, orphan drugs. Indeed, in NICE's Highly Specialised Technologies (HST), the base case threshold, at £100,000 per QALY, is well above the normal range. However, this flexibility applies to the willingness to pay for health benefits between disease/therapy groups and therefore is unlikely to be helpful in the case of add-on therapies in a single patient group.

Adjusting the cost calculation

Flexibility in cost calculations may arise either around the definition of the resources to be included in the ICER or the price of those resources. The inclusion of wider societal impacts beyond the usual health care perspective, such as productivity costs and carer costs, may at first seem attractive. However, any positive cost over the period of extended survival will increase (i.e. worsen) the ICER.

The issue addressed by the DSU report centres on the treatment of 'related' and 'unrelated' costs in added years of life. Although, as NICE recommends, it is appropriate to exclude future 'unrelated' costs, the DSU notes that distinguishing between related and unrelated costs presents major problems in defining the two categories. It is therefore unlikely to be a useful source of flexibility.

As far as valuing resources is concerned, a reduction in price for the technology being appraised is not, by definition, feasible to bring the ICER within the maximum acceptable. Potential room for manoeuvre may be the pricing of existing and companion technologies, depending on the type of technology involved.

While non-drug technologies (including administering treatment) should, in theory, be priced at close to an efficient level, prices of medicines tend to be set through a process of negotiation. Flexibility on price is a relatively straightforward proposition if the company produces both the standard of care and the add-on product. It is less so if different companies are involved or standard care is a generic product, for which the price is already close to the minimum possible (a point made in NICE's appraisal of bevacizumab). The room for manoeuvre will therefore depend on the context.

Adjusting the valuation of benefits

As with costs, an adjustment to either the scope or the value of benefits could be considered but, as with costs, the impact of broadening benefits to include carer QALYs is not always obvious when bereavement is factored in. So can the value of patient benefit provide the answer?

In NICE's methods, an End of Life (EoL) adjustment is possible for specified patient groups (Box 1). In these situations, NICE can consider, firstly, a weighting of QALYs in added years which reflects the quality of life of healthy individuals of the same age and, secondly, the weighting needed to be applied to QALYs to generate a cost per QALY within the normal range of maximum acceptable ICERs (up to a maximum weighting of 1.7).

Box 1: NICE's end of life criteria

For survival gains at the end of life, the Appraisal Committee must be satisfied that:
Patients have a short life expectancy of normally less than 24 months;
Treatment has the prospect of extending life normally by a mean of 3 extra months or more;
Survival gain estimates are sufficiently robust and can be shown or inferred from PFS or OS;
Reference case economic modelling assumptions are plausible, objective and robust.

Abbreviations: OS, overall survival; PFS, progression free survival.
Source: NICE. Guide to the methods of technology appraisal 2013[2]

The impact of the EoL criteria can be detected through the implied cost-effectiveness threshold. As price discounts offered to bring the ICER to an acceptable level are usually confidential, it is not always possible to determine the acceptable ICER for EoL technologies (often cancer drugs). However, an early review of NICE decisions in this category suggests that a benchmark ICER close to £50,000[3] has been established in EoL cases. There is therefore scope for an add-on technology to be accepted even where current treatment exhausts the conventional threshold.

In the case of HST, not only is the base case acceptable ICER higher than that for other technologies but the guidance also enshrines the principle that the unit value of a QALY can increase with the number of QALYs gained. Although the QALY weightings proposed (as high as 3 for a QALY gain of 30 or more) relate to a magnitude of benefit beyond most technologies, such arguments may have broader application.

In the case of pertuzumab, NICE concluded that, although it did not strictly meet the criteria for an EoL therapy, it was nevertheless worthy of special consideration. Not only was the absolute benefit, a median 15.7 months in survival, thought to be unprecedented, but guidance also emphasised that the proportional improvement was considered to be exceptional.

Implications for HTA

While an ICER above conventionally accepted levels even at zero price might seem to present an insurmountable obstacle to achieving a positive HTA recommendation, this small group of case studies from the NICE archives suggests that appraisal processes can adjust even to these cases. The critical consideration in the two cases considered here which received a positive recommendation was the way in which benefits are valued particularly near the end of life.

Given that the considerations behind NICE's EoL criteria may reflect societal preferences more generally (although the evidence is not conclusive[4]), they may be applicable in other contexts where decision making criteria are less transparent. Importantly, while flexibility around the value of benefits is conditional upon the criteria being met, other criteria can be introduced, such as the exceptional 'proportional' benefit noted in the appraisal of pertuzumab.

Significantly, these examples reinforce the point that a technology's benefits may not be realised until some time after launch. For both pertuzumab and cetuximab, a positive recommendation was granted only on reconsideration of the evidence after a period of additional evidence collection (under the Cancer Drugs Fund). An added ingredient in both positive decisions was the negotiation of a commercial access agreement between government and the company.

While the details of these agreements are not generally made public, they could point the way towards the use of more flexible pricing approaches by companies at initial appraisal rather than at the stage of re-evaluation, as a response to the uncertainties surrounding benefits. Perhaps it is time to revisit novel pricing mechanisms such as risk sharing and pricing by indication as a means of appropriately capturing the added value of add-on products.

References

1 Davis S. Assessing technologies that are not cost-effective at zero price. Sheffield: Decision Support Unit (2014).

2 NICE. Guide to the methods of technology appraisal 2013, <https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781> (2013).

3 Barham, L. End-of-life treatments: what will NICE accept?, <https://pharmaphorum.com/articles/end-of-life-treatments-what-will-nice-accept/> (2016).

4 Shah, K.K., Tsuchiya, A., Wailoo, A.J. Valuing health at the end of life: A review of stated preference studies in the social sciences literature. Social Science & Medicine, 204, pp.39-50 (2018).

Written by
Clive Pritchard
clive@wickenstones.com
www.wickenstones.com

WICKENSTONES
PARTNERS IN BUILDING VALUE

Wickenstones is a global strategy consultancy with expertise in evidence, value and access