NICE, Social Values, and Balancing Objectivity and Equity

Suzanne R. Hill · Leslie G. Olson

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In this issue of *PharmacoEconomics*, Paulden et al. [1] criticize the latest proposal from the National Institute of Health and Care Excellence (NICE) to update its technical guidance on health technology appraisal (HTA). The criticism is both technical and ethical, and Paulden et al. are not always clear about the difference. Where has this come from, and what are the potential implications for other HTA agencies of the proposed amendments to the NICE guidance?

The story starts, according to the authors, with the UK Department of Health requesting modifications to NICE's methods to allow for "value assessment of branded medicines under Value-Based Pricing [VBP]". The request was that NICE's methods should, among other requirements:

1. "Include a simple system of weighting for burden of illness that appropriately reflects the differential value of treatments for the most serious conditions";
2. "Include a proportionate system for taking account of wider societal benefits";
3. "Not include a further weighting for therapeutic innovation and improvement"; and
4. "Adopt the same benefit perspective for all technologies falling within the scope of VBP, and for displaced treatments".

VBP is an attractive proposal. According to Jayadev and Stiglitz [2], it can increase innovation and reduce the cost of pharmaceuticals. The argument is that linking the purchaser's willingness to pay a higher price to 'additional value' provides an incentive for genuine innovation rather

than 'me-too' developments (it should be noted that Jayadev and Stiglitz do not propose VBP as a stand-alone strategy: they suggest that public funding of clinical trials and of pharmaceutical research and development is also needed). The challenge, as NICE and Paulden et al. recognize, is how to define 'additional value' and how to include it in the process of economic appraisal.

One example relevant to the consideration of 'additional value' is interventions for treatment of the most seriously ill patients. Since 2009, NICE has used an 'end-of-life' criterion to justify paying more for treatments that provide small absolute gains in life expectancy for patients with a short life expectancy. The effect is to allow new and expensive oncology treatments to be considered cost effective at a much higher incremental cost-effectiveness ratio (ICER) threshold—although the number of positive recommendations from NICE on this class of drug is still criticized as being too small [3, 4]. The proposed amendment is to replace this with a more general weighting for treatments offering small absolute benefits, whether in survival or quality of life, where survival is short or quality of life is poor. Whether this change will in practice lead to different decisions than the end-of-life criterion is unclear, especially when it is combined with willingness to pay for the "innovative nature of technology". Paulden et al. may be correct that this approach will systematically privilege new and expensive technologies to treat advanced malignancy.

Paulden et al. also question whether small absolute gains in survival, even if they are large in relative terms, really do represent 'additional value'. Others have raised the same issue, suggesting that it is necessary to think carefully not only about the value ascribed to small absolute gains in life expectancy, but also about how drug development is approached [5].

S. R. Hill (✉) · L. G. Olson
University of Melbourne Medical School, University of
Melbourne, Parkville, VIC 3010, Australia
e-mail: suzannerhill@gmail.com

The value of small absolute but large relative survival gains is an ethical issue. A problem not discussed in Paulden's paper is the reliability of trial-based estimates of effect size, particularly in oncology. The technical issues of interpretation of trial outcomes raised by recent developments in trial design are fundamental to reliable economic models. As just one example, noted by Mehta et al. [6], adaptive trial designs that allow enrichment for biomarker-positive patients may need novel statistical methods. Other methodological questions of some urgency are how to adjust appropriately for crossover of treated populations in trials and whether progression-free survival is an adequate surrogate outcome for overall survival across all types of cancer. It is hard to imagine how, in the present state of understanding of these methodological questions, these factors might be explicitly weighted in assessing the 'certainty of the ICER' as proposed by NICE.

Another amendment criticized by Paulden et al. is the 'selective discounting' amendment; they have previously called it "ambiguous, inconsistent and unjustified" [7]. While the theory behind differential discounting can be argued, its impact is generally to make cost-effectiveness ratios more favourable than they would otherwise be. Paulden's argument is largely ethical and is discussed further below. It should be noted that differential discounting is especially relevant to the appraisal of vaccines, and that its impact can be very large. For example, the appraisal of the novel meningococcus B vaccine in Ontario [8], which used standard discounting, found that the estimate of the cost effectiveness of the vaccine for an infant vaccination programme was C\$4.76 million/QALY [quality-adjusted life-year] gained. The submission to the Australian Pharmaceutical Benefits Advisory Committee (PBAC) argued for use of differential discounting to estimate an ICER of between AUS\$45,000 and 75,000. Without the discounting change, the ICER was greater than AUS\$200,000/QALY gained [9].

Paulden et al. also raise "inconsistencies due to the failure of NICE to consider opportunity cost", noting that in the UK, investment and disinvestment decisions about health care are taken by local decision makers. In other health systems, the same authority may carry out the HTA and make the final purchasing decisions, or the link between the economic appraisal and other pharmaceutical pricing policies, such as reference pricing, is more explicit. Price negotiation based on the results of HTAs has been recently adopted in Germany [10] and has been used in Sweden and Australia, among other countries, for some years. Budget impact analysis in health systems that link HTA and purchasing—sometimes with a capped budget, as in New Zealand—may be a reminder about the need to consider opportunity cost, whether by including it in the cost-effectiveness ratio or through explicit estimates of total expenditure.

Perhaps this is the heart of the argument. As noted above, the initial purpose of these amendments was to enable the move towards VBP. As argued by Danzon et al. [11] with respect to value-based differential pricing, "each payer can achieve appropriate prices by setting an incremental cost-effectiveness ratio (ICER) threshold and letting companies choose prices, given their drug's effectiveness and the payer limiting reimbursement to utilization that meets the ICER threshold". But, as noted by Neumann et al. [12], the origin of an ICER threshold can be "murky". As demonstrated by the current debate over the price of sofosbuvir, a product can meet a cost-effectiveness threshold yet still be unaffordable if utilization cannot be limited. So perhaps the real challenge for NICE lies in having to consider cost-effectiveness thresholds in isolation from budget impact because it does not have to make the investment decision.

At the heart of the argument of Paulden et al. is an ethical claim: that all QALYs are of equal value. That has many merits as an ethical position, but the question is whether there is something wrong with abandoning it, if abandoning it reflects community values. Paulden et al. also refer to NICE's precise definition of terms such as 'short life expectancy' or 'long-lasting clinical benefit' as "arbitrary". While sharp dividing lines disadvantage some people in ways that may be unfair, they have ethical advantages of certainty and transparency. Again, what matters is whether the choice reflects community values.

NICE has never shied away from the fundamental question of how to incorporate social values into decisions about access to health technologies. There is an extensive literature on approaches to this question, and two points should be noted. One is that diverse individuals are relatively consistent in the median rank score for preventive health care but are much more variable for 'lifesaving' interventions, so it is not obvious that there can be an aggregated 'community' preference [13]. The second is that how to incorporate these preferences into decision-making based on cost effectiveness remains unresolved. Explicit weights are an attractive and transparent solution. But the validity of those weights, as argued by Paulden et al., is critical.

The former Chair of NICE, Michael Rawlins, has made his view clear: "Although competent HTA bodies should be able to exercise scientific judgments they have no legitimacy to impose their own social values. These must ultimately be informed by the general public" [14]. Mechanisms for giving fair expression to community values are, of course, the key. Those that NICE has in place represent world-best practice, but many difficulties remain to be resolved. As Paulden et al. recognize, there is need for research, transparency and continuing discussion about how best to do this, not only for NICE, but also globally.

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