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Health Policy Analysis

Comparing the ICERs in Medicine Reimbursement Submissions to NICE and PBAC—Does the Presence of an Explicit Threshold Affect the ICER Proposed?

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ABSTRACT

Objectives: The English National Institute for Health and Care Excellence (NICE) and the Australian Pharmaceutical Benefits Advisory Committee (PBAC) require evidence that a new medicine represents value for money before being publicly funded. NICE has an explicit threshold for cost effectiveness, whereas PBAC does not. We compared the initial incremental cost-effectiveness ratios (ICERs) presented by manufacturers in matched submissions to each decision-making body, with the aim of exploring the impact of an explicit threshold on these ICERs. **Methods:** Data were extracted from matched submissions from 2005 to 2015. The ICERs in these submissions were compared within each pair and with respect to a cost-effectiveness threshold. **Results:** Fifty-eight pairs of matched submissions were identified. The median difference between the ICERs ($2635/quality-adjusted life year [QALY]) was significantly greater than zero (Wilcoxon signed-rank test, $P = 0.0299$), indicating that the proposed ICERs in the submissions to NICE were higher than those in the matched submissions to PBAC. On 93% of occasions, NICE ICERs were within –$17,772 to +$48,422 of the corresponding PBAC ones (Bland-Altman analysis), demonstrating poor agreement. When an implicit threshold of AUD$50,000/QALY was assumed for PBAC decision making, only eight pairs of submissions had discordant ICERs falling above or below the respective threshold. **Conclusions:** The significantly higher ICERs in the submissions to NICE than those to PBAC may be a consequence of NICE's explicit willingness-to-pay threshold, and/or other health system factors. Industry may be assuming an implicit threshold for PBAC when constructing their ICERs despite the lack of acknowledgement of such a threshold.

Keywords: incremental cost-effectiveness ratio (ICER), NICE, PBAC, reimbursement, threshold.

Introduction

When it comes to priority setting and resource allocation in health care, decision makers are often faced with difficult choices. Limited resources make it impossible to subsidize every technology or provide affordable access to everyone. Before a new technology is reimbursed, its efficacy, effectiveness, and safety need to be analyzed. In this process, the increasing costs of health care and the consequent need to ensure value for money have resulted in a "fourth hurdle" in medicine reimbursement policies, which requires the demonstration of a medicine's cost effectiveness through the process of economic evaluation [1].

Although medicine reimbursement decisions do not, and should not, rely solely on the cost effectiveness of a medicine, undeniably it is considered one of the most important criteria in reimbursement decision making in many countries of the world [2]. Both the National Institute for Health and Care Excellence (NICE) in England and the Australian Government's Pharmaceutical Benefits Advisory Committee (PBAC) require evidence that a new medicine represents value for money before it is publicly funded.

Incorporating cost effectiveness in the decision process raises questions about a society's willingness to pay for better health. Some organizations have explicitly specified their own cost-effectiveness threshold value in terms of the incremental cost for an additional quality-adjusted life-year (QALY) gained compared with the existing treatment; others have denied an explicit value, although implicit values may be used in their decision

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making. For example, NICE has stated that it is most appropriate to use a threshold range of £20,000 to £30,000 per QALY gained [3,4], unless for end-of-life treatment where a threshold higher than £30,000/QALY is acceptable [5]. In Australia, no explicit threshold has been acknowledged [6,7], although research has indicated that there is a relationship between the incremental cost per QALY gained and the probability of rejection of a medicine [8]. The pharmaceutical industry claims that experience suggests an acceptable threshold is in the range of AUD$45,000 to AUD$60,000 per additional QALY gained [9]. Lowe and Dyson also stated that "PBAC decisions in the past have shown that the ICER is of the order of $50,000" [10].

The lack of standardization in conducting an economic evaluation gives wide scope to parties performing cost-effectiveness analyses [11]. If the producers of the economic models are aware of the existence of a threshold of willingness to pay, they may be able to exploit this information. Thresholds set by public agencies like NICE could incentivize manufacturers to target their economic models to a certain ICER. One of the few existing studies covering this area of research found that ICERs submitted to NICE by manufacturers differ significantly from those submitted by independent academic assessment groups [12]. Walley and Breckenridge claimed that a whole new industry emerged in the United Kingdom, with consulting companies undertaking NICE appraisals on behalf of pharmaceutical companies, guaranteeing to produce a submission with an ICER below NICE's threshold [13]. This means that the desired favorable result of a submission would be known ex ante and that ICERs would be expected to cluster around the known threshold or predominantly fall below it.

There is growing evidence suggesting that the involvement of industry in cost-effectiveness analyses is more likely to bring about favorable results [12,14,15]. However, so far, there is no published study comparing the ICERs from economic evaluations submitted to funding organizations with and without explicit willingness-to-pay thresholds by the same manufacturers for exactly the same purpose. We aimed to conduct this analysis by comparing paired submissions to NICE and PBAC, to examine whether there is any difference between the paired ICERs in the submissions to these two funding organizations.

Methods

In this study, we compared the ICERs in submissions to NICE with those in the matched submissions to PBAC from the same manufacturers, for the same medicines, same clinical indications, same populations, and with the same comparators to examine whether the initial ICERs presented by manufacturers to each of these two funding organizations differed. The context of decision making in these two countries was also explored in an attempt to explain any observed differences in these paired ICERs.

Functioning of NICE and PBAC Decision Process

In both England and Australia, manufacturers are required to apply for their medicines to be publicly subsidized. In England, NICE provides guidance to the National Health Service within its program of technology appraisals. When NICE was initially set up in 1999, the evidence and analyses were supplied by both the manufacturer and an academic assessment group. Since introducing a Single Technology Appraisal (STA) process in late 2005 (a process which imitated—to a large extent—the process used by PBAC), the evidence and analyses have been principally provided by the manufacturer [16], and evaluated by an independent evidence review group. In Australia, applications for listing of medicines on the Pharmaceutical Benefits Scheme are independently assessed by PBAC, which then provides advice to the Federal Minister for Health. In both countries, the manufacturer is required to carry out an economic evaluation as part of a submission presented in support of the application. More details of the submission processes are described elsewhere [4,17–20].

Selection of Submissions/Data Extraction for the Study

English data were sourced from publicly available NICE technology appraisals from the inception of STA until May 2015. The treatment, clinical indication, population, comparator, manufacturer, submission date, and ICER were extracted from all submissions to NICE over the period of interest. Corresponding Australian data were obtained from confidential commentaries on submissions to PBAC, the advice of PBAC's Economics Sub-Committee and PBAC meeting minutes. We identified all submissions from the same sponsor for the same medicine, that were evaluated by both NICE and PBAC for the same clinical indication within the same population, and in which the cost effectiveness of the proposed medicine was compared with that of the same existing treatment. We only included submissions in which an ICER was expressed in terms of cost per QALY gained. As we were interested in the behavior of manufacturers in submitting their initial economic evaluation, only submissions in which the manufacturer sought listing of the medicine for the specific indication and population for the first time were included. If the ICER was revised during the evaluation process, the original estimate was used. The extracted data were double-checked by a second researcher and discussed with team members, when necessary.

To ensure comparability of ICERs, the scenario that was most comparable between English and Australian submissions was chosen (i.e., same intervention and comparator, with the same dosage regimen). To ensure that only the original ICERs proposed by the manufacturers were analyzed, resubmissions were only included if the original submission did not present the result in terms of the incremental cost per QALY gained, or if the requested listing in the resubmission was revised and was more consistent with that in the counterpart submission.

Statistical Analysis

We compared the ICERs in the submissions to NICE with those in the corresponding submissions to PBAC by analyzing the matched pair data. To enable the comparison, ICERs were converted into international dollars per QALY gained (Int$/QALY) using purchasing power parity (Total) conversion factors reported for the year of submission [21]. We also compared the ICERs in both submissions to NICE and PBAC with NICE's threshold. The upper and lower limits of NICE's threshold (£30,000/QALY and £20,000/QALY) were also converted from pound sterling to international dollars using purchasing power parity reported for the respective year of NICE and PBAC submissions. First, we examined the distributions of the ICERs and of the differences between the initial ICER and NICE threshold. Second, we conducted a Wilcoxon signed-rank test for the matched pair data to determine if the proposed ICERs submitted to NICE differed significantly from those in the matched submissions to PBAC. Third, we presented Bland-Altman analyses for the paired submissions to determine the level of agreement between the submitted ICERs. Finally, we tested whether an implicit threshold was affecting submissions to PBAC. We assumed an explicit threshold of £30,000/QALY for NICE (upper limit of the range) and an implicit threshold of AUD$50,000/QALY for PBAC and compared the proportion of the matched English and Australian ICERs above or below the respective threshold (McNemar's chi-squared test). As NICE's threshold of £20,000 to £30,000 per QALY gained has

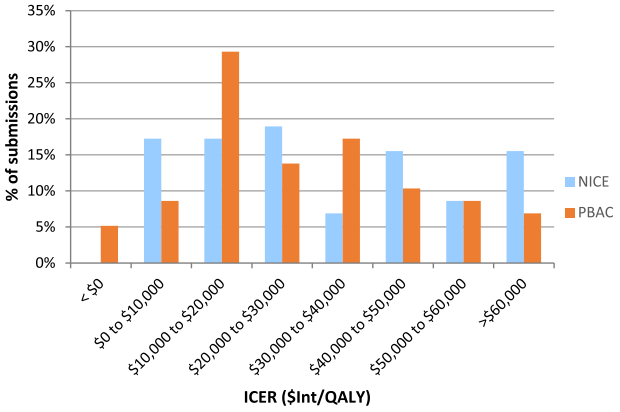

Fig. 1 – Distribution of ICERs.

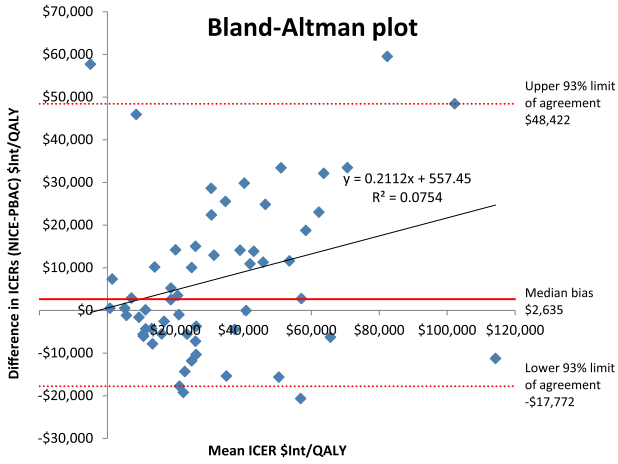

Fig. 3 – Bland-Altman plot.

remained the same in NICE's method guidance since 2004 [22], and as it is also debatable whether the threshold should change over time [23], a constant threshold value in pound sterling or in Australian dollars has been used in this study.

Results

We identified 58 pairs of ICERs in submissions to NICE and PBAC. The distribution of ICERs is presented in Figure 1.

The difference between the ICERs (in both submissions to NICE and PBAC) and NICE's threshold was calculated, and is presented in Figures 2A and 2B.

The majority of both NICE and PBAC ICERs fell below NICE's specified threshold of £30,000/QALY, with the proportion being 69% and 79%, respectively. About 22% of NICE ICERs were within ±$Int10,000/QALY when compared with the threshold of £30,000/QALY, whereas the corresponding proportion for PBAC ICERs was 17%. The same analysis was performed using NICE's threshold of £20,000/QALY and 24% of NICE ICERs were within ±$Int10,000/QALY when compared with the threshold, whereas the corresponding proportion for PBAC ICERs was 34%. Of NICE ICERs and PBAC ICERs, 54% and 60%, respectively, fell below NICE's threshold of £20,000/QALY.

The ICERs were, on average, Int$7,393 higher in the submissions to NICE (mean Int$36,060/QALY) than in the submissions to PBAC (mean Int$28,667/QALY), although the differences between the paired ICERs were not normally distributed. On the basis of the matched pair data, we found that the median difference (Int $2,635/QALY) between the ICERs presented to NICE and those presented to PBAC was significantly greater than zero (Wilcoxon signed-rank test, $P = 0.0299$).

The Bland-Altman analysis is presented in Figure 3. As differences between the paired ICERs are not normally distributed, we presented 3.5 percentile and 96.5 percentile of the distributions [24]. On 93% of occasions, NICE ICERs were within –Int$17,772 to +Int$48,422 of the corresponding PBAC ones. These limits of agreement were wide, indicating poor agreement between the proposed ICERs in the submissions to NICE and PBAC.

Given the previously stated industry assumption that there is an implicit willingness-to-pay threshold of AUD$50,000/QALY in Australia, we compared the proportion of the matched NICE and PBAC ICERs above or below their respective thresholds. Of the 58 submissions to NICE, 69% (40 of 58) had an ICER equal to or lower than £30,000/QALY. Similarly, 69% of the submissions to PBAC had an ICER equal to or lower than the assumed threshold of AUD$50,000/QALY. Thirty-six pairs (62%) of submissions fell below the respective thresholds, and 14 pairs (24%) fell above the respective thresholds. There were four pairs each of submissions that had discordant results in both directions. The McNemar's chi-squared test indicated that for a threshold of £30,000/AUD$50,000 per QALY gained, there was no statistically

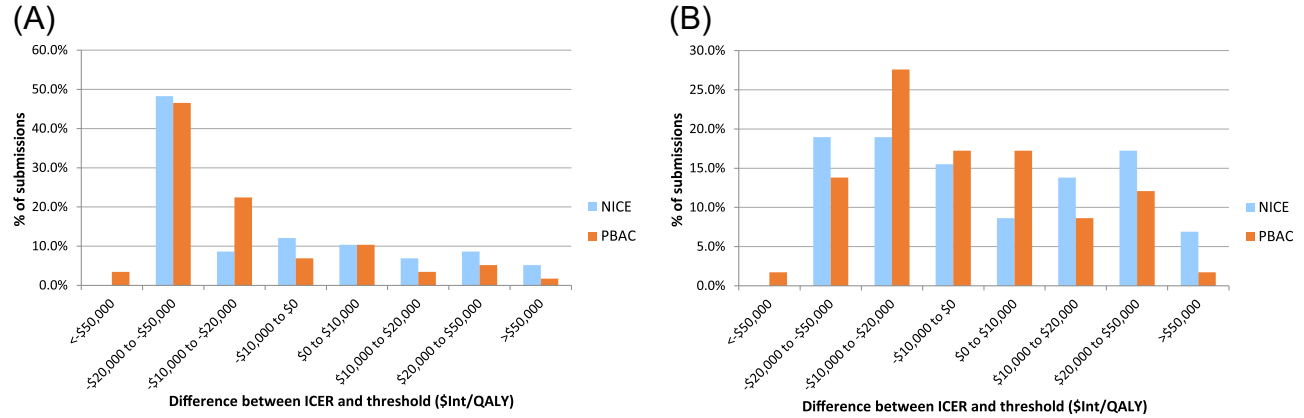

Fig. 2 – A, Distribution of differences between ICER and NICE threshold of £30,000/QALY. B, Distribution of differences between ICER and NICE threshold of £20,000/QALY.

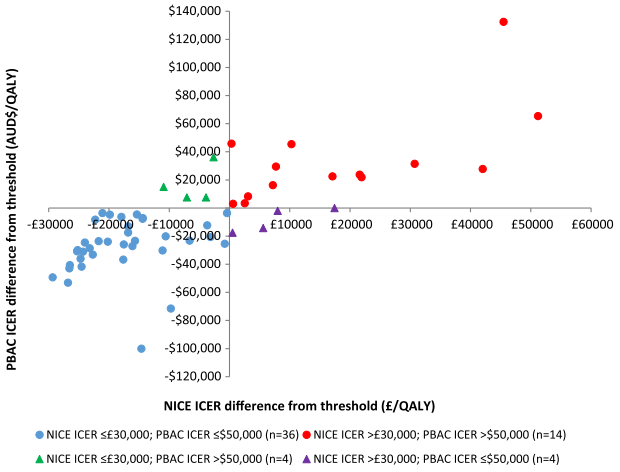

Fig. 4 – The number of NICE and PBAC submissions with an ICER above or below their respective thresholds (NICE explicit threshold £30,000/QALY and PBAC assumed implicit threshold AUD$50,000/QALY). McNemar's chi-square = 0.00; Prob > chi-square = 1.00.

significant difference in the number of mismatched pairs above or below the nominated thresholds (Figure 4).

To examine whether submissions to one decision-making body consistently preceded the submission of the matched application to the other decision-making body, we found that among the 58 pairs of submissions, 17 pairs (nearly 30%) were reported in the same calendar year, whereas 32 submissions (55%) to PBAC preceded those submitted to NICE. Submissions to NICE were more likely to be after their matched submissions to PBAC within our sample. The proportion of PBAC submissions with a higher or lower ICER, compared with the matched NICE submissions, did not seem to change with the relative timing of the two submissions. There was no clear evidence from our study that the manufacturers learnt from the experience of submitting to one reimbursement authority and consequently adapted the ICERs in their submissions to the other.

Discussion

This study compared the ICERs proposed in submissions to NICE with the ICERs in matched submissions to PBAC and found that NICE ICERs were, on average, higher than the corresponding PBAC ICERs, and the difference between the paired ICERs was statistically significant.

The lower ICERs observed in the submissions to PBAC compared with those in the submissions to NICE could be a result of a range of factors, including true differences in the use of health resources and/or expected health outcomes in the two countries, as well as the behavior of manufacturers in tailoring submissions to meet the expected decision making criteria to increase the chances of receiving public funding approval.

In comparison with the willingness-to-pay cost-effectiveness threshold values, the majority of the submissions had an ICER equal to or lower than the respective threshold value (either explicit or implicitly assumed) in both jurisdictions, and the submissions were fairly consistent with regard to whether they fell above or below the explicit/implicit threshold within the matched pairs. These results suggest that manufacturers believe there is an implicit willingness-to-pay threshold for PBAC decisions. Whether the threshold is explicit or implicit does not appear to affect the decision to submit an ICER that is higher or lower than the purported cost-effectiveness threshold, although the magnitude of the ICER may be different. This likely results from the fact that the sponsors of the submissions treat explicit and implicit thresholds equally. As value for money is one of the major considerations in decision making, it is also possible that manufacturers do not present submissions for reimbursement of medicines for which the ICER is considerably higher than the known or expected threshold unless there is a strong justification for it.

It is widely accepted that regardless of whether an explicit or implicit cost-effectiveness threshold is used when making coverage decisions, a number of other factors, in addition to willingness to pay, play an important role in decision making, such as scientific rigor, degree of uncertainty, and the innovative nature of the technology, as well as the severity of the disease, existence of alternative treatments, licensing for end of life treatment, and small populations [7,10,25]. An earlier modelling study indicated that cost effectiveness, together with uncertainty of the evidence and the burden of disease, explains NICE's decisions better than cost effectiveness alone [25]. Harris et al. also found that willingness to pay in PBAC decision making is clearly related to the characteristics of the clinical condition, perceived confidence in the evidence of effectiveness and the relevance of the evidence, as well as total cost to government [7]. Given that, in our study, we have chosen the paired submissions for the same medicine with the same indication, population, and comparator, the evidence base of the submission and the clinical condition are unlikely to have a substantially differential impact on decision making, although the two decision-making authorities may value these additional factors to a different degree. It is anticipated, therefore, that the paired comparison in this study is less likely to be impacted by these factors of decision making.

The discrepancy in ICERs in the submissions to PBAC and NICE could be a result of the differences in health system and clinical practice, as well as the consequent differences in the use of health resources. Previous studies on the generalizability of economic evaluations from one location to another have indicated that variations in health systems and clinical practice, and differential resource use and unit prices across regions and countries, may potentially have a large influence on transferring the results of economic evaluation from one country to another [26,27]. In future research, it would be informative to collect data on the cost and outcome components of the economic evaluations and examine whether these inputs are potentially causing the differences in the resulting ICERs between countries.

The existence of an explicit threshold may have contributed to the observed differences in ICERs to NICE and PBAC. With a publicly stated explicit threshold for NICE, the sponsors would have more certainty in targeting the threshold value. For the sponsors preparing submissions to PBAC, the threshold value is more uncertain, and thus a lower ICER may have been presented in the hope of increasing the chance to get a positive decision. Unfortunately, this study was unable to test this hypothesis without controlling for all other factors that could influence decision making and, consequently, the presented ICERs.

In addition, mechanisms for reimbursement decisions and funding differ between these two countries [28]. NICE is responsible for developing guidance but is not obliged to fund the recommended technologies or negotiate or publicly set prices [29]. Budget impact was not a factor in NICE decision making until April 2017, when a budget impact test was introduced for technologies within the Technology Appraisal programs [30]. In contrast, in Australia, over the period covered in this study, PBAC was, and still is, required to consider the costs and consequent budget impact of the proposed

medicines and negotiate the price with the manufacturers, if required, because the costs of newly listed medicines must be met within the existing health budget. When the listing of new medicines has an enormous opportunity cost, PBAC may adjust its cost-effectiveness threshold so that the budget impact is manageable. For example, when considering new interferon-free medicines for the treatment of hepatitis C, PBAC stated that "these treatments would be cost effective at $15,000/QALY" [31]. The flexibility to adjust the willingness-to-pay threshold in consideration of budget impact in PBAC's decision-making process may have affected the manufacturers' behavior in preparing submissions and may partly explain why the ICERs in the submissions to PBAC are, on average, lower than those in submissions to NICE.

One limitation of our analysis was the possible impact of major policy changes on NICE processes—such as the end-of-life decision making scheme, which was introduced in 2009, and the availability of the Cancer Drug Fund from 2011 (amended in 2016). The end-of-life criteria adopted by NICE allow interventions with an ICER over £30,000/QALY to be recommended [5]. It would potentially have been informative if we could have compared the ICERs between the two jurisdictions in subgroups of end-of-life treatments or non–end-of-life treatments. Unfortunately, we were unable to perform such an analysis, given the small sample size, but this could be attempted in the future with updated data collected over a longer period.

To our knowledge, ours is the first study directly comparing the ICERs proposed in submissions to the two decision-making bodies.

Conclusions

Using publicly available (NICE) and confidential (PBAC) data about the incremental cost effectiveness of medicines in two countries, we compared the ICERs in paired submissions to PBAC and NICE and found that, on average, the ICERs in the submissions to PBAC are statistically significantly lower than those to NICE. When an implicit AUD$50,000/QALY threshold was also assumed for PBAC decision making, the submitted ICERs to NICE and PBAC were largely consistent in being above or below their corresponding threshold. This suggests that industry is assuming an implicit cost-effectiveness threshold for PBAC of AUD$50,000/QALY when constructing its ICERs despite the lack of acknowledgement, or evidence, for such a threshold. It also appears that the existence of an explicit or implicit threshold does not affect the decision to propose an ICER that is higher or lower than the threshold. Although the exact reasons for the observed differences between the ICERs in the submissions to the two decision-making bodies are not elucidated by this study, the differences in the health systems, clinical practice, and funding mechanisms in these two countries could have contributed to the observed differences between the paired ICERs, along with NICE's stated willingness to pay.

Further research is warranted to examine the reasons for the differences in the ICERs between these two countries and to provide clarity on the factors that influence the public funding of new medicines.

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