Valuing Life - Decision-Making for Medicines in Australia: A Retrospective Analysis (2020-2023)

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INTRODUCTION

- The value of a life and how it is measured and used in health economic evaluation and reimbursement decisions has been a debated topic for decades.
- It has been argued the value attributed to a person's life in the Australian health care system is less than as in other parts of the Australian government and has not been increased since the early 2000s (Dunlevy, 2023).
- Funding for new healthcare technologies is an important area of government health expenditure in Australia, with the Pharmaceutical Benefits Advisory Committee (PBAC) making recommendations on drugs covered under the Pharmaceutical Benefits Scheme (PBS). Legislation requires PBAC to only recommend medicines which are "cost-effective" but does not define what "cost-effective" means.
- There has been some research into exploring the definition of "cost-effectiveness" in Australia, with several studies published looking into submissions to the PBS specifically, to determine the characteristics of a submission that lead to a positive decision for a medicine.
- One paper (Harris 2008) used a quantitative analysis to elicit the role of value for money in public insurance coverage decisions for drugs in Australia. The study was a retrospective analysis of all major submissions to the PBAC between 1994 and 2004 and tried to determine the relative influence of factors in decisions for new drugs in Australia by using a probit multiple regression model to explore multiple variables.
- Harris (2008) did not find evidence of any single threshold value of cost-effectiveness, but the results did suggest that there has been a strong relationship between perceived value for money (i.e., ICER) and the likelihood of public reimbursement for drugs in Australia.

References:

Dunlevy, S. (2023), Price of a life: Australians wait two years longer for breakthrough medicines than US citizens, News Corp Australia Network, The Daily Telegraph.

Harris AH, Hill SR, Chin G, Li JJ, Walkom E. (2008). The Role of Value for Money in Public Insurance Coverage Decisions for Drugs in Australia: A Retrospective Analysis 1994-2004. Medical Decision Making. 28(5):713-722.

OBJECTIVE

- The objective of this study was to analyse recent PBAC decision-making using the same methodology as Harris (2008) to understand if the absolute level of value of life implicit in this decision making has shifted in more recent years and if so, the factors contributing to the PBAC's decision making.

METHODOLOGY

Method of Data Extraction

- Evidence presented as public summary documents (PSDs), was used to investigate the relationship between submission components – such as the incremental cost-effectiveness ratio (ICER), financial impact, disease severity and evidence base – and the likelihood of a positive recommendation for public funding.
- All major submissions to the PBAC between March 2020 and March 2023 where the PBAC decision relied upon a cost-effectiveness analysis (n=202) were considered.
- An Excel database was created based on the variables codified in the Harris (2008) paper (e.g., "PBAC outcome" = Recommended, Rejected, Deferred; "ICER" = $reported, "Life threatening" = 1 (if yes), 0 (if no), see **Figure 1**) and additional variables thought to be of interest in this analysis ("Rare", "Number of resubmissions", "Co-dependent").
- Data extraction/review of PSDs was split randomly amongst, and conducted by, experienced Health Technology Assessment consultants.
  - Extracted data was reviewed by a second consultant (for double checking/conflict resolution and data cleaning).

Data Item	Description	Scoring
Incremental cost per QALY	Incremental cost per additional QALY	$0,000[a]
Cost to government	Annual predicted additional financial cost to government of listing	$m
Clinical significance	Did the PBAC consider the size (point estimate) of the treatment effect to be clinically important	1 = Yes 0 = No
Precision of clinical evidence	Statistical reliability of the measure of the size of the treatment effect	P ≤ 0.05 = 1 P > 0.05 = 0
Level of evidence	What is the level of the key clinical evidence presented to the PBAC?	Head-to-head RCT = 3 Indirect comparison RCT = 2 Nonrandomized = 1
Quality of studies	12-item checklist on selection and absence of bias in trial design and analysis[b]	High quality = 3 Moderate quality = 2 Low quality = 1
Relevance of evidence	Comparator and population in trial appropriate	1 = yes 0 = no
Life threatening	Condition associated with premature mortality (< 5 year survival)	1 = yes 0 = no

Figure 1: Examples of variables extracted and scored (codified)

Method of Data Analysis

- The data were analysed firstly on R software to capture descriptive statistics (e.g., distribution of PBAC outcomes [recommended, rejected, deferred], proportion of submissions with life-threatening or rare diseases, etc.).
- The probability of recommending a medicine for funding was estimated using multivariate probit regression models, similar to the Harris (2008) analysis, and analysed on R software.
- In the multivariate regression model the outcome variable (PBAC outcome) was coded as "Recommended" (1) or Rejected/Deferred (0).
- Results were compared to the Harris (2008) analysis.

RESULTS: Summary Statistics

Table 1: Summary and comparison of data with Harris (2008)

Variable	THEMA, 2023 (n=202)	Harris, 2008 (n=103)
PBAC Outcome		
Recommended	81 (40%)	31 (30%)
Rejected	101 (50%)	48 (47%)
Deferred	20 (10%)	24 (23%)
Rarity of disease		
Rare	81 (40%)	NR
Not rare	121 (60%)	NR
Life-threatening disease		
Life-threatening	83 (41%)	18 (17%)
Not life-threatening	119 (59%)	85 (83%)
Alternative therapy options		
Alternative therapy available	82 (41%)	46 (45%)
No alternative therapy options	120 (59%)	57 (55%)
Co-dependent submission		
Co-dependent	19 (9%)	NR
Not co-dependent	183 (91%)	NR
Considered before		
Previously considered	102 (51%)	65 (63%)
Not previously considered	100 (49%)	38 (37%)

Note: NR, not reported.

Overview of data

- In total, 202 cost-effectiveness submissions were reviewed by THEMA (2023), covering the PBAC meetings between March 2020 and March 2023, while the Harris (2008) analysis reviewed a total of 103 submissions for the period between 1994 and 2004 **(Table 1).**
  - The proportion of recommendations and deferrals increased in the latest analysis, with a similar rate of rejections.
  - Approximately 40% of submissions in the recent analysis were for "rare" conditions, "life-threatening" conditions and for therapies that were not first-line.
  - More "life-threatening" conditions were seen in the recent analysis, while a similar proportion of first-line therapies were submitted compared to the Harris (2008) analysis.
  - Approximately 9% of submissions were co-dependent in the recent analysis (i.e., also considered by The Medical Services Advisory Committee [MSAC] for co-dependent technologies).
  - Fewer submissions (51%) have been considered previously (i.e., resubmissions) in the THEMA (2023) analysis compared to the Harris (2008) analysis (63%).

PBAC outcomes across ICERS

- There appears to be no correlation between the different ICER categories and the PBAC outcome, with the distribution of decisions very similar across ICERs **(Figure 2).** While the ICER is a significant predictor for the probability of recommendation (see regression analysis below), the relationship is not as strong as in the Harris (2008) analysis **(Figure 3).**

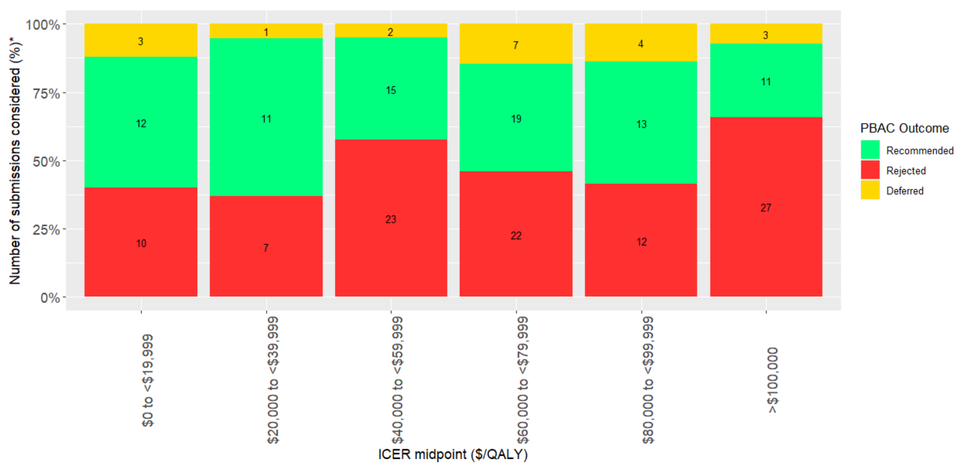

Figure 2: PBAC Outcomes across ICER categories

Note: The y-axis refers to percentages (%), while the numbers written on the stacked bars are absolute numbers (#).

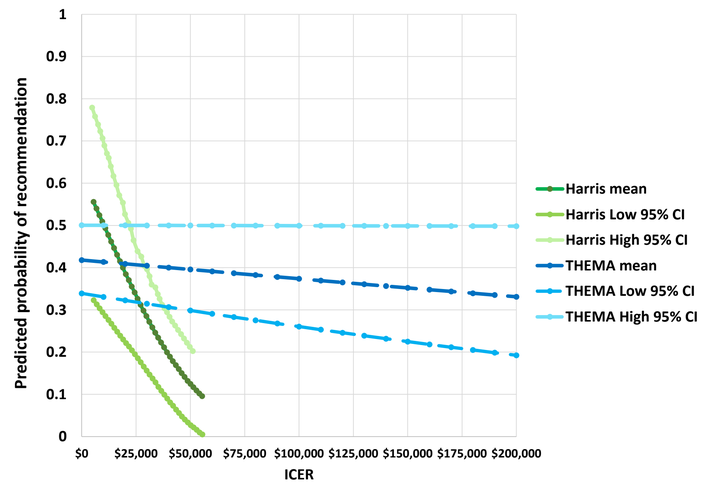

Figure 3: Probability of PBAC recommendation against ICER (Harris 2008 vs THEMA 2023)

RESULTS: Regression Analysis

Marginal effects of recommendation

- The best fitting THEMA (2023) regression model (based on log likelihood and AIC) was compared to the best fitting Harris (2008) regression model (reported).
- The recent analysis (THEMA 2023) shows higher overall means **(Table 2)** for all variables compared to Harris (2008).
- The proposed ICERs and costs to the government are higher in the recent analysis, with more submissions presenting clinically significant and with relevant trial evidence.
- There were less resubmissions and more submissions for life-threatening diseases in the recent analysis.
- Cost-effectiveness (i.e., the ICER), does have a significant effect on recommendation in the recent analysis, however, the marginal effect is small overall, whereas the ICER had a greater marginal effect on decision making for drugs in Harris (2008).
- Uncertainty analysis on the ICER, cumulative cost to government, life-threatening conditions, clinical significance, evidence from RCT studies and relevant evidence were not significant in the recent analysis.
- First-line therapies, economic model validity and the number of resubmissions appear to have a significant effect in the recent analysis.
- The recent analysis additionally showed rare conditions to be a significant driver of a positive PBAC outcome.
- Overall, it appears the absolute and relative influence of factors in decision making of new medicines in Australia has changed over time. All else equal, the value of life (i.e., the ICER) appears to be becoming less influential in PBAC decision making.

Table 2: Probit Regression Results Eliciting Influential Factors for the Decision to Recommend Listing (Harris 2008 vs THEMA 2023)

	THEMA 2023 (n=202)		Harris 2008 (n=103)	
Variable	**Mean**	**Marginal Effect^**	**Mean**	**Marginal Effect^**
ICER ($0,000 mid-point)	1.18	-0.0212*	4.6	-0.06**
Uncertainty of ICER ($0,000 mid-point)	2.52	0.0041	1.95	0.002
Annual gov. cost ($m mid-point)	42.72	NA	17.28	-0.01*
Cumulative gov. cost ($m mid-point)	159.10	-0.0003	NA	NA
Life-threatening disease	0.41	-0.0652	0.17	0.44**
Rare disease	0.40	0.3681**	NA	NA
No alternative therapy available	0.41	-0.1452*	NA	NA
Resubmission (considered before)	0.50	0.2414*** +	0.63	0.15*
Clinically significant	0.61	-0.0046	0.50	0.28**
Level of evidence (RCT)	0.79	-0.2396	NA	NA
Relevant trial evidence	0.65	0.0977	0.56	0.12
Flawed validity of economic model	0.46	-0.6187***	NA	NA
Clinically significant * life-threatening disease	0.27	NA	0.12	-0.23**

Note: ^The "marginal effect" is the change in the probability of recommending a listing for a unit change/increase in each variable ($10,00 for ICER and Uncertainty in ICER, $m in gov. costs, and 1 for categorical variables), with all other variables set at their mean. +Resubmissions modelled as the number of resubmissions in the THEMA analysis.
* p<0.05; ** p<0.01; *** p<0.001; Gov, government; NA, not applicable; RCT, Randomised Control Trail.

LIMITATIONS and CONCLUSIONS

- The results of this analysis should be interpreted in the context of its limitations including:
  - PSDs lack full information/granularity (e.g., ICER only reported as a range, therefore used mid-point) and information on some data items was not available or interpretation was uncertain.
  - Assessors were not strictly blinded, introducing investigator judgments/biases made on the scoring of items.
  - Comparisons with the results of Harris (2008) should be made with caution as Harris and co-authors did have full access to PBAC minutes. Nevertheless, the shift in the impact of the ICER on PBAC decision making is likely to be greater than the impact of these limitations.
- First-line therapies (p<0.05), economic model validity, number of resubmission (p<0.001), and rarity of disease (p<0.01) were all found to be statistically significant factors influencing the listing of medicines in Australia in the recent analysis, differing from Harris (2008).
- The ICER did have an independent statistical influence on decision-making (p<0.05), however, had a small marginal effect compared to Harris (2008).
- Life-threatening diseases and cost to government were not flagged as statistically significant in the recent analysis (p>0.05), also differing from Harris (2008).

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