Bring out Your Dead: A Review of the Cost Minimization Approach in Health Technology Assessment Submissions to the Australian Pharmaceutical Benefits Advisory Committee

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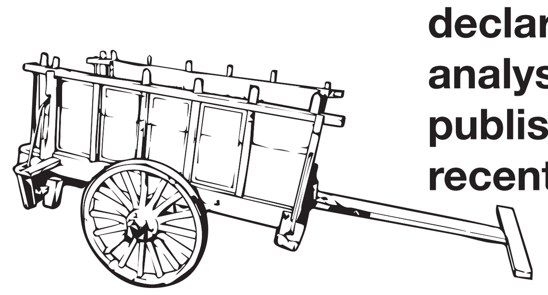
The Context

Bring out Your Dead:



Two decades ago, Briggs and O'Brien declared the death of cost minimization analysis (CMA). While subsequently published literature supported that claim, recent sources confirm its widespread use.

Timeline of publications on cost minimization

2001

'We pronounce the (near) death of CMA...'

Briggs and O'Brien
The Death Of Cost Minimization Analysis?
Health Economics, 2001. 10(2): p.179-184

2013

'CMA is not only dead but it should also be buried'

Dakin and Woodsworth
Cost-Minimization Analysis Versus Cost-Effectiveness Analysis, Revisited
Health Economics, 2013. 22(1): p.22-34

2019

'The opinion that CMA is inappropriate in most situations has strengthened over the last two decades'

Wailoo and Dixon
Report bt the NICE Decision Support Unit
The Use Of Cost Minimization Analysis For The Appraisal of Health Technologies

2020

'In day to day life, unless somebody is telling them two drugs are really different, [the most commonly used economic evaluation approach for formulary decisions in the US] is probably the cost minimization [approach]'

SOA Podcast - Society of Actuaries
Health Section: *Pharmacoeconomics, Oct 2020*

268 of the 514 (52%) new medicines recommended by the PBAC in Australia between 2010 and 2018 were on the basis of a CMA

Lybrand and Wonder
Analysis of PBAC submissions and outcomes for medicines (2010-2018)
International Journal of Technology Assessment in Health Care, 2020. 36(3): p. 224-231.

What is cost minimization analysis?

CMA reduces the assessment of alternative treatment options to comparing costs under certain conditions.
The benefits of using a CMA include:

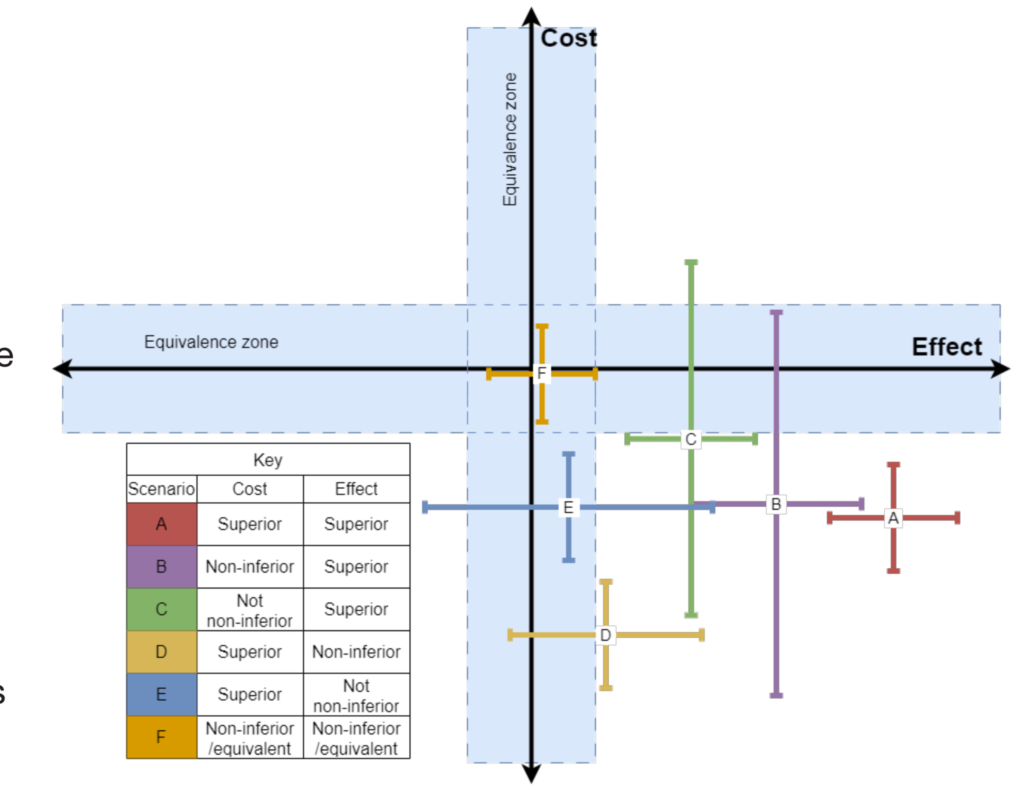
- It avoids the model risk associated with other economic evaluation approaches, such as determining the incremental change in effectiveness.
- The introduction of the medicine should be budget neutral, although this may vary.

Theoretically sound CMA requires:

1. **Clinical evidence:** clinical trials must support a conclusion of equivalence or non-inferiority
2. **Non-inferiority:** non-inferiority must be based on health outcomes that do not include a clinically meaningful difference within its confidence interval
3. **Outcomes:** outcomes include both efficacy and safety, and may need to include secondary health outcomes to support the overall claim of non-inferiority
4. **Safety:** the safety profile (& potentially the delivery/ convenience considerations) should not be different
5. **Costs:** costs should include the total cost of care over a relevant period, not just the cost of the medicine(s)

Challenges with using CMA include:

- **Interpretation of evidence:** Clinical trials that fail to demonstrate the superiority of any treatment option can be misinterpreted as indicating an absence of difference and inappropriately used to justify CMA.
- **Scope of evidence:** Evidence is rarely generated to establish non-inferiority for the full range of potentially relevant health outcomes, intermediary outcomes, and safety information.
- **Statistical uncertainty:** Alternative treatment options will generally not be identical across all dimensions, even if they are truly equivalent
- **Relevance of information:** Accepting equivalence of the treatment options may obfuscate the relevance of differences in point estimates to include in cost estimates
- **Application of judgment:** Establishing a non-inferiority margin can be difficult or considered arbitrary, indicative, or irrelevant
- **The range of comparisons:** A new medicine may have multiple indications and various comparators.



The cost-effectiveness plane allows for displaying different potential scenarios for comparing a new medicine with alternatives. For example, more costly and more effective medicines are plotted in the top right.

CMA is appropriate when relevant confidence intervals (e.g. effect and safety) do not include clinically relevant differences - outside of the equivalence zone. Of the six scenarios plotted, only A, B, D, and F are appropriate for CMA

The Research

Objectives

1. To identify the factors that influence recommendations by the PBAC regarding the subsidy of medicines based on CMA including factors and uncertainty that can be managed by the pharmaceutical company's market access team (i.e. its risk management of the submission process).
2. To assess whether the PBAC adheres to the appropriate application of CMA and the PBAC Methodology Guidelines.

Background

In Australia, the PBAC recommends which medicines receive public subsidy through the Pharmaceutical Benefits Scheme (PBS).

The PBAC methodology guidelines suggest that CMAs should be used when the evidence aligns with the more robust definition (outlined above).

Past assessments of recommendations by the PBAC either exclude CMAs or include them with other economic evaluation types, thereby obfuscating the importance of key factors. Of the six most influential factors identified as important in past research, three are irrelevant for CMAs - budget impact, the incremental cost-effectiveness ratio (ICER), and the ICER's uncertainty.

Consequently, the other three factors (trust in the clinical evidence, severity of disease, and whether the medicine had previously been considered) would be confounded for CMAs, preventing meaningful conclusions without a focused assessment.

Key details of analysis

Data sources: Public Summary Documents (PSDs) provide the rationale and information supporting the PBAC recommendation, including 'information on the clinical and cost-effectiveness of medicines' relative to its comparator.

Process: Relevant information was extracted from PSDs of cost-minimization submissions assessed between 2005 and 2022. Deferred submissions are excluded from this analysis. A second reviewer independently collected a 5% sample of submissions to assess consistently.

Theoretically justified variables:

T1: The potential for inferior safety was suggested;
T2: The potential for inferior efficacy was suggested;
T3: Having a different safety profile from its comparator; and
T4: A nominated non-inferiority margin was exceeded.

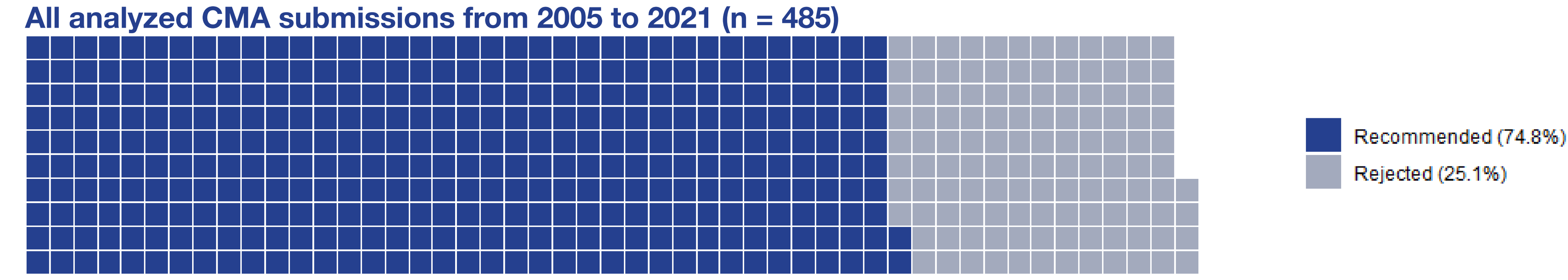
Statistical analysis: One-way statistical analysis was performed on the collected variables. A generalized linear model was fitted, with the four theoretically justified control variables fitted. Other variables were selected through iterative feature selection using the Bootstrapped LASSO method for the stability of selected variables.

Key challenges and limitations:

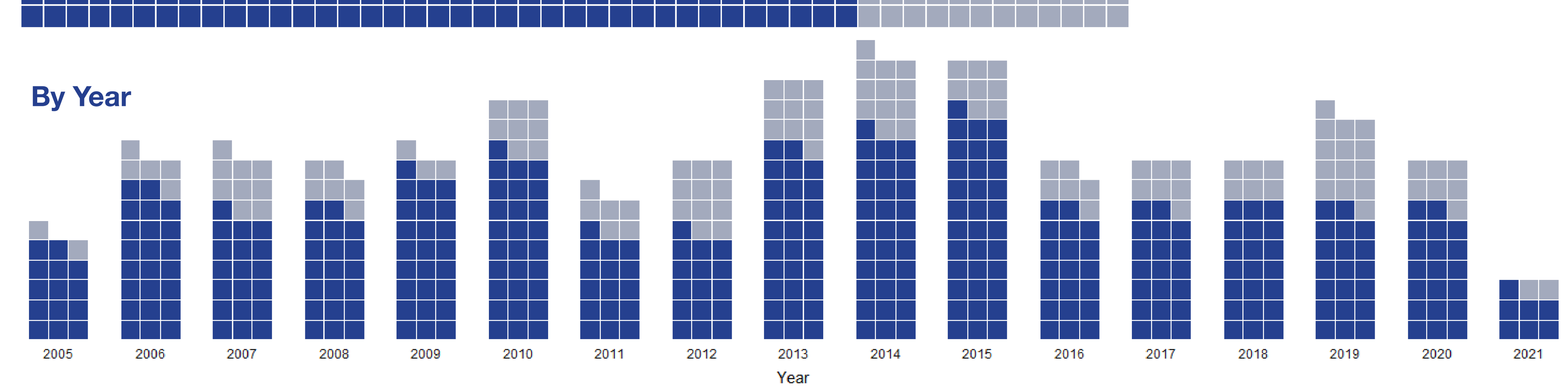
- Defining and recording consistent thresholds for qualitative descriptions of the deliberation process, which is critical to the outcomes of this research.
- This recording process is ultimately subjective - but the final dataset will be published for scrutiny.
- Fulsome information is not publicly reported.
- The level of information in PSDs was not consistent, often related to the ultimate recommendation (or rejection).
- The use of CMA is (mostly) a sponsor's choice, so there may be self-selection influencing the use of CMA.
- Analysis reflects major submissions between July 2005 and March 2021, but future work will expand the analysis dataset to incorporate 2021-22 and additional variables.

Results

All analyzed CMA submissions from 2005 to 2021 (n = 485)

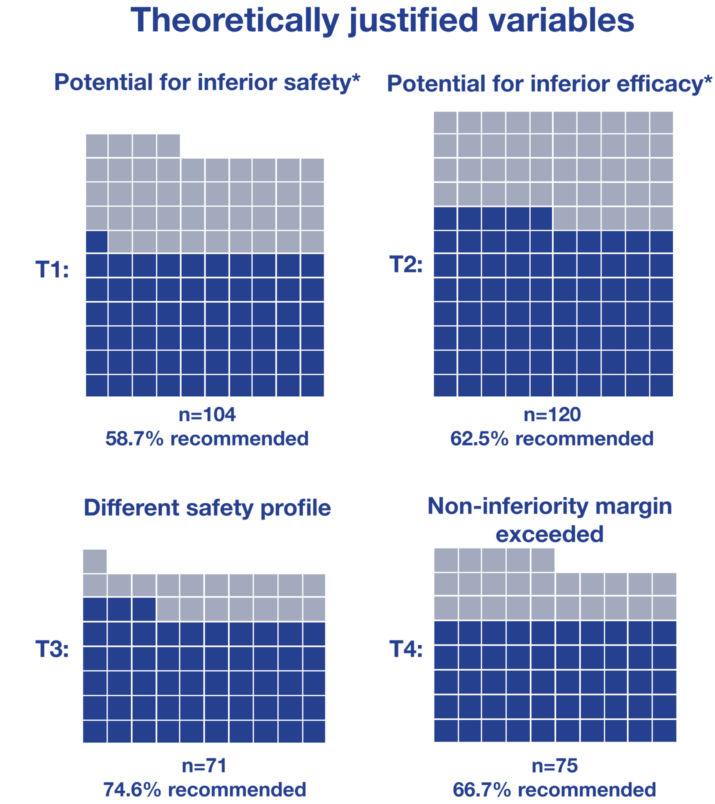


By Year



Note: one square = one submission
*** indicates p-value < 0.05**

Theoretically justified variables



Variables selected by the bootstrap LASSO model

Variable	Coefficient
Intercept	1.14*
Potential for inferior safety (T1)	-1.01*
Only unfavorable point estimates	-0.94*
Immunosuppresent medications	1.30*
Only one comparator influences the recommendation	0.69*
Potential for inferior efficacy (T2)	-0.56*
Month of assessment (cosine)	0.33*
Listing sought for more than one population	0.66
Different safety profile to comparator (T3)	0.08
The nominated non-inferiority margin was exceeded (T4)	-0.08

Discussion & Conclusion

- While the variables tested for our theory do lead to a lower likelihood of recommendation, the Methods Guidelines suggest these submissions should be excluded from using CMA and instead should use cost-effectiveness analysis.
- The Methods Guideline defines a process not strictly followed in practice based on the findings, that include:
  - The potential for inferior efficacy was raised in 120 submissions and 85 of these were recommended (T2).
  - Neither a different safety profile (T3) or a non-inferiority margin being exceeded (T4) were statistically significant in the model, and the former has the same rate as overall.
- Key stakeholders in Australia should consider whether the approach accepted for cost-minimization is appropriate or whether the Methodology Guidelines require revision.
- Non-adherence to the Guideline has negative consequences:
  - It reduces the ability of a pharmaceutical company to confidently predict an outcome for a new medicine.
  - It could introduce inferior medicines resulting in patients having suboptimal outcomes.
  - This would also increase costs to the healthcare system.

Implications for US healthcare

- CMA may be the most widespread economic evaluation approach in formulary decisions by healthcare payers in the United States.
- CMA aligns with the mandate of the Centers for Medicare and Medicaid Innovation (CMMI) for the demonstrations to reduce (or maintain) the cost of healthcare while improving (or sustaining) the healthcare quality. While in practice, the Office of the Actuary has not used CMA in conjunction with its statutory authority to expand CMMI demonstrations into Medicare or Medicaid, the approach could be applied with some modifications.