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Management of uncertainty in evaluating new medical technologies requires consideration of societal risk preferences and balancing risk.

- Uncertainty is an inherent part of the health technology assessment (HTA) evaluation process, potentially present in all aspects ranging from place in therapy, clinical treatment effect, duration of effect and economic and financial analysis assumptions and inputs
- Management of uncertainty should be shared between the sponsor and payer, although the low tolerance of risk among Australian decision makers frequently leads to rejected applications for funding
- Patient access to innovative medical technologies would be improved by a more balanced approach to managing uncertainty, including balanced risk-sharing between the sponsor and payer

Possible policy solutions

1. Develop an agreed framework to move to a more balanced risk position. The intent is for PBAC to adopt the most likely/plausible outcome rather than an overly cautious/conservative outcome during the evaluation therefore potentially enabling more first time PBAC recommendations. In the context of an individual submission this could include two new solutions:
    A. Introduce opportunities for interactions between the sponsor and evaluator to agree plausible assumptions early in the evaluation. Where there is disagreement, an alternative recommendation with appropriate justification should be made.
    B. Propose a meeting between ESC and the Sponsor to agree a base case economic model which represents the most plausible scenario. This effectively separates the modelling assumptions from the PBAC budget or price assumptions.[1]
2. Adopt the methodology for indirect comparisons accepted in other HTA countries (NICE in the UK, CADTH in Canada) for the purpose of demonstrating clinical superiority and

1 For example: similar style meetings occur in UK

cost-effectiveness. Other HTA agencies, such as NICE and CADTH, have developed detailed guidelines on the proper management of uncertainty that address this issue.

Why is uncertainty an issue?

A low tolerance for uncertainty is the status quo in Australia's HTA decision making processes and policies. As a result, the PBAC principally manages uncertainty by preferencing highly conservative scenarios and estimates.

It has become common practice to use uncertainty in clinical data, economic modelling assumptions and estimates of budget impact as a justification for reducing prices, imposing uneven or rigid risk-sharing arrangements and tightly restricting listings. Increasing tolerance for uncertainty within the Australian HTA system would result in arrangements with risk that is shared in a more balanced way between the industry and government.

Interpretation of clinical data

For some therapies, the conclusion of value is based on a single clinical outcome measure, e.g. overall survival. This narrow and conservative approach is particularly problematic for the evaluation of rare diseases and diseases with heterogeneous aetiology. The clinical significance of new treatments should also include other endpoints such as secondary clinical outcomes, patient reported outcomes and carer benefits to evaluate the value of innovative medications more holistically and help contextualise uncertainty.

Approach to translating clinical outcomes to economic modelling and view of long-term outcomes

Evaluations and considerations are often inconsistent with the PBAC guidelines or with accepted academic best practice. For example, the use of truncated time horizons, artificial waning of treatment effect, and forced convergence of modelled outcomes are frequently used to manage clinical and economic uncertainty. When combined, the result is an unsupported and clinically implausible value which significantly undervalues the additional benefit therapies offer (i.e. incremental QALY gain) and further reduces the price of medicines.

For HTA submissions with a clinical claim of superiority, the low tolerance for uncertainty associated with clinical evidence and its subsequent conservative application in modelled economic evaluation may materially impact PBAC decision making.

A common result of the current approach to managing uncertainty is delays in positive PBAC recommendations and therefore delays in patient access to new treatments, particularly for innovative medicines taking a cost-effectiveness approach. Between March 2021 and March 2022, the PBAC rejected 62 major (Category 1 and 2) submissions. Uncertainty in the ICER or magnitude of benefit was mentioned in 37 (60%) of the cases.[2] On average, it takes 2.2 submissions for medicines with superior efficacy claims supported by a CEA to receive a

2 *Commercial Eyes Analysis, Presented by Douglas Miller ARCS 2022*

positive PBAC recommendation compared with 1.2 submissions for medicines where a CMA approach is taken. [3]

Application of health economic analysis tools

Whilst the PBAC guidelines allow the use of tools such as indirect treatment comparisons (ITCs) and network meta-analyses (NMAs) for any submission, they are generally accepted only when a cost-minimisation approach is taken rather than to support a claim of clinical superiority and cost effectiveness. This has become an increasingly challenging paradigm over the past 10 years and will impact medicines access in the future. An example of why this is problematic is outlined in the box below.

The challenging paradigm - scenario:

- PBAC rejects a new therapy for reimbursement (medicine "A") and it is not available to patients.
- The next innovation (medicine "B") enters Australia – its RCT evidence has used medicine "A" as its comparator, however this doesn't reflect Australian clinical practice where medicine "A" is not used.
- Because medicine "B" has used a different comparator from what is locally available, the sponsor of medicine "B" must perform an ITC with the locally used medicine in its cost effectiveness submission – something which the PBAC does not accept routinely.
- Medicine B is rejected on the basis of uncertainty, which is inherent in an ITC, unless the sponsor accepts the cost minimised price. This approach also relegates real world evidence (RWE) to the role of minor assumption validation, rather than as supportive clinical evidence.

Approach to budget impact modelling

The PBAC recommendations appear increasingly focused on expenditure estimates and managing uncertainty by preferencing highly conservative assumptions, rather than the most likely assumptions, in estimates of budget impact. Accepted estimates of utilisation and expenditure frequently do not reflect optimal treatment of all eligible patients. As such, expenditure caps have become a duplicative tool that further reduces cost-effectiveness.

Feedback

Do you have any thoughts on the policy ideas in these papers? We'd love to hear your feedback! Please let us know at this email address: HTA-Reform@medicinesaustralia.com.au.

3 *MAESTrO Database. Analysis of PBAC submissions and their related outcomes & timelines. December 2020*