



RISKY BUSINESS: DECISION MAKING IN HEALTH CARE WITH ECONOMIC MODELLING UNCERTAINTY

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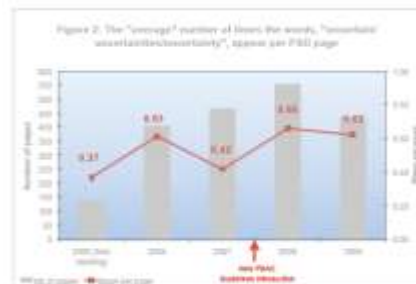
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LOOKING BACK: THE TREND APPEARED TO BE INCREASED UNCERTAINTY


These new Guidelines sought to reduce the uncertainty for the PBAC. The results show that the "average" number of times that the words, "uncertain/uncertainties/uncertainly", appeared per PSD page was significantly higher after the new PBAC guidelines introduction.

The introduction of version 4 of the PBAC Guidelines in 2008 might have led to an increase in the complexity and, thus, uncertainty faced by PBAC during their deliberations around reimbursement of pharmaceuticals in Australia. There was a significant 25% increase in the number of times that the words, "uncertain/uncertainties/uncertainly", were found per PSD page compared with the period prior to the introduction of the version 4 of the Guidelines (2003-2008).


Source:
Chollet, Lindsay and Gonzalo
Complexity increases
uncertainty: The impact of
PBAC Guidelines (version 4)
on PBAC decision making
4th Asia-Pacific ISPOR Meeting



WHAT WERE THE REASONS?

- Explicit gaps between clinical evidence available and economic evidence required
 - Methods have increased in sophistication
 - Uncertainty is inherent in the clinical data, but can be exaggerated by the economic claim
 - Modelling techniques cannot substitute for lack of data
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OTHER FACTORS AT PLAY: THE LANDSCAPE IS CHANGING

- Parallel process: clinical place may not be finalised
 - CED as an emerging international trend
 - High cost drugs as an emerging trend
 - Rare conditions, new more tailored treatments
 - New agents: more options in the treatment algorithm, more options for place in treatment
 - Shifting comparators
 - Pharmacogenomics (co-dependents, sub-groups)
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UNCERTAINTY?...SO WHAT?

- Uncertainty is a fact of life in HTA
 - Particularly for the ICER (outcomes are in the denominator)
 - Also for utilisation and costs
 - Knowing something is uncertain is not helpful
- So...how should we use the U word?
 - Uncertain or unknown or unknowable?
 - What direction and why?
 - Can it be managed and how?


WHY UNCERTAINTY MATTERS: CURRENT LANDSCAPE FOR NEW MEDICINES

- The promise:
 - New drugs offering prospect of survival gain for a population of patients with few options (unmet clinical need)
 - Early access is potentially of benefit to patients now
- The problem:
 - Early data provides a limited basis for decision makers to apply rigorous evaluation to consider the incremental benefits and costs relative to new treatments
 - Such evaluation is inherently uncertain, and may over-estimate benefit
 - The more promising the treatment the higher the cost
- The challenge:
 - Balancing the benefits of early access and the needs of patients against the opportunity costs to the community and the risk of less than anticipated health gain
 - When is there too much uncertainty?

WHEN DOES UNCERTAINTY MATTER MOST?

- Unclear data on quantifiable treatment effect (cross-over, surrogate outcomes, small numbers, trial designs)
 - No or very limited data to inform transitions in model and extrapolation (time horizon and convergence)
 - Lack of information on patient relevant outcomes (impact on QOL, survival)
 - Trials that are not applicable to the clinical context
 - Models that do not calibrate with utilisation and costs
 - Wildly varying ICERs with plausible assumptions
 - Utilisation and costs (potential for leakage, initiation and stopping criteria, overall costs)
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THE CLINICAL EVIDENCE

- Premature and often inherently limited data available
 - Often phase 1 or 2 trials
 - Small numbers
 - Open label
 - Surrogate outcomes (eg PFS)
 - Confounded by cross-over
 - Limited information on adverse events
 - Often requiring indirect comparisons
 - Different doses, different settings
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WHAT IS A MEANINGFUL HEALTH GAIN?

- How does an observed gain in PFS translate to OS?
 - Particularly in the context of extensive cross-over
 - May capture effect of second line vs third line treatment
- Taking account of QOL impacts of the disease and treatment
- Community question – but gains measured in weeks rather than months need to be debated


MODELLING ISSUES 1: EXTENSIVE CROSSOVER

- Reliability of methods to address cross-over
- High degree of cross-over
 - Number of patients who inform the estimates from adjustment methods
 - Progression (that triggers cross-over) defined by protocol based definitions of progression rather than clinical methods
- Whether ITT results support a difference in OS
- Whether assumptions for the crossover adjustment methods are fulfilled


MODELLING ISSUES 2

- Reliance on indirect comparisons, sometimes with historical data on the comparator
 - Structure of models (eg number of health states, how treatment health states are captured, how post-progression health states are captured)
 - Extrapolation methods
 - Time horizon of the model, given the nature of the data
 - Limited quality of life data
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WHAT SENSITIVITY ANALYSES ARE MOST INFORMATIVE FOR DECISIONS?

- If a model relies on a particular statistical analysis, present alternatives
 - If extrapolation is necessary, different methods, different starting points, vary convergence
 - If QOL drives QALYs test the impact of the weights, the method, the instrument (and show the results partitioning QALY gains into LY gains and QALYs)
 - One way deterministic SA are useful to identify the key sources, directions and range
 - Multi-way important for obvious reasons
 - PSA/CEAC are useful, but as an addition
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YOU CANNOT “MANAGE” UNCERTAINTY WITH.....

- Bold assertion/Robust rhetoric
 - More data, but from the wrong trials
 - Statistical analyses as a substitute for more data when the data are the problem
 - New techniques/methods without assessment of their impact (ie without SA to these methods)
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FURTHER ISSUES

- Uncertainty can usually be resolved with additional data
 - But it usually resolves in one direction
 - New treatment is not quite as cost-effective as the early data and model predicted
 - Consistent pattern that interim analyses predict a greater treatment effect than final data
 - Common pattern that PFS gain does not translate to the same OS gain
 - Adverse events tend to emerge with more data
 - A positive recommendation that allows early access cannot be easily undone
 - Finding a way to share these financial and health outcome risks between funders, the community, patients and sponsors
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HOW DOES THE PBAC DEAL WITH UNCERTAINTY?

- Reject – when the clinical data or the model cannot be relied on for DM
 - Defer – when there are potential (and imminent) answers/solutions to the unknowns
 - Risk share (including caps and rebates)
 - Indicate a lower price is the most acceptable way forward
 - Managed entry – an option but not an easy solution
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ROLE OF POST-MARKET REVIEWS

- DUSC utilisation and PBAC reviews focus attention on VFM in practice
 - Impact of new therapies on cost-effectiveness
 - Shifts in clinical practice over time that impact on utilisation, costs, cost-effectiveness
 - How often does treatment occur, in whom?
 - Are the health gains promised realised? (and what if there are health gains, but not as big as predicted?)
 - Are cost-savings realised in practice?
 - Are stopping rules applied as at time of listing?
 - Important information – but it then raises the question of how to respond
 - Adjust the price?
 - Adjust the restriction?
 - Disinvestment>
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MOVING FORWARD

- Uncertainty is a fact of HTA life
- Needs to be characterised, but also needs to be managed
- More useful to think about how to increase confidence in decision making
 - Risk share arrangements
 - Managed entry (with caveats)
 - Price as a way to increase confidence
 - Combination of all three