



**Submission to the Department of Health on
The Draft Version 5.0 PBAC Guidelines**

April 2016

Optum (previously HTAnalysts) has operated in Australia for 14 years and has prepared PBAC, MSAC, NICE, CADTH, PHARMAC and various other European, Asian and Latin American reimbursement submissions, as well as serving as a government HTA evaluator.

This submission outlines key areas of the draft guidelines where there may be opportunities for improvement.

Optum key recommendations are as follows:

- Alignment of Sponsor responsibilities and Evaluator capabilities;
- Draft Guidelines should better define the criteria for the choice of comparator(s);
- The request for the provision of specific types of data (e.g. individual patient data) may require further clarification to ensure suitability, security and practicality;
- Some of the more complex methodologies proposed should only be applied when necessary to ensure that the submission is fit-for-purpose;
- Justification and external validation of the modelling approach should be refined.

Overarching comments

Technical versus pragmatic focus

The draft guidelines place a greater focus on technical detail in comparison to the current guidelines. Although the approach in many places reflects best practice, Optum believe complying with the draft guidelines will require additional investment from Sponsors, in some cases for a minor reduction in the uncertainty of decision making. This balance should be considered when revising the draft guidelines.

Alignment of Sponsor responsibilities and Evaluator capabilities

The draft guidelines set out clearly the responsibility of the Sponsor to present adequate detail for PBAC. Optum recommend that the Department ensure that evaluation groups have consistent capabilities to align with the requirements of the Draft Guidelines.

Issues with access to data

The proposed requirement for the provision of individual patient data (IPD) to enable particular statistical approaches to be performed (eg matching-adjusted indirect comparisons and simulated treatment comparisons) may be challenging for Sponsors. Optum believe this can be addressed by using independent third parties with agreed a priori statistical analysis plans rather than the sole stipulation to submit IPD. Further, for many of the proposed uses, submission of Sponsor IPD will not be at all helpful as non-Sponsor comparator IPD will not be available.

Section 1: Context

Clinical claim (Section 1.1)

Optum welcome the proposed structure of Section 1. The requirement to clearly state the clinical claim and propose any special pricing arrangements gives the Sponsor an opportunity to define the purpose of the submission. Optum believe there is an opportunity for the Draft Guidelines to provide Sponsors with further guidance on how to present a robust clinical claim and describe an unmet clinical need in Section 1.

Comparator (Section 1.1)

The current guidelines stipulate that the main comparator is the most commonly used treatment. It is noted that in the Draft Guidelines there is a requirement for further justification for selection of the main comparator, along with a description of other relevant comparators including future comparators. The ambiguity in the definition of a comparator provides uncertainty for Sponsors and decision makers. This might be informative if there is an undisputable change in the comparator landscape occurring concurrently at the time of the submission, it should not be a routine consideration or requirement. The guidelines should seek to provide more clarity and certainty in relation to comparators by removing wording such as ‘future comparators’.

Section 2: Clinical evaluation

PRISMA format for presenting initial search results (Section 2.2)

Optum welcomes the proposed PRISMA format for presenting literature search results and exclusion criteria codes which allows for consistency in identification of relevant trials from both Sponsor and Evaluator perspectives.

Indirect comparison methodology (Section 2.6)

It is noted that guidance on the proposed indirect comparison methodologies presented in Section 2.6 is comprehensive and can be technically challenging for the Sponsor to adequately address. The proposed requirement for the provision of IPD to enable indirect comparisons to be undertaken (eg matching-adjusted indirect comparisons and simulated treatment comparisons) can be problematic for Sponsors and decision makers. Furthermore, such indirect comparisons require a high-level understanding of the complex statistical methodologies involved, and therefore can be difficult and complex to undertake. The guidelines should direct Sponsors to weigh the additional rigour of adopting complex indirect comparison methods against the methodological challenges, understanding and questionable reduction in uncertainty.

Applicability of trial evidence to Australian population (Section 2.7)

Optum welcome the proposed inclusion of Section 2.7 as this would allow the Sponsor an opportunity to address the applicability of the clinical trial evidence to the proposed PBS population, immediately following the presentation of the clinical trial results. This proposed change in the submission structure will improve readability and aid decision making.

Section 3A: Cost-effectiveness analysis

Terminology

It appears that there is some ambiguity in the terminology used in Section 3A. It would be more appropriate to be specific and use Markov cohort model or cohort level state transition model rather than an 'individual modelling technique'. In the draft guidelines it should be stated clearly that cost-utility analysis is a subtype of a cost-effectiveness analysis. Optum recommend adding a clarifying note to that effect.

Justification of modelling approach (Section 3.2)

The recommended justification of the chosen model structure as requested in the Draft Guidelines should be sufficient to validate the approach taken. Presenting two or more models in addition to scenario analyses in the submission significantly increases the time and resource for the Sponsors and Evaluators without a corresponding benefit to the decision making.

PBAC access to data and model (Section 3.2)

Optum agree that it is appropriate to provide electronic access to a copy of the economic evaluation, and that all variables in the economic model can be respecified. In practice, it may prove difficult to provide access to all sources of data in the model, as often, in more complex models IPD is used. Under these circumstances, releasing IPD can be problematic and moreover may contain identifiable information.

Transition probabilities (Section 3.4)

The Draft Guidelines propose a five-step approach in justification and quantification of the claimed relationship between the change in treatment effect in the proposed surrogate measure and the change in treatment effect in the target clinical outcome used for the economic evaluation. Optum agree that where the transformation of a proposed surrogate measure to a change in target clinical outcome has been previously assessed and validated by the PBAC, justification and quantification would not be necessary, although this is often not clear in public summary documents. Similarly, where there are surrogate to final outcome measure relationships that have a strong body of evidence and that have been widely accepted in certain therapeutic areas (eg progression free survival to overall survival), using the five-step approach for transformation seems unnecessary and inefficient.

The requirement to adopt the five-step approach where it is warranted can be technically challenging to Sponsors because of the complex statistical methodologies involved. In many cases, it is not clear if adopting the five-step approach would reduce uncertainty for decision makers as in fact uncertainty may be introduced in each step. Optum recommend that the Guidelines should provide Sponsors the opportunity to weigh the additional rigour against the methodological challenges, understanding and reduction in uncertainty.

Optum question the practicality of the requirement for assessing the proportional-hazards assumption in circumstances where time-to-event data is used in the economic model. Further guidance should be given in the scenario where this assumption is not met, which frequently occurs, and what impact such violation would have on the validity of the calculated ICER.

Regarding model extrapolation, Optum welcome the suggestion of the need to use standard as well as more complex approaches (e.g. multiple inflexion points) to fit and extrapolate time-to-event data when necessary. However, further advice is needed regarding the practical application of these approaches due to the technical demands of the methodologies.

Model validation (Section 3.7)

Optum agree that validation of certain aspects of economic models (eg cross-validation with other published models) is an important component of good modelling practice. The validation tool designed by the Assessment of the Validation Status of Health Economic Decision Models (AdVisHE) is thorough; however, Optum think that it would not be applicable to the majority of cost-effectiveness models developed for PBAC submissions.

The requirement to ensure the chosen economic model has operational validity (i.e. face validity, cross validation) could pose challenges and potential for error. In particular, the requirement for face validity, whereby an expert such as a clinician or health care professional judges the appropriateness of the chosen model structure and inputs, may not be appropriate for inclusion in PBAC submissions. Clinicians and health care professionals may not have the relevant expertise to critique and validate economic models, as often it can be difficult to design an economic model which identically replicates real life clinical practice. This approach may lead to more complicated models being designed incorporating aspects that do not impact the ICER and add greater uncertainty to the PBAC.

Undertaking external review for model validation is impractical. It would be difficult for Sponsors to justify the additional time and costs required to engage an external modelling expert. Part of the responsibility of the contracted Evaluation groups, partially funded by Cost Recovery fees, is to validate the economic model. The additional benefits of external validation are unclear and it's uncertain how they will influence the evaluation of the model.

Section 4: Predicted use of the medicine in practice

Special pricing arrangements or risk sharing arrangements (Section 4.2)

Optum welcome the opportunity for Sponsors to present proposed risk-sharing or special pricing arrangements and the impact these would have on the estimated net cost to Government. Optum acknowledge the preference that such arrangements need to be transparent and the existence of arrangements are made public; however, elements of the risk-sharing arrangement that are deemed commercial-in-confidence by the Sponsor need to remain strictly confidential.

Part B: Information requests for specific product types

Optum suggests the current list of products requiring additional guidance should be expanded to include rare disease products, biosimilars and products which may be of public interest.

Appendices

Appendix 3: Minimal clinically important difference

Although Optum acknowledge the need to specify a minimal clinically important difference (MCID), in some cases it will be challenging to establish an MCID in accordance with the Draft Guidelines. In particular, where clinical opinion is evolving for therapies in new clinical areas, consensus on MCID is unobtainable. Furthermore, single outcome MCIDs do not cater for therapies that have multiple benefits, where the sum of the benefits is more relevant in determining clinical significance. In addition, MCIDs are not necessarily transferable between acute and long-term changes in the outcome in question, or between patient groups of different ages or clinical presentations.

Appendix 7: Surrogate to final outcomes

See comments on 'Transition probabilities (Section 3.4)' above.

Appendix 8: Non-health outcomes

Optum recommend that further guidance is required in relation to the determination of societal perspective and non-health outcomes that extend beyond willingness-to-pay and productivity. In particular, the role of carers and family members is critical to the consideration of many new therapies which reduce the burden of treatment and the burden of the disease. The Draft Guidelines should also direct Sponsors with regard to capturing patient or carer preferences, which is an important consideration in many new therapies.

Conclusion

Upon review of the Draft Guidelines, Optum has noted that many changes have been incorporated throughout each section. The alterations and adaptations to the current Guidelines should be intended to improve the process of applying to the PBAC and Optum acknowledge that many steps are being taken to achieve this. It is hoped that the recommendations identified in this submission will assist in further refining the Guidelines to ease implementation, improve the quality of PBAC submissions and better support decision making.

Optum appreciate the opportunity to respond to the Draft Guidelines. Optum would be open to further discussion or explanation regarding any of the comments put forward in this submission, and would welcome the opportunity to participate in any future education workshops in relation to further refinement of the Draft PBAC Guidelines.