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Re: Public Consultation on the draft revised Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines

Disclaimer: The views in this submission are personal and do not necessarily reflect those of any of our clients

Before I provide some limited comments on the draft revised guidelines I need to begin with a mild criticism of the process. I do not think the process for stakeholder engagement in the PBAC Guidelines review has been thorough enough. I think it is entirely inadequate that the industry which uses these guidelines every single day are provided with less than a month to comment on them.

The following might be considered a false comparison by some but I think it is relevant. Each individual protocol of each individual health technology assessment considered by MSAC remains open for public consideration for up to six weeks. Conversely, 250 pages of materials which will shape the way our country conducts health technology assessment for probably the next decade remains open for public consultation for less than a month. Not only that, the nature of the engagement needs to be different.

I think a better way of eliciting consumer, professional and broader feedback would be to organise a similar meeting as the meeting conducted recently (15th March). It would go for a whole day, it would not be limited in terms of participant attendance and it would get a range of views/debates on particular topics/issues within the guidelines. There was some debate and feedback at this meeting but it was not comprehensive enough and it appeared the meeting was designed to present and justify the revised guidelines rather than help shape them.

Consequently, I believe there are aspects to these revised guidelines which do not well enough consider the perspective of the people responsible for preparing the submissions. Some of these aspects I will discuss.

Now to some, hopefully, constructive feedback.

Section 1

I like the new Section 1.1 (in particular the "Rationale for PBS listing") where the sponsor can make a "pitch" and/or set the scene and rationale for the submission. This is an important addition to the guidelines (Why is it limited to half a page? 2 or 3 pages is probably enough to make this worthwhile). However, within this otherwise "overviewy" type section we have subsections which are absolutely critical to the framing of the whole submission. Namely, the patient populations and the main comparators. I do not think it is appropriate to mix a general overview of the submission with important structural components of the submission. These important structural components warrant dedicated second level sub-sections.

This might sound like semantics but when evaluating submissions I think you will find different submissions will put different claims about who are and are not the patients and what is and

isn't the comparator in different parts within this Section 1.1. It will also be mixed in with other potentially less important and "pitch" related claims of the submission.

I do think when evaluating the submissions it will be important for evaluators, ESC and PBAC to think, what is the comparator and why? They can then go straight to Section 1.X in every single submission. Who are the patients that are the subject of this submission? Section 1.Y.

I am concerned the main comparator section is less pronounced than what it was and the definitions of what constitute a main comparator seem to have become more vague. The requirement for multiple comparators has become broader which will inevitably lead to bigger submissions.

The revised guidelines list three criteria where multiple comparators are necessary. Do all three of these conditions need to be met or just any one of them. Are there any circumstance where a single main comparator can be appropriate despite these conditions being met. For example, "Comparisons with multiple comparators may be less relevant when there is convincing evidence of therapeutic equivalence between these comparators". But who decides the evidence is convincing and how do we prove therapeutic equivalence without doing the comparison itself? Can we rely upon PBAC precedence for example?

There is an inevitable circularity to what needs to be presented in Section 1. Patient populations determine comparator, comparator determines clinical need and positioning and so on. However, I do find it frustrating in the current guidelines, and the same is happening here, that we have to justify our patient population and comparator(s) before presenting the current clinical management algorithms. I change my mind on the best order of these things all the time, and I am sure this happened during the review of the guidelines. In the interest of trying to be constructive perhaps something like this could be considered. 1.1 Clinical issue addressed by the submission and rationale for PBS listing (2 to 3 page limit); 1.2 Clinical management algorithms (current and proposed); 1.3 Details of the proposed intervention 1.4 Proposed patient population (would fall straight out of the clinical management algorithms section, 1.5 Main comparator (would also fall straight out of Section 1.2).

Section 2

I welcome the streamlining of Section 2. I also believe moving assessment of the applicability of the evidence base to a position before the clinical claim is a step in the right direction.

Section 3

I do not particularly like the new structure of Section 3. The sections entitled "Transition probabilities", "Health outcomes", and "Resource Use and Costs", should fall within a broader section entitled "Model variables". I particularly don't like the section entitled "Transition probabilities" because not all economic models necessarily have transition probabilities. Also, "Transforming surrogate health outcomes to target clinical outcomes" is not something that can only be done with transition probabilities. Extrapolation is not something only done with transition probabilities. Transition probabilities are not the only model variables which need to be extrapolated. It seems like this "transition probabilities" section has only been created to accommodate left over parts of Section C which could not be used in Section 2. Rather, the broader section entitled "Model variables" could encompass all the issues discussed within these three sections without having to describe model inputs as something they are not.

"The submission of an individual-level model should be accompanied by a cohort-based model that implements a nested, less complex model structure"

This is a bad idea and I don't see how it can be implemented in practice. At face value it appears as one of those things which could have been avoided by broader consultation with

people who prepare PBAC submissions. I agree with the revised guidelines where they state that individual-level simulation models should only be used if a cohort model is not feasible. However, if a cohort model is not feasible then it is not feasible and the guidelines should not be encouraging us to prepare a model in circumstances where it is not feasible. To be honest, I have really only ever needed to resort to the use of microsimulation on a handful of occasions. However, in these examples (see attachment for one such example[1]) I would not even know where to begin to try and make the model a cohort based model structure. The attached model has over one million possible combinations and permutations of possible "cohort-like" health states. How do I actually implement this in a less complex structure? Do I just create the 1 million plus health states in a cohort model? Which pieces of evidence do I ignore in order to make the cohort model feasible? I acknowledge this can actually be done because it is just different ways of representing the exact same mathematical structure. However, to suggest a cohort model would be necessarily less complex is simply incorrect. In many respects, we are using individual patient simulation to make the structure less complex (e.g.: small number of health states with individuals holding on to the memory) whereas as a nested cohort model as advocated in the guidelines would likely have a more complex structure (albeit with a more transparent and easier analysis).

I understand this is just a single sentence in a 200 plus page document and perhaps I am over-reacting. However, I think this this is important. I can see the situation whereby we have had to use an individual patient simulation because we are modelling a continuous variable (e.g.: Hba1c), together with other evolving risk factors (e.g.: time since MI predicts probability of next MI) in a non-linear heterogeneous population (e.g.: diabetics). Then, the evaluation will say something like "the sponsor did not accompany their individual-level model with a cohort based model" and therefore the model structure is not justified. No, the model should only be unjustified if the analyst used a microsimulation when it wasn't necessary and the evaluators could not comprehend it. If the submission can make the case that a cohort model is not feasible and a microsimulation model is therefore necessary then that should be enough. Replicating the structure of an alternate model to justify the one you did use is inefficient for sponsors, for evaluators and for the PBAC.

The revised guidelines do point to this approach where they say: "The justification for a more complex model structure that requires an individual-level model should reference the characteristics of the model structure that reduce the feasibility of implementing the structure as a cohort-based model. The justification should also describe how these features are expected to produce a more accurate representation of disease pathways, costs and patient outcomes." Rather than expecting sponsors to supply multiple models, the guidelines could go in to more detail about the kinds of conditions which would render a microsimulation model advantageous and a cohort model infeasible. The four criteria presented by Professor Karnon at the ISPOR meeting on 17th March would be a worthwhile inclusion in to the guidelines in place of the expectation that a separate cohort model be presented.

Alternatively, perhaps the individual patient simulation model approach can be justified by relaxing the assumptions which gave rise to the need for individual simulation within the individual simulation itself. For example; rather than run a heterogeneous population through the model, run a representative population and see what happens; remove the assumption that prior MI predicts future MI and see what happens, and so on. These approaches will be much more efficient than multiple models.

I think more thought needs to go in to the model validation section. This section has been lifted directly from and external source (AdVisHE) without particular consideration of how it will be implemented in practice. I think there will be resource constraints as to who is going to be performing the model validations. For example, I would like to think someone like myself could be considered a "modelling expert" but at the same time I can understand why the PBAC would consider my advice prejudicial because I work for the industry who developed the model. So what value does having a model reviewed by people who work in and are paid by

the same industry for the same purpose actually add to PBAC decision making? For what it is worth, I have worked on projects where I have reviewed a model on behalf of a client, and I have suggested changes (and vice versa). So this validation process is happening on an ad hoc basis but it is unlikely this process is being made known to the PBAC. But even if it had, would it have made a difference? How much of this validation should ESC and PBAC themselves be responsible for? Is there another process whereby we could receive such validation from members of ESC or PBAC prior to the submission being made?

I find Section 3.8 is a bit out of place and should be swapped with Section 3.9. That is, present the results first before describing why they are uncertain. I think it will be easier if the uncertainties are described and consequent sensitivity analyses are presented together.

Section 4

Something should be done about Section E / 4. I suspect, that compared to 2006 when these guidelines were written, there are a lot more risk share agreements and the budget impact analyses have specific practical purposes beyond PBAC consideration. I refer to my comments in the previous round of feedback.

Conclusion

Finally, my apologies for being so negative. I acknowledge the effort gone in to the revision of the Guidelines and there is every chance I may have misinterpreted things and/or some of my concerns were considered and decisions different to my opinion made. Hopefully there is something useful in here for the consideration of the committee.

I look forward to using the revised guidelines.

Kind regards,

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References

Tilden D, Jackson D, Tay-Teo K, van Bavel J. Assessing the Cost Effectiveness of Broadening Access to alendronate for the Prevention of Osteoporotic Fracture in Australia. Poster Presentation to the 14th ISPOR Annual European Congress Madrid, Spain 5-8 November 2011

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