Considering uncertainty when setting a ceiling price for technologies using a cost effectiveness threshold: a note to the PMPRB Technical Working Group.

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Background

The Patented Medicines Price Review Board (PMPRB) are considering using a cost effectiveness threshold to identify a ceiling price for new patented medicines in Canada [hereafter referred to as Value Based Pricing Ceiling (VBPc)]. As part of the process for revising its review process, PMPRB has established a technical working group to comment on technical/methods issues relating to this proposal, that have been identified in the consultation process. One of the technical issues that PMPRB are seeking commentary on is the mechanisms for dealing with uncertainty in the evidence base, within analyses undertaken for VBPc. In this note, we describe the nature of the uncertainties in the evidence base and how they may be addressed analytically within the standard framework of cost effectiveness analysis, in a timely manner from the perspective of the PMPRB's objective of providing timely access to innovation.

The contents of this note should not be interpreted as providing any comment on the desirability or otherwise of VBPc in Canada. Further, the contents of this note should not be interpreted as representing the views of the Institute of Health Economics, its Board, Members or funders, on any of the issues relating to VBPc in Canada.

The remainder of this note is structured as follow: first we describe the categories of uncertainty that a VBPc process *could* consider, the constituent components of those categories and how they relate to the decision that a VPBc setting body such as PMPRB is charged with making; then we rehearse key concepts from decision science: decision uncertainty, the expected cost of making the wrong decision, value of information, and the associated concept of expected net benefit of sampling; finally we describe how these concepts could be used by PMPRB to identify a VBPc. We end with a short note on why the PMPRB (or any VBPc authority) should not considering uncertainty in the Incremental Cost Effectiveness Ratio for a specific product in setting a ceiling price.

Categories of uncertainty potentially pertinent to VBPc process

There are two models of the cost effectiveness threshold; often referred to as the Demand side and Supply side Threshold respectively. The Demand side threshold can usefully be differentiated from the supply side threshold by labelling it the Willingness to Pay for Health. (ref) The Supply side threshold represents the value of the health displaced by the adoption of a new technology under a fixed and fully allocated health system budget. This is often referred to as the Opportunity Cost of adopting a new technology – even though this is not a technically correct use of the term Opportunity Cost. (ref). Both forms of the cost effectiveness threshold are empirical quantities, which in principle can be measured with a degree of uncertainty. For the purposes of this note, is does not matter whether the VBPc is established with reference to a Demand or Supply side threshold.

If we only know the cost effectiveness threshold with uncertainty, there is a risk that the empirical value will be higher or lower than the true value. The econometric studies that typically provide empirical estimates produce an expected value and a description of the uncertainty around that expected value via Standard Errors. These data can be used to characterise a probability distribution that describes the range of credible values for the threshold and the probability that any specific value in the credible range is the true value. This

information allows analysts to examine two important questions: (1) What is the probability that that using the estimate of the cost effectiveness threshold to set a ceiling price, we introduce a technology to the market that will displace more health than it produces, because the estimated threshold is higher than the actual threshold (Type 1 Error); and (2) What is the probability that that using the estimate of the cost effectiveness threshold to set a ceiling price, we exclude a technology from the market that would produce more health than it displaces, because the estimated threshold is lower than the actual threshold (Type 2 Error).

In addition to uncertainty regarding the true value of the cost effectiveness threshold, there is uncertainty about the true value (cost effectiveness) of the technologies. Much, although not all, of this uncertainty derives from uncertainty in the evidence base for the new technology, the technologies it is being compared to and the epidemiology and natural history of the condition that the technology targets. In this context, the evidence base includes resource use, costs and quality of life, as well as the more conventional concerns of effectiveness and safety. Uncertainty in the evidence base will contribute to (a) the risk of adopting a technology that should not be adopted because its actual value is greater than the threshold even though the estimated value is below the threshold; and (b) rejecting a technology that should be accepted because its actual value is less than the threshold even though its estimated value is greater than the threshold. The uncertainty regarding each component of the evidence base can be assessed from the perspective off whether resolving the uncertainty would be expected to change the decision. This is the foundational observation of Value of Information Analysis, a well established set of techniques from decision science. In the next section, we will provide a brief description of the concepts and specific applications of Value of Information Analysis.

Decision making, uncertainty and value of information

Decisions are by definition dichotomous. We choose to do one thing and in doing so, we choose not to do the alternative. Evidence, by contrast, tends to be uncertain and thus sits on a continuum of probability. Cost effectiveness analysis synthesises all available (and relevant)

evidence to estimate the expected incremental costs and incremental effects of the new therapy compared to one or more currently used therapies. Because the evidence is not certain, the estimates of the costs and effects are drawn from distributions, which reflect the uncertainty in the evidence base pertaining to the clinical pathway patients would follow when receiving the alternative therapies, the resource use, costs and health related quality of life associated with the different components of those clinical pathways.

As indicated above, decision making using cost effectiveness analysis requires the specification of a threshold value for the incremental cost effectiveness ratio, above which the new therapy is considered poor value and below which it is considered good value. When the uncertainty in the cost effectiveness is recognised and quantified – as it is in cost effectiveness analyses that comply with good practice guidelines – we can quantify the probability that the decision based upon the expected incremental cost effectiveness ratio will be the wrong decision (either rejecting a good value therapy or accepting a poor value therapy). The probability of making the wrong decision is called the 'Decision Uncertainty'. Cost effectiveness analysis allows us to go further than simply characterising Decision Uncertainty; it allows us to attach a value to making the wrong decision. If we make the wrong decision, then we will be giving up health – by either adopting a technology that displaces more health elsewhere in the system due to its true excess cost, or by continuing to fund a technology within the health care system that actually produces less health than the new technology would if we adopted it. The cost effectiveness threshold ($s per Unit of Health gained) can be applied to the health loss associated with making the wrong decision, to quantify if the decision is wrong. The expected cost of making the wrong decision is obtained by weighting this by the probability of making the wrong decision given current evidence.

There are broadly two responses to concern about making a wrong decision given the current evidence. The first is to collect more evidence, which improves the evidence base and thereby reduces the decision uncertainty. The second is to modify to the point where the cost of making the wrong decision is less than the cost of delaying the decision to allow more evidence to be

collected. Both of these approaches can be formalised through the using the Value of Information framework. The easiest way of thinking about the value of information is as the reduction in the expected cost of making the wrong decision attributable the additional information provided research, net the cost of undertaking the research.[1] When we consider the value of the additional information provides by a specific research study and net out the cost of the research, this is referred to as the Net Benefit of Sampling.

Having reviewed these key concepts, we now turn to consider how a VBPc framework could take account of uncertainty in the value of the cost effectiveness threshold.

Incorporating uncertainty in the value of the cost effectiveness threshold into a VBPc

We start by re-iterating that the cost effectiveness threshold is an empirical quantity that can be estimated with uncertainty, therefore we can characterize the uncertainty and its value using the methods of probabilistic analysis and value of information analysis that are recommended in the Canadian Agency for Drugs and Technologies in Health (CADTH) Guideline for Economic Evaluations: Canada. (2017).

The cost making the wrong decision with regard to uncertainty in the threshold is two-sided - setting a price that is too high because the threshold value is actually lower than the estimate leading to a loss of health; and setting the price too low leading to the technology being withheld from the market, because the actual threshold is higher than the estimate. It follows that the expected value of the wrong decision is the sum of these two factors.

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[1] The definition of cost of the research includes any health gains foregone and/or harms incurred whilst the research is undertaken as well as all financial costs associated with the research.

The VBPc setting authority does not know the price that is consistent with a company's minimum willingness to accept. Given the consistent messages from all levels of government that the policy objective prioritises access to new therapies, it is appropriate for the analyst to adopt a risk averse position and assume that company's minimum willingness to pay requires only a marginal increase in the cost effectiveness threshold and thereby maximize the probability that we have incorrectly excluded them. Hence the probability of making a Type 1 error is the portion of the distribution of the threshold parameters that is above the expected value. The cost of a Type 1 error is the sum of the net benefit calculated using the range of threshold values above the expected value weighted by the probability that each value is the true value multiplied by the population that would benefit.

The cost of a Type 2 error due to threshold uncertainty is slightly different because the technology is provided but it is possible that the ceiling price is over-rewarding it. Therefore, the cost of making the wrong decision is the sum of the *difference* between the net benefit estimated using the expected threshold and each possible threshold value below the expected value, weighted by the probability that it is the actual value. This is then multiplied by the size of the patient population to get the total cost.

If the sum of the cost of these two types of error is not equal to zero, and there is no reason a priori why it should be, then the threshold should be increased or decreased to identify the value which minimizes the sum of the two effects. Theoretically, when the minimum loss identified by this process is non-zero, consideration should be given to the question of whether the cost of further research to reduce the uncertainty in the true value of the threshold is greater than the value of the uncertainty. Pragmatically this would likely not be practical, as this would be a technology specific assessment, and the desirability of consistent and timely VBPc decisions would indicate argue against such an approach. However, period reviews of the total loss attributable to uncertainty in the value of threshold across a portfolio of assessments, would provide empirical evidence on the value of further research to improve the evidence on

the cost effectiveness threshold used.

Uncertainty in the Incremental Cost Effectiveness Ratio and VBPc

It is worth noting that there is uncertainty in the value of the technology, that this uncertainty is empirical and hence in principle can be addressed using the same concepts as outlined above. We would also note that if such an approach is adopted it should focus only on the components of the evidence base that the company could realistically influence through the design of the Research and Development programme that brought the product to market – broadly safety, effectiveness, resource utilisation and health related quality of life.

However, in the context of a VBPc framework, we argue that value of the uncertainty in the evidence base for the technology can be considered out of scope. We hold this position for two reasons. First, the function of the VBPc authority is to set a maximum price consistent with access to the market. In the form described above, we have set a specific risk attitude – averse to Type 1 errors – and this risk attitude may not be the one that health care payers wish to adopt. Health care payers have considerable experience of addressing uncertainty in the evidence base for a technology and understand their attitude to such risk and their preferred strategies for managing it. It is not obvious that there is value in the VBPc authority acting in the space.

Secondly, increasingly innovative technologies are receiving conditional licensing approval; i.e. the regulator provides temporary market access in order to allow research that will reduce the uncertainty in the evidence base for their value. If this same uncertainty were considered by the VBPc authority, this would drive down the price of the technology and reduce the likelihood that the technology would enter this market. The policies of the licensing and VBPc authorities would be in direct conflict.

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