

Economics section of the MSAC Guidelines

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11 Economic analysis

Introduction

When MSAC assesses a new service, it is required to consider the comparative cost and cost-effectiveness of the service as well as the effectiveness and safety. Therefore, applications and assessment reports should include an economic evaluation, based on the clinical evidence, of substituting the new service for the main comparator(s) in the population and setting for which subsidy is proposed (see Section 8 for guidance on the selection of an appropriate comparator). A financial analysis, examining the financial implications of subsidising the service, should also be presented.

The economic evaluation allows MSAC to assess the comparative costs and benefits (in terms of health or other socially relevant outcomes) associated with the proposed service versus the comparator when used in the Australian health care system. The primary basis for the comparison should be the clinical evidence on the use and comparative gains from the service that is presented in Section 10. However, the economic evaluation may also need to consider resource use and outcomes beyond that presented in the clinical evidence. This section of the guidelines describes an appropriate approach to constructing an economic analysis to inform a decision.

Both the economic evaluation and financial analysis should be presented from the perspective of society. This is the preferred approach because it requires consideration of all relevant costs and benefits incurred by society. Costs and benefits should be presented in both disaggregated (separated according to who sustains the costs and benefits) and aggregated formats. Costs and benefits should be aggregated to the following three levels:

- taking a government perspective (ie including costs and benefits incurred by the government, particularly MBS or any other relevant government program);
- taking a health care perspective (ie including only costs related to provision of health care resources regardless of who incurs them, and including only health outcomes); and
- taking a societal perspective (ie including all costs and benefits).

MSAC recognises that it can be impractical to include every relevant cost and benefit in an economic analysis. It is therefore acceptable to prioritise costs and benefits and to exclude from an analysis those costs and benefits that will have no or negligible impact on the incremental results. The measurement and valuation of some costs and benefits, particularly those considered outside the health care perspective (eg production changes), may not be practical. In these instances, applicants should consider providing a narrative description of these costs and benefits.

All economic evaluations have three basic attributes:

- input variables (which are the variables that affect the estimation of the cost-effectiveness of the service, such as resources, transition probabilities and outcomes);

- a structured arrangement to manipulate those variables (eg by presentation of a decision tree, which is a means of illustrating a set of logical and quantitative relationships between the input variables); and
- the outputs that form the results.

Sensitivity analyses should be conducted to clarify the specific input variables or structural features of the analysis that have the greatest effect on the results of the economic evaluation. This allows the robustness of the results and conclusions of the evaluation to be assessed.

Although there are some agreed principles, there is no universally accepted ‘best’ method for assessing costs and outcomes in economic analyses of health interventions. However, it is important that there is a consistent approach to economic evaluation to allow a comparable approach to services considered by MSAC and other government agencies. This section of the guidelines provides guidance on how to present the three attributes of an economic evaluation and its sensitivity analyses in a format that is transparent and consistent with the principles and practices acceptable to MSAC.

11.1 Population and setting for the economic evaluation

In this section of an application or assessment report, the analysts should provide information to allow MSAC to assess whether the evidence presented is applicable and generalisable to the population and setting for whom the service is proposed.

The terminology used for the key populations and settings that need to be analysed in this section of the application or assessment report are shown below.

Definitions for populations and setting that should be taken into account in the evaluation

Term	Description
Target population and setting	Population and setting for which government subsidy of the service is being requested
Study population and setting	Population and setting for which evidence of efficacy and safety has been presented in Section 10
Wider population and setting	Broader population and setting in which the service is likely to be used if included on the MBS (or other relevant government program)

11.1.1 Defining the population

The application or assessment report should provide a description of the demographic and clinical characteristics for the population upon which the economic evaluation is based. This analysis should be presented using summary statistics where appropriate, including information about the distribution around means. Examples of characteristics that could be considered include:

- age
- sex
- ethnicity
- clinical condition
- severity of clinical condition
- previous interventions
- any specific diagnostic, initiation or continuation criteria patients are required to satisfy.

The application or assessment report should also examine the degree of consistency across demographic and clinical characteristics for the population included in the economic evaluation versus:

- the target population
- the study population.

11.1.2 Defining the setting

The application or assessment report should describe the setting in which the service and its main comparator(s) are assumed to be used in the economic evaluation. Examples of elements of settings that could be detailed include:

- the position of the service in the overall algorithm for diagnosing, treating or managing the disease or condition (eg prevention, first-line treatment, second-line treatment)
- any limitations on the dose or quantity of the service delivered to the patient
- any limitations on the duration or frequency of delivery of the services
- any required co-administered interventions (including any additional diagnostic tests required)
- any contra-indicated interventions
- any unique characteristics of the referrer or provider (eg specific qualifications or training)
- any specific requirements in terms of geography, facilities or location of delivery of service (eg limited to hospital setting or to approved laboratories; specification of any specific equipment or facilities that need to be available).

The application or assessment report should also examine the consistency between the setting assumed in the economic evaluation versus:

- the target population
- the study population.

11.1.3 Justifying restrictions

In the case where it is proposed that eligibility for a service be restricted to a subgroup of patients with a clinical condition, the proposed restriction should be justified as follows:

1. The intention of the requested restriction should be indicated in the application or assessment report.
2. To help minimise usage beyond the intention of the requested restriction, for each population or setting element included in the wording of a restriction, the application or assessment report should:
 - identify and define the element unambiguously; for example:
 - risk factors associated with the medical condition
 - markers of severity or progression of the medical condition
 - name of intervention, dosage and duration criteria for previous interventions as appropriate
 - specify objective criteria in preference to subjective criteria in identifying the element
 - justify any thresholds within these criteria (these thresholds and justifications should be consistent with study eligibility criteria and subgroup stratification criteria as appropriate)
 - resolve copyright issues over any proposed instrument before proposing its use as part of a restriction.
3. The application or assessment report should present a discussion addressing the trade-offs between the clinical preference for simple, unambiguous listings versus increasingly complex restrictions designed to limit new services to those relatively few patients for whom the proposed service might be justified as being acceptably cost-effective at the price requested.

The further the eligibility criteria specified in a restriction shift practice away from otherwise uninfluenced practice, the more incentive there is for referrers/providers and patients to seek subsidy despite the restriction. The approach listed above (identifying and justifying any restrictions) is intended to help justify the choice of restriction from the alternative options that might apply. This approach becomes more important as the restriction becomes more complex or more expensive for Medicare Australia (or any other relevant body) to administer.

If the proposal is for eligibility for a service to be restricted to a subgroup of patients with a clinical condition, the potential for use of the service in a wider population or

setting than the target population and setting, if government subsidy of the service is recommended, should also be assessed.

11.1.4 Presenting the information

Table 11.1.1 shows a hypothetical example where it is proposed that a new treatment be made available as a second-line agent for the management of adults with hyperthyroidism to provide a suggested format for presentation of information about the target, study and wider populations and settings.

Where there are differences, or potential differences, between any of the groups, economic analyses should be presented for each of the scenarios.

When presenting economic evaluations for different populations, the application or assessment report should consider whether changes in the population have implications for the cost associated with the proposed service (eg if economies of scale may be captured by using a service in a wider population). Further advice is provided in Section 11.7.1 (see 'Presenting the cost of the proposed service').

Table 11.1.1 Example of a comparison of the characteristics of target, study and wider populations and settings

Population	Target	Study	Wider
Clinical condition	Hyperthyroidism due to any cause	Hyperthyroidism due to Graves' disease	Hyperthyroidism due to any cause
Comment:	Only patients with hyperthyroidism due to Graves' disease were recruited to the only randomised trial comparing service A with service B (Jones et al 2000) but subsidy is requested for all patients with hyperthyroidism, regardless of aetiology. Smaller, non-comparative studies (Brown et al 1995, Smith et al 1997) have examined the efficacy and safety of Service A in patients with hyperthyroidism due to other causes. The effect size observed in these studies was similar to that observed in Jones et al, 2000; however, it is acknowledged that <etc> This is discussed in greater detail in Section 10.		
Age	Adults	18–75 years	Adults
Comment:	Although only patients aged up to 75 years were eligible for entry to the randomised controlled trial comparing service A with service B (Jones et al 2000), service A has been used in patients over the age of 75 with similar effects as in other adult populations (Smith et al 1990) <etc> This is discussed in greater detail in Section 11.6.		
Gender	70% females 30% males	50% females 50% males	70% females 30% males
Comment:	Although the proportion of females with condition X recruited to the trial reported by Jones et al 2000 was lower than the proportion of females with hyperthyroidism in the Australia, a test for interaction did not demonstrate gender to be a treatment effect modifier <etc> Further details are provided in Section 10.		
Initiation criteria	Serum TSH < 70% x Serum T ₃ > 120% y	Serum TSH < x Serum T ₃ > y	Serum TSH < 85% x Serum T ₃ > 110% y
Comment:	Subsidy of service A is requested for a more severely affected population than recruited to the trial reported by Jones et al, 2000. Subgroup analysis demonstrates serum TSH and T ₃ levels at baseline to be a treatment effect modifier, with a greater relative response rate to service A in patients with levels of serum TSH below 70% x and levels of serum T ₃ greater than 120% y. It is acknowledged that there may be some use beyond the population for whom subsidy of service A is sought. Thus, sensitivity analyses are presented examining the effect on incremental cost-effectiveness and financial implications of use of the service beyond the population for whom subsidy is sought.		
Setting	Target	Study	Wider
Position in management algorithm	Second line	Second line	Second line but some first-line use
Comment:	Consistent with the randomised controlled trial (Jones et al 2000) comparing service A with service B, subsidy is proposed for use of service A only in patients failing to respond to service C. However, it is acknowledged that there may be some use of service A in the first-line management of hyperthyroidism (ie as a substitute for service C instead of service B). Thus, cost-effectiveness analysis is also presented versus service C.		
Limitations on frequency of use	Patients will be permitted to receive service A as a subsidised service on two separate occasions	Patients were permitted to receive service A on two separate occasions	Patients will be permitted to receive service A as a subsidised service on two separate occasions
Comment:	The number of times the service may be delivered to the patients on a subsidised basis is consistent with the number of times the patients were able to receive the service in the clinical trial reported by Jones et al 2000.		

11.2 Clinical basis of the economic evaluation

This section of an application or assessment report should provide a summary of all the differential effects (effectiveness and safety) between the service under MSAC consideration and the comparator in the target population and setting, based on the data presented in Section 10.

11.2.1 Preparing a clinical balance sheet

All of the benefits and harms that can be expected in a typical group of Australian patients should be presented in a 'clinical balance sheet'. This will help MSAC make a judgment regarding the likely balance of benefits and harms that can be expected if the intervention is widely used in Australian patients.

The clinical balance sheet should be prepared with reference to the following management alternatives:

- a monitoring approach (which reflects the natural history of the condition)
- the intervention
- the comparator(s).

The clinical balance sheet should describe the outcomes of each alternative, including the probabilities of uncertain outcomes (eg by inclusion of the 95% confidence limits around point estimates). An indication of the strength of the evidence (eg by indication of the source of the data) should also be provided. Similarly, the table should also describe the potential harms associated with each alternative (including the direct burden or discomfort associated with the alternative and the complications and adverse effects associated with the alternative).

Table 11.2.1 provides a suggested format for the presentation of a clinical balance sheet and includes data for a fictitious example where it is proposed that a new surgical procedure be used as a first-line treatment for women with symptomatic uterine fibroids.

Table 11.2.1 Example clinical balance sheet for managing symptomatic uterine fibroids

Examples of potential treatment benefits or harms	Alternatives for management		
	Monitoring	Nonsurgical procedure (comparator)	New surgical procedure (proposed service)
BENEFITS			
Survival (in women with a mean age of 35 years) Source: RCT reported by Jones et al, 2008.	At 10 years: 88% (95% CI: 86%, 90%)	At 10 years 90% (95% CI: 86%, 94%)	At 10 years 84% (95% CI: 82%, 86%)
Difference vs comparator	-2% (95% CI: x%, y%)	-	-7% (95% CI: x%, y%)
Reduction in menorrhagia Source: RCT reported by Jones et al, 2008.	At 2 years 20% (95% CI: x%, x%)	At 2 years 75% (95% CI: x%, x%)	At 2 years 100% (95% CI: x%, x%)
Difference vs comparator	-55% (95% CI: x%, x%)	-	+25% (95% CI: x%, x%)
Pelvic pain Source: RCT reported by Jones et al, 2008.	At 2 years 20% (95% CI: x%, x%)	At 2 years 60% (95% CI: x%, x%)	At 2 years 88% (95% CI: x%, x%)
Difference vs comparator	-40% (95% CI: x%, x%)	-	+22% (95% CI: x%, x%)
HARMS			
Restrictions on activities of daily living Source: RCT reported by Jones et al, 2008.	Ongoing pain may limit activities	Activities limited for 1–2 days post-procedure	Activities limited for 10–20 days post-procedure
Difference vs comparator	Ongoing pain	-	Longer recovery time post-procedure
Short-term complications DVT Source: RCT reported by Jones et al, 2008 and post-marketing surveillance reported in Black et al, 2008.	0%	4%	7%
Difference vs comparator	-4% (95% CI: x%, x%)	-	+3% (95% CI: x%, x%)
Long-term complications Source: RCT reported by Jones et al, 2008 and post-marketing surveillance reported in Black et al, 2008.			
Difference vs comparator		-	

RCT = randomised controlled trial; DVT – deep vein thrombosis; CI = confidence interval

11.2.2 Defining the risk profile

The majority of economic evaluations are based on an assumption that the objective of the decision maker is to maximise expected utility (which may be measured in terms of quality-adjusted survival) and that the decision maker is risk neutral. Such assumptions have been demonstrated to be empirically flawed under certain conditions. It has been postulated in the literature that people are risk-averse when considering potential gains, and that, in some situations, people prefer to minimise regret rather than maximise utility.

To enable MSAC to consider the performance of a service according to objectives other than utility maximisation (eg if a new service is associated with an increased risk of death compared with the comparator(s)), it is important that changes in the profile of risks associated with the proposed service compared with the main comparator(s) are explained in the clinical balance sheet. In the example shown in Table 11.2.1, increased efficacy of the surgical procedure is associated with an increased risk of death; this may be an important consideration (beyond the impact on expected quality-adjusted survival) if people are risk averse when considering potential gains.

11.2.3 Assessing benefits and harms

The economic evaluation presented to MSAC needs to capture the benefits and harms identified in the clinical balance sheet. As discussed in Section 11.5, the first step of the stepped economic evaluation should effectively be a cost-consequences analysis based on the benefits and harms identified in the clinical balance sheet.

If there are any differences in outcomes (in terms of benefits and harms) reported for the study population and setting, compared with those estimated for the target population and setting; or wider population and setting (eg as may have been shown by subgroup analysis), summaries of the outcomes for each population and setting should be presented in a way that allows them to be compared and contrasted. The reasons for, and sources of, the differences in outcomes across these populations and settings should be discussed.

The application or assessment report should discuss the generalisability of results for the study population and setting to the target population and setting and summarise any approach adopted (eg subgroup analysis — see Section 10) to adjust study results for the characteristics of patients in the target population.

11.3 Selection of the most appropriate economic evaluation to use

The aim of this section of the application or assessment report is to identify the most appropriate type of economic evaluation to present from the options shown in Section 11.3.1.

11.3.1 Classifying effectiveness and safety of the proposed service

To identify the most appropriate evaluation, the application or assessment report should first classify the proposed service using the grid provided in Table 11.3.1. This classification should be based on the differential effectiveness and safety of the service under consideration compared with the appropriate comparator(s) when used in the target population and setting (ie the information presented in Section 11.1). In classifying the service, it may also be necessary to consider changes in the profile of risks associated with the proposed service, compared with the main comparator(s).

In classifying a service, the quality and strength of the available evidence should be taken into consideration. As discussed in Section 10, MSAC has a strong preference for making decisions on the basis of data from randomised controlled trials and will be most influenced by the results of direct randomised trials as the most rigorous source of data. However, MSAC has considered and will continue to consider all levels of evidence.

Where there are trade-offs between incremental effectiveness and incremental safety; that is, where there is reduced effectiveness but improved safety (cell G in Table 11.3.1); or where there is improved effectiveness but reduced safety (cell C in Table 11.3.1), consideration will be required as to whether there are net clinical benefits or net harms to patients, overall. This may involve a valuation of the different effects associated with a service and/or modelling of various outcomes. Assumptions made in reaching the conclusion about whether a service has net clinical benefits should be stated explicitly.

Table 11.3.1 Classification of a service under MSAC consideration

		Comparative effectiveness versus comparator				
		Improved		No worse (noninferior)	Reduced	
Comparative safety versus comparator	Improved	A		D	Net clinical benefits	G (i)
					Neutral benefits	G (ii)
					Net harms	G (iii)
	No worse (noninferior)	B		E	H	
	Reduced	Net clinical benefits	C (i)	F	I	
		Neutral benefits	C (ii)			
Net harms		C (iii)				

11.3.2 Selecting the type of evaluation to use

Cost-effectiveness, cost-consequences, cost-utility and cost-benefit analyses all compare the costs and benefits of the proposed service with those of its main comparator(s) but use different units of measurement, as follows:

- *Cost-effectiveness analysis*
Costs are measured in monetary terms and outcomes are presented as a single representative outcome measured in natural units.
- *Cost-consequences analysis*
Costs are measured in monetary terms and outcomes are presented in the form of an array of outcomes measured in their natural units rather than a single representative outcome as presented in a cost-effectiveness analysis. The presentation of such an analysis is particularly informative where the proposed service is associated with a different profile of effects that are not adequately captured by a single outcome measure (eg where there might be trade-offs between the two interventions in terms of the directions of the changes in effectiveness and safety and within effectiveness and safety). As such, it is a form of disaggregated analysis of changes in patterns of health care resource provision and changes in health outcomes and can be presented before presenting other types of aggregated economic evaluation, such as a cost-utility analysis.
- *Cost-utility analysis*
Costs are measured in monetary terms and outcomes are measured in terms of survival that is adjusted for quality of life; for example, quality-adjusted life years (QALYs), healthy year equivalents (HYEs).
- *Cost-benefit analysis*
Both costs and benefits are measured in monetary terms. (See Box 11.1 for further discussion of why cost-benefit analysis is not the preferred analysis by MSAC.)

- *Cost-minimisation analysis* is an economic evaluation that identifies the least costly service after noninferiority has been indisputably demonstrated for both effectiveness and safety.

Table 11.3.2 shows the type of economic evaluation that should be presented for each classification from Table 11.3.1.

Table 11.3.2 Type of economic evaluation that should be presented for various classifications of a service under MSAC consideration

Cell in Table 11.3.1	Classification	Type of economic evaluation
A	The service is more effective than the appropriate comparator and is associated with improved safety.	Cost-consequences, cost-effectiveness, cost-utility, cost-benefit
B	The service is more effective than the appropriate comparator and is no worse than the comparator in terms of safety.	Cost-consequences, cost-effectiveness, cost-utility, cost-benefit
C	The service is more effective than the appropriate comparator but is associated with reduced safety.	
	(i) Overall, there are net benefits to patients as the benefits from improved effectiveness outweigh the harms from reduced safety and/or changed risk profile.	Cost-consequences, cost-effectiveness, cost-utility, cost-benefit
	(ii) Overall, the service is no worse than the comparator because the benefits from improved effectiveness at least offset the harms from reduced safety and/or changed risk profile.	Cost-consequences, cost-effectiveness. This may be reducible to cost-minimisation (ie presentation of an incremental cost-effectiveness for the base case may be inappropriate if net clinical benefits are assumed to be zero)
	(iii) Overall, there are net harms to patients as the harms from reduced safety and/or changed risk profile outweigh the benefits from improved effectiveness.	No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this service.
D	The service is no worse than the comparator in terms of effectiveness but is associated with improved safety.	Cost-consequences, cost-effectiveness, cost-utility, cost-benefit
E	The service is indisputably demonstrated to be no worse than the comparator in terms of both effectiveness and safety.	Cost-minimisation. In the case where there is any uncertainty around the conclusion that the service is no worse than the comparator in terms of effectiveness and safety, cost-

Cell in Table 11.3.1	Classification	Type of economic evaluation
		consequences, cost-effectiveness, and/or cost-utility analyses should be provided.
F	The service is no worse than the comparator in terms of effectiveness but is associated with reduced safety.	No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this service.
G	The service is less effective than the comparator but is associated with improved safety.	
	(i) Overall, there are net benefits to patients as the benefits from improved safety and/or changed risk profile outweigh the harms from reduced effectiveness.	Cost-consequences, cost-effectiveness, cost-utility, cost-benefit
	(ii) Overall, the proposed service is no worse than the comparator because the benefits from improved safety at least offset the harms from reduced effectiveness and/or changed risk profile.	Cost-consequences, cost-effectiveness (which may be reducible to cost-minimisation ie presentation of an incremental cost-effectiveness for the base case may be inappropriate if net clinical benefits are assumed to be zero)
	(iii) Overall, there are net harms to patients as the harms from reduced effectiveness outweigh the benefits from improved safety and/or changed risk profile.	No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this service.
H	The proposed service is less effective than the comparator and is no worse than the comparator in terms of safety.	No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this service.
I	The proposed service is both less effective than the comparator and is associated with reduced safety compared with the comparator.	No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this service.

From Table 11.3.2, it can be seen that an economic evaluation should be presented in all reports to be considered by MSAC except when a service is indisputably demonstrated to be associated with net clinical harms to patients (as it is unlikely that MSAC will recommend government subsidy of the service).

The application or assessment report should state what type of economic evaluation is being presented. All analyses should explicitly consider all the advantages and disadvantages of the proposed service that are listed in the clinical balance sheet, compared with the comparator. However, there are some circumstances where simplified analyses will be appropriate and acceptable (see Section 11.5 for further details).

An iterative approach to the classification and type of analysis may be required. For example, a valuation of the different effects associated with a service, and/or modelling of various outcomes, may be required before a service can be definitively classified according to the second column of Table 11.3.2. In these cases, the structure of the economic evaluation and the assumptions made in valuation of outcomes must be presented clearly. Adequate sensitivity analysis should also be provided to allow MSAC to gauge the robustness of the classification selected. Thus, although the service may ultimately be classified as being no worse than the comparator (eg where improved effectiveness is considered to offset reduced safety), such that a cost-minimisation analysis is considered ultimately appropriate, a cost-consequences and a cost-effectiveness analysis that explicitly shows the valuation of the various outcomes should also be presented. Sensitivity analyses should also be presented which examine the effect of varying assumptions in the valuation of outcomes.

Note that the various types of analyses should not be considered mutually exclusive. In many cases it will be appropriate for more than one type of analysis to be presented. As discussed in Section 11.5, a stepped economic evaluation is requested. Such an analysis will commence, typically, with a cost-consequences analysis and will progress, where appropriate, through various steps where various aspects of modelling are introduced such that, ultimately, a base-case cost-effectiveness or cost-utility analysis is presented. A trade-off between the most appealing outcome upon which to base the economic evaluation from a theoretical point of view and the degree of uncertainty in the estimate of incremental cost-effectiveness is often required. Extrapolation of outcomes beyond the evidence will introduce uncertainty in estimates of incremental cost-effectiveness. For example, the estimate of incremental cost-effectiveness generated by a study-based analysis (ie based directly on the outcome from a study) may be relatively robust. However, in moving to a cost-utility analysis (which is theoretically more appealing but where assumptions of utilities for various health states may be required), additional uncertainty may be introduced.

Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (ie the conclusion is often not indisputable). Therefore, when an application or assessment report concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should also be provided by presentation of cost-consequences, cost-effectiveness and/or cost-utility analyses.

Box 11.1 Cost–benefit analysis

Cost–benefit analyses are not preferred by MSAC because they are not likely to be helpful to most MSAC deliberations. The reasons for this are as follows:

- The methods for deriving monetary valuations of health gains presented to date have not satisfactorily minimised the hypothetical nature of the responses elicited or the incentives for the respondents to provide values that reflect a desire to have the MBS subsidy proceed in the full knowledge that the respondent will not directly incur this cost. Although it is theoretically possible to improve the realism of the scenarios and of the questions asked to elicit plausible monetary values, there remains a residual uncertainty in aligning the provision of resources valued in monetary units with welfare outcomes, which are apparently valued in the same monetary units.
- Cost–benefit analyses typically assign preference weights including other welfare changes, beyond the primary focus of MSAC on health outcomes (these include production changes and process changes), which have tended to reflect the construction of the scenario or attribute used to elicit the monetary valuation rather than to reflect the weights assigned by MSAC when considering a fuller range of other relevant factors, particularly equity.
- There remain considerable problems with interpreting willingness to pay (WTP) responses in the context of the Australian health care system where individuals do not typically face market prices.
- The use of WTP to elicit monetary valuation for a cost–benefit analysis, which will be influenced by an individual’s income and assets, is inconsistent with the principles underpinning the MBS, a subsidy program with an objective of ensuring equity of access.
- Cost-benefit analysis is typically applied in the context of a fixed decision rule, which does not incorporate the breadth of equity and ethical considerations that are relevant to MSAC decision making.
- Although it is possible to use utility-based instruments in studies to estimate the strength of preference for different health outcomes, this is not yet practical for monetary-based instruments.

However, in recognition that monetary valuation might be informative, in situations where utility valuation is problematic, MSAC will accept the presentation of cost–benefit analyses.

This may occur where there is a perceived lack of sensitivity of utility valuation to perceived increments in health outcomes (eg where there are short-term changes in health outcomes, differences in health outcomes that are too small to be detected with utility-based instruments, and differences across adverse effects profiles for two interventions that are otherwise similar in terms of comparative effectiveness). However, it is requested that such analyses be provided as supplementary to cost-utility or cost-effectiveness analysis. If both a cost-utility or cost-effectiveness analysis and a cost–benefit analysis are presented, the application or assessment report should discuss the differences in the results and any differences in conclusions. The evidence that supports any claim that differences in results between utility-based valuation and monetary based valuation is attributable to a special characteristic of the health state should also be documented.

11.4 Literature search

Applicants should search the literature for published cost-effectiveness analyses of the proposed service. Chapter 11 (Health Economics Information) of Etext on Health Technology Assessment Information Resources¹ outlines appropriate approaches to the location of cost-effectiveness analyses. The InterTASC Information Specialists' Sub-Group from the Centre for Reviews and Dissemination at the University of York² outlines appropriate search filters for identifying cost-effectiveness analyses in the literature. A list of all of the published reports that are retrieved by the search should be provided in the application or assessment report.

The economic analyses that are directly relevant to MSAC's considerations (ie economic evaluations performed for the same population and setting in which the service will be used) should be identified using a tight set of inclusion and exclusion criteria, which should be detailed in the application or assessment report. The application or assessment report should also provide a critical review of the included studies.

An independent economic evaluation may not be required if there is already a high-quality economic evaluation in the public domain that provides an estimate of incremental cost-effectiveness for the proposed service in a population and setting that is similar to the proposed Australian population and setting. Such an evaluation needs to be based on the appropriate:

- therapeutic and management setting
- patient population
- input variables.

In these circumstances, an assessment of the most appropriate publicly available evaluation should be presented in the report for MSAC according to the requirements of these guidelines. That is, the evaluation available in the public domain should be assessed according to Sections 11.5 to 11.8 of these guidelines and all details requested in Sections 11.5 to 11.8 should be provided in the application or assessment report.

Where a model in the public domain is considered to have an appropriate structure, but is populated with values for variables that do not correspond to the values that would apply in the Australian population and setting, it may be appropriate to use the model, but to update values for the variables to values that would apply in the Australian context. Again, the model should be assessed according to Sections 11.5 to 11.8 of these guidelines and all details requested in Sections 11.5 to 11.8 of these guidelines are to be provided in the application or assessment report.

If a search of the literature fails to identify any directly relevant economic evaluations, an independent economic evaluation should be conducted. Sections 11.5 to 11.8 of these guidelines describe the information required and how the economic evaluation should be presented.

¹ <http://www.nlm.nih.gov/nichsr/ehta/chapter11.html>

² <http://www.york.ac.uk/inst/crd/intertasc/econ.htm>

11.5 Structure of the economic evaluation

The aim of the economic evaluation is to use the clinical studies presented in Section 10 to determine the economic cost of substituting the proposed service for the main comparator in the setting for the requested listing (the base-case economic evaluation). MSAC requires a full and transparent description of the variables used in the economic evaluation. Generally, two steps are involved:

- a study-based economic evaluation (effectively, a cost-consequences analysis), which is based on the study variables (eg population, setting, time horizon)
- a modelled economic evaluation, in which study-based variables are modified using modelling techniques ('translated') to take account of differences between the study variables and the target variables for the proposed service.

11.5.1 Study-based evaluation

If the study population and setting are the same as the target population for the proposed service, and outcomes have been reported for all patient-relevant endpoints, it may be appropriate to present a simple economic evaluation based directly on the results of the included studies. A study-based economic evaluation can have a simple structure, such as that shown in Figure 11.5.1.

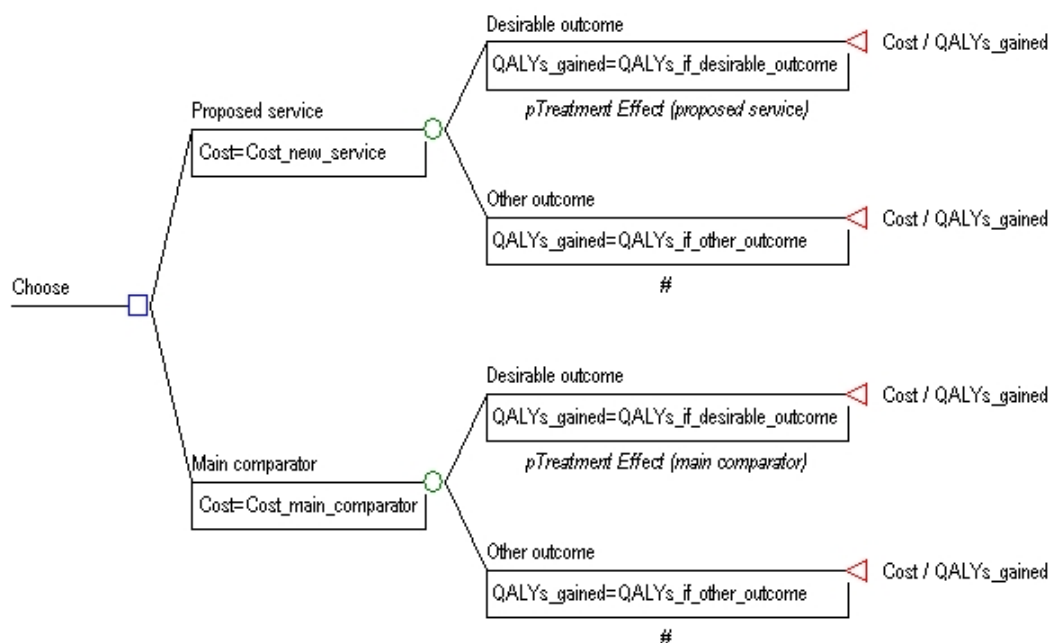


Figure 11.5.1: Example of the structure of a basic economic evaluation

11.5.2 Stepped economic evaluation

Frequently, the results of the available study/studies provide insufficient information on which to base a judgement about the clinical and economic performance of the proposed service relative to that of the comparator. In these circumstances (which are

a matter of judgement), a stepped economic evaluation (which introduces the various aspects of modelling in separate steps) will be useful to MSAC. Examples of reasons for presentation of a stepped economic evaluation rather than just a study-based analysis include:

- the study population and setting may be different to the target population and setting
- the outcomes measured in the studies may not be the final outcomes of interest for the proposed service
- a range of outcomes are of interest
- the time frame of outcomes measured in the studies may be inadequate
- resource-use patterns measured in the studies may not fully reflect those expected in practice (eg some resources may not be measured in the studies, and some ‘protocol-driven’ resources may be included that are not relevant to the proposed provision of the service).

Presenting a stepped evaluation

In order to ensure that the manner in which available information is incorporated into the economic evaluation is transparent, MSAC requires the presentation of a stepped economic evaluation that starts with a study-based cost-consequences analysis and progresses through various steps of the modelling in turn (population and setting, outcome, time horizon, resource use, etc). These steps may require the presentation of additional evidence. Guidance for the presentation of this evidence is provided in Section 11.6.

MSAC recognises that the conduct of a complex economic evaluation for a service may be associated with costs that could exceed the costs of actually providing that service. Therefore, a simple economic evaluation, such as a study-based economic evaluation or a simplified model, is acceptable if the following criteria are both met:

- the service is likely to be used by small numbers of patients; and
- the total government expenditure on the service is likely to be small.

To ensure consistency across economic analyses considered by MSAC, the preferred elements of a base-case economic evaluation are summarised in Table 11.5.1.

Table 11.5.1 Key elements of the base-case economic evaluation

Element of economic evaluation	MSAC's preference for the base-case analysis	Section providing further details
Perspective	Societal perspective. However, costs and benefits should be presented aggregated to the following three levels: <ul style="list-style-type: none"> • taking an MBS (or other relevant government program) perspective (ie including costs and benefits incurred by the MBS or any other relevant government program) • taking a health care perspective (ie including only costs related to provision of health care resources regardless of who incurs them, and including only health outcomes) • taking a societal perspective (ie including all costs and benefits). 	Introduction to Section 11, and Section 11.8
Comparator	Currently available service that is most likely to be replaced by the new service	Section 8
Type of economic evaluation	Cost-effectiveness analysis	Section 11.3
Source of evidence	Systematic review	Section 10
Values of parameters	Unbiased, plausible estimates. Where there is room for judgement and considerable uncertainty around the value of a parameter, a conservative approach to the valuation of that parameter should be adopted.	Section 11.5
Outcome on which evaluation should be based	The outcome measure that most closely and validly estimates the final health outcome from a patient perspective. Health-related quality-adjusted life years (QALYs) should be used where feasible.	Section 11.7.2
Discount rate	An annual rate of 5% for both costs and benefits	Section 11.5

A description of the structure of each step of the economic evaluation should be provided. This description should include:

- an explicit statement of the options for which costs and benefits are being estimated in the economic evaluation, and the justification for the selection of options included in the evaluation
- a description of each of the events and health states possible in the economic evaluation
- justification of the selection of health states for inclusion in the economic evaluation (and those excluded to avoid excessive complexity)
- a description of the relationships and interactions between the various events and health states possible in the economic evaluation (including detail of the transitions possible between the health states)

- a description of assumptions (both implicit and explicit) made in the construct of the economic evaluation
- a decision-tree diagram summarising the structure of the economic evaluation.

The application or assessment report should present a justification for the overall structure of the base-case economic evaluation, particularly in relation to:

- the natural history of the condition being managed, prevented or diagnosed
- the management algorithm that applies currently and the management algorithm that will apply should the service be included on the MBS (or other relevant government program)
- the management algorithm that applied in the studies used as evidence to demonstrate the safety and effectiveness of the proposed service
- the structure of other relevant models reported in the public domain.

The report should also identify and consider assumptions built into the structure of the economic evaluation and comment as appropriate.

Defining and justifying the time horizon

The time horizon over which costs and benefits of a service and its comparator are measured in each step of the evaluation should be defined and justified. The application or assessment report should define and justify the time points at which events are assumed to occur and the duration of time spent in health states (include details of cycle length for Markov models). The appropriate time horizon for follow-up will relate to the natural history of the disease, the treatment pattern and the time period over which outcomes from the service or main comparator could be expected to occur. For example, the time horizon over which costs and health benefits of a diagnostic test for an acute event (eg a non life-threatening infection) should be considered may be relatively short, whereas the appropriate time horizon to consider for a treatment for a chronic illness will be longer.

Discounting

Where costs and benefits of a service and/or its comparator are presumed to be borne over more than one year, the present value of future costs and benefits should be used in the economic evaluation. This means that discounting should be applied to both costs and benefits sustained in the period beyond the first year. Costs and benefits should be discounted at an annual rate of 5%. As discussed in Section 11.8.2, sensitivity analysis examining the impact of discounting should be performed.

Describing the methods used

The methods used to generate results of the economic evaluation should be described; for example:

- expected value analysis (or cohort analysis)
- Monte Carlo simulation (the application or assessment report should specify whether first-order and/or second-order distributions are sampled)

- Markov models (the application or assessment report should specify whether a half-cycle correction has been included or justify its exclusion).

Dealing with uncertainty

The value of information from a complex economic evaluation diminishes as greater uncertainties are introduced through the process of modelling. The application or assessment report should consider the extent to which the value of more extensive analysis will be limited by the quality of the underlying data and the extent to which uncertainties in the clinical evidence will be amplified by modelling. Progression through modelling steps should continue only as long as the results generated are likely to be of value and informative to MSAC.

The type of presentation that is likely to be of greatest value to MSAC may vary with the level of evidence available. For example, in some circumstances the evidence base may be extremely weak (eg where a claim that a service is safe and ‘promising’ in terms of effectiveness is based on low-level evidence, such that the claim cannot yet be considered proven). In such cases, a threshold analysis that examines incremental cost-effectiveness over a range of possible benefits, and that essentially seeks to determine the minimum extent of benefit that would be required in order for the service to be considered acceptably cost-effective, may be more informative than reporting of an incremental cost-effectiveness ratio based on a single point-estimate of incremental effectiveness.

The objective of cost-effectiveness analysis should be to provide an unbiased, plausible estimate of the incremental cost-effectiveness of the interventions being compared. Where an element of judgement is required, and where there is considerable uncertainty around the value of a parameter, a conservative approach to the assignment of a value to that parameter should be adopted for inclusion in the base case.

11.6 Additional evidence required to conduct the economic analysis

11.6.1 Translating the clinical evidence for an economic evaluation

In many cases, the values for one or more variables incorporated into the economic evaluation cannot be derived directly from the clinical evaluation presented in the clinical section of an MSAC report. In these cases, additional information may be required in order to translate the clinical evaluation to match the proposed listing, and thus the framework of the economic evaluation.

Depending on the nature of the clinical evaluation, the results may need to be applied, extrapolated or transformed (collectively referred to in these guidelines as ‘translated’) as described below:

- If the study population or the setting in which the service is used in a study is not the same as the target population and setting in which the service will be used in practice, the profile of risks of events in practice may not be identical to those observed in the study. In this case, further analyses may be required to allow the results from the study to be *applied* to the target population and setting. Examples of studies to address applicability issues include subgroup analyses and surveys of the patterns of health care resource provision in Australia corresponding to one or more health states included in a modelled economic evaluation.
- If the length of follow-up of participants in the studies is not long enough to capture all of the impacts on resources or outcomes that are likely to be observed in practice, the clinical evaluation needs to be *extrapolated* to the time horizon over which an impact on resources or outcomes is likely in practice. Examples of studies that might assist in addressing extrapolation issues include extrapolating integrals of time-to-event analyses and a review of the literature for single-arm follow-up studies of the natural history of the condition to estimate rates of disease progression.
- If the outcomes measured in the studies are not the patient-relevant final outcomes of the target population, the clinical evaluation needs to be *transformed* to take account of the patient-relevant final outcomes (eg in terms of QALYs gained). Examples of studies that might assist in addressing transformation issues include transforming comparative treatment effects measured on surrogate outcomes to final outcomes and scenario-based studies to value health outcomes using utilities.

These additional studies provide a clearer and more systematic basis to support the necessary variables for inclusion in the economic evaluation. As indicated by the examples above, the types of additional studies relevant to this process of translation can vary widely (ie the definition of the term ‘study’ can be broadly interpreted to mean a description of the findings of an analysis or investigation).

11.6.2 Preparing an analytical plan

The application or assessment report should define any application, extrapolation, transformation or other issues that need to be considered to enable translation of the clinical evidence to economic evaluation.

Each translation issue should be converted into a succinct research question that could be addressed by an additional study. The application or assessment report should then present and justify a focused analytical plan (which specifies details of data, sources, methods and analyses) to address each translation issue identified.

Finally, the application or assessment report should present the results of each additional study undertaken to address each translation issue identified and discuss where and how such results are applied in the economic evaluation.

Additional guidance on the presentation of additional evidence to inform the economic evaluation can be found by referring to Section C of the *Guidelines for Preparing Submissions to the Pharmaceutical Benefits Advisory Committee* (the PBAC Guidelines).³

11.7 Inputs to economic evaluation

Inputs to an economic evaluation include all the variables that impact upon the estimation of the cost-effectiveness of the service, such as resources, transition probabilities and outcomes.

11.7.1 Defining resource variables

Resource variables primarily affect the numerator (ie estimates of incremental costs associated with a service compared with the comparator) of the incremental cost-effectiveness ratio. Four categories of resource items may be included in an economic evaluation:

- health care resources (ie relating to the intervention, including dealing with adverse events associated with the intervention)
- resources consumed in sectors other than the health care sector
- patient and family resources (ie out-of-pocket expenses incurred by patients or family members plus the value of any resources they contribute to the treatment or management process)
- production changes (eg from patients or family members losing time from work while participating in a treatment or management process).

As a societal perspective is to be adopted in applications and assessment reports, costs to patients, costs to governments, costs to health insurance agencies and any other costs to society should all be included in the evaluation. However, resources should be presented in a disaggregated format initially and then in increasing levels of aggregation, such that costs are presented from each of the following perspectives:

- the government perspective; in particular, the MBS (or other relevant government program) perspective
- a health system perspective (including costs regardless of who bears them but only those which are directly related to health status)

³ <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacguidelines-index>

- a societal perspective.

This is to enable MSAC to gauge the impact of including resources that are not directly related to health in the analysis of cost-effectiveness.

Determining resources for inclusion in an economic evaluation

There are three stages to the inclusion of resources in an economic evaluation:

- identifying the relevant resources
- measuring or quantifying use of the resources
- valuing the resource (ie assignment of unit costs for the resource).

Identifying resource variables

Differences in the use of the following health care resources as a consequence of substituting the service under consideration for the main comparator should be taken into account:

- medical services including procedures
- hospital services
- diagnostic and investigational services
- pharmaceuticals (eg those co-administered with a service or those used to treat side effects)
- community-based services
- any other health care resources (eg occasionally because of the condition being treated or the age of the patients), consideration of resources such as social services (home help, day care, meals on wheels, nursing, physiotherapy and allied health services, etc) may be material to the estimation of incremental costs and should therefore also be taken into account.

Where a placebo is included in an evaluation as part of the comparator, no costs should be assumed to be associated with the placebo itself.

Given that there is a wide range of resources to consider in an economic evaluation, it may be unrealistic to expect all relevant resources to be measured and valued. Where the extent of use of a resource is identical in both arms of an analysis (ie such that costs associated with these resources are common to both arms of a comparison), these resources can be excluded from consideration as they will not affect the choice between the two interventions. It may also be reasonable to exclude resources that are associated with insignificant costs or that do not have a material influence on incremental costs.

Measuring and quantifying resource variables

Data are required to quantify the effect of the service on use of resources in terms of physical units (eg days in hospital, visits to a GP). The level of use of resources may be measured prospectively in the course of a clinical study, by retrospective review of relevant records, or by administration of a questionnaire or survey or through the use of diaries. The source of the estimate of the degree of use should be specified. It is important that extrapolations and modelling of resource use beyond that available

from the primary evidence be distinguished from data populating an economic evaluation that are directly derived from the primary evidence. Where a choice is made to use data that are not consistent with data from the primary evidence, the justification for this choice should be presented.

Analyses should be based on the best evidence available. However, it is recognised that deficiencies exist in the evidence base available to gauge the difference in resource use between a service and its comparator. For example, some parameters may be estimated with a low degree of precision or evidence may have been gathered in other healthcare systems. In these cases, the limitations of the data and details of any attempts to overcome these limitations should be stated. Appropriate sensitivity analysis should be conducted to explore the impact of uncertainty in the quantification of resources on the results of the economic evaluation.

Valuing resource items

The theoretical cost for a resource is its opportunity cost (ie the value of the foregone benefits because the resource is not available for its best alternative use); however, opportunity costs are generally not available. Usually, a pragmatic approach to the estimation of unit costs is taken (eg use of existing market prices). However, owing to imperfections in health care markets, market prices may not reflect opportunity costs (eg hospital charges may deviate from costs if one activity is cross-subsidised by another).

Unfortunately, there are no clear guidelines available to guide an analyst as to when they should attempt to adjust observed market prices to reflect true opportunity costs. However, in order to ensure consistency and comparability across economic evaluations considered by MSAC, it is essential that economic evaluations use consistent measures of medical and other services and cost them in a consistent manner. The *Manual of Resource Items and their Associated Costs* (referred to as ‘the PBAC Manual’ in these guidelines),⁴ a companion to the *Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee* (referred to as ‘the PBAC Guidelines’ in these guidelines),⁵ was developed to ensure such consistency in submissions to the PBAC. Where costs are available for a resource by reference to the PBAC Manual, these costs should be used in economic evaluations presented to MSAC. If there are pressing reasons for deviating from the cost recommended by the PBAC Manual (note the circumstances below where deviations from the PBAC Manual may be accepted), the application or assessment report should:

- provide the justification for preferring an alternative cost
- specify the source of (or describe the generation of) the alternative cost
- provide results of analyses using both the cost recommended by the PBAC Manual and the preferred cost (to permit MSAC to gauge the effect of using the alternative cost).

⁴ <http://www.health.gov.au/internet/main/publishing.nsf/content/health-pbs-general-pubs-manual-content.htm>

⁵ <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacguidelines-index>

Circumstances where deviation from using the costs in the PBAC Manual may be acceptable

The PBAC Manual recommends use of the full MBS scheduled fee as a cost for medical services, which is not entirely consistent with a societal perspective because it may not include all relevant patient co-payments. As discussed above, a societal perspective should consider costs to patients, costs to governments, costs to health insurance agencies and any other costs to society. Although MBS fees are generally a relatively small component of total costs in PBAC applications, they can be much more important for MSAC considerations. Therefore, MSAC prefers the use of the price for a service, including patient co-payments. Use of the median co-payment in combination with the full MBS service fee is more likely to reflect the opportunity cost associated with a service than the use of mean co-payments. Median patient co-payments associated with MBS items are obtainable from Medicare Australia by application through the MSAC Secretariat.

It is important to note that, where the fee for an MBS item includes a component that is an allowance for costs of capital equipment, the economic evaluation should not separately include any additional provision for capital outlays associated with the procurement of equipment used to deliver the service (as this would result in double counting of capital outlays).

The PBAC Manual recommends that, where costs associated with a hospitalisation are required in an evaluation, these should be estimated using National Public Sector Cost Weights, as reported by the National Hospital Cost Data Collection. However, on the grounds that the public sector cost weights include costs for radiography, pathology, medical services, training of medical staff and so on, whereas these are excluded from the private sector cost weights, MSAC prefers that costs associated with an episode of hospitalisation be estimated on the basis of National Private Sector Cost Weights, as reported by the National Hospital Cost Data Collection.

If there is a material difference between the National Public Sector Cost Weight and the National Private Sector Cost Weight associated with a particular AR-DRG, and if costs associated with hospitalisation are a material driver of costs associated with a proposed service or the main comparator(s), a sensitivity analysis substituting the National Public Sector Cost Weight for the National Private Sector Cost Weight should be provided.

Defining costs for resource items not included in the PBAC Manual

The unit costs should be as current as possible. If a unit cost is not recommended by the PBAC Manual, or if there are pressing reasons to use a unit cost other than that recommended in the PBAC Manual, the application or assessment report should provide:

- the source of each unit cost
- a description of the generation of the unit cost
- the justification for the methodology used to derive the unit cost.

Ensure that each unit cost is consistent with the perspective of society (ie costs to government, patients and other parties are all to be considered and specified).

Where more than one unit cost for a service is available (eg if there is more than one supplier for the service), the lowest price for the service (that can be used for the population and in the setting being considered) should be assumed in the economic evaluation. There may be reasons not to assume the lowest price (eg the lowest price is not an adequate reflection of the opportunity cost of the resource). Where the lowest price is not assumed in the base case analysis, the application or assessment report should provide:

- the justification for selecting an alternative price
- evidence to support the selection of the alternative price
- sensitivity analysis assuming the lowest price.

Presenting the cost of the proposed service

The application or assessment report should provide the cost for the proposed service in a disaggregated form. It should also detail any likely patient co-payment(s), such as payments to cover capital equipment that would not be eligible for subsidy under Medicare (eg office equipment), and the proposed full Medicare fee (or other government-subsidised fee component).

Where possible, the proposed cost for the service should be justified (eg by comparison of the proposed price with the price for comparable services listed on the MBS or other relevant government program).

The Medicare fee (or other government-subsidised fee component) should be presented itemising any portion of the fee attributable to capital costs and the portion of the fee attributable to variable costs associated with delivering the service.

In the case where part of the proposed fee is an allowance for capital outlays, an estimate of the capital cost per service over the life of the machine should be presented. The following steps are recommended for determining an appropriate allowance for capital costs:

1. Provide an itemised list of assets that will be required to deliver the anticipated number of services.
2. Provide an estimate of the total capital outlay that will be required over the useful life of the assets.
3. Annuitise (applying discounting at an annual rate of 5%) the initial capital outlay over the useful life of the assets, permitting the estimation of the net present value of the assets.
4. Divide this cost by the use of capacity over the useful life of the asset (where information on capacity utilisation is not available, use a benchmark assumption that capacity is utilised at 80% under a long-run perspective).

Where it is known that the equipment is not going to be used to ‘capacity’ or when the equipment is used for multiple purposes, the application or assessment report should provide:

- evidence-based estimates of extent of use of the machine for the service being considered and for other services
- a reasonable consideration as to potential uses of any ‘spare capacity’
- adequate justification for the proportion of time a piece of capital equipment is deemed to be used for the service in question.

As health professionals may become more efficient in the use of health technologies over time, the costs in the early stage of a technology’s life cycle may not be a good predictor of costs in the long run. Therefore, where appropriate, the application or assessment report should include adjustments for the effects of potential learning curves on capital costs associated with a proposed service over time.

It may be appropriate to provide an economic analysis for more than one population, such as for a wider population (ie where there is potential for use of the service beyond a proposed restriction; see Section 11.1). Variations in the size of the population are likely to have implications for the number of services likely to be delivered. In the case where the proposed fee includes an allowance for capital equipment, it may be appropriate to modify the unit cost of the proposed service, for example, to account for differences in capital cost per service over the life of the machine that may occur as a consequence of a change in the number of services anticipated to be delivered.

Disaggregating hospitalisation costs

There are several instances where the application or assessment report may need to present disaggregated costs for an episode of hospitalisation. For example:

- where an intervention will be associated with a shorter length of stay compared with the comparator
- where there is a change in the extent of resources provided during a hospitalisation
- where the cost for an episode of hospitalisation relates to an average cost for a heterogenous group of patients
- where the evaluation seeks to examine cost-effectiveness in only a subgroup.

In the case where an AR-DRG cost weight relating to an episode of hospitalisation reflects the average cost in a heterogeneous group of patients (eg patients diagnosed under various International Classification of Disease (ICD) classifications) and it is anticipated that there are material differences in costs applying to individual subgroups, it may be possible to obtain cost weights by ICD classification.

In other cases, the application or assessment report should follow the advice of the PBAC Manual on disaggregation of hospitalisation costs when considering the breakdown of a unit cost for an episode of hospitalisation. Where it is claimed that an intervention will be associated with a shorter length of stay, disaggregating costs for an episode of hospitalisation by estimation of an overall average cost per day is likely to be inappropriate. In the absence of accurate costings for daily costs of hospitalisation, the PBAC Manual recommends assuming a cost-per-day equivalent to the cost per day for the lowest cost-weight available. Given imprecision in the estimate of component costs, and problems in calculating the contribution of various

populations to an average cost of hospitalisation, the PBAC Manual recommends justification of the approach adopted for sourcing component costs or costs in various populations (eg use of state-based cost weights as opposed to the national cost weights).

Appropriate sensitivity analysis should be conducted to explore the impact of uncertainty in the valuation of resources on the results of the economic evaluation.

Presenting resource costs

All steps taken to calculate resource costs in the economic evaluation should be presented in a manner that permits verification and replication of the calculations. Estimated costs should be presented in both disaggregated and aggregated formats. Individual costs should be specified for each type of resource provided and according to who is bearing the costs.

The application or assessment report should first construct and present a table clearly identifying the present value of health care resources, patient and family resources and resources consumed in other sectors, including:

- each type of resource included in the economic evaluation (the name and definition or description, where appropriate, should be provided)
- its natural unit of measurement
- the unit cost used to value that resource in the economic evaluation (any goods and services tax (GST) that might apply should be excluded from the unit cost)
- the bearer of the cost (if more than one party bears costs, the proportions borne by the various parties should be specified)
- the source of the unit cost.

Names of resource variables and details of sources should be sufficiently precise to permit verification and replication of the economic evaluation. For example, for an episode of hospitalisation, the AR-DRG item number with the details of the report from which cost-weights are taken should be specified.

Table 11.7.1 shows a recommended grouping of items into categories and suggested format for the resources table.

Table 11.7.1 List of health care resources and unit costs to be included in the economic evaluation

Resource item	Unit of measurement	Unit cost	Bearer of cost	Source of unit cost
Medical services				
GP attendance	Visit	\$x	\$y – MBS \$z – patient	MBS item 23 — costs from Medicare Australia*
Initial specialist attendance	Visit	\$x	\$y – MBS \$z – patient	MBS item 104 — costs from Medicare Australia*
Subsequent specialist attendance	Visit	\$x	\$y – MBS \$z – patient	MBS item 105 — costs from Medicare Australia*
Hospital services				
Hospitalisation for retinal procedure	Hospital stay	\$x	\$x – government	Average cost per DRG according to AR-DRG Public Sector Estimated Cost Weights Round 7 — Item C03Z
Diagnostic and investigational services				
Ultrasound of orbital contents	Visit	\$x	\$y – MBS \$z – patient	MBS item 55030 — costs from Medicare Australia*
Pharmaceuticals				
Tobramycin eye drops	Bottle (5 mL)	\$x	\$y – PBS \$z – patient	PBS item 2328 M — average co-payment estimated assuming a % of patients are general and remainder are concessional.
Tobramycin eye ointment	Tube (3.5 mL)	\$x	\$y – PBS \$z – patient	PBS item 2329N — average co-payment estimated assuming a % of patients are general and remainder are concessional.
Allied health care services				
Initial consultation with clinical counsellor	Visit	\$x	\$y – private health insurance \$z – patient	Table 1, Section 8.2, Manual of Resource Items — assuming b% of patients have private health insurance and the average rebate from insurer is \$d.
Subsequent consultation with clinical counsellor	Visit	\$x	\$y – private health insurance \$z – patient	Table 1, Section 8.2, Manual of Resource Items — assuming b% of patients have private health insurance and the average rebate from insurer is \$d.

* Costs from Medicare Australia can be obtained by application to the MSAC Secretariat.

Manual of Resource Items = PBAC *Manual of Resource Items and their Associated Costs*

(<http://www.health.gov.au/internet/main/publishing.nsf/content/health-pbs-general-pubs-manual-content.htm>)

The application or assessment report should then estimate and present the number of natural units (eg number of GP consultations, number of packs of a pharmaceutical)

of each resource used at each stage in each arm of the economic evaluation. The amount of resource supplied is the relevant economic measure rather than the amount of resource consumed. The source for the estimate of amount of resource used should be provided either in text or as tables. If using data or opinion that differs from the evidence provided in Section 10, the justification for this selection should be provided.

For each type of resource provided, the number of natural units should be multiplied by the present value of the unit cost. Future costs should be valued at current prices. This is consistent with using constant prices in the evaluation. Accordingly, no allowance for future inflation should be included in estimation of future costs. As discussed in Section 11.5, where costs are considered to be borne over more than one year, the present value of future costs should be used in the economic evaluation. This means that discounting (at an annual rate of 5%) should be applied to costs sustained in the period beyond the first year.

The costs for each service of interest and the difference in costs across the two (or more) services of interest should be calculated over the time horizon of the economic evaluation.

Table 11.7.2 provides a suggested format for presentation of a summary of the information required. When summarising costs in this tabulated format, rounding of total and incremental costs to the nearest dollar may be appropriate.

Table 11.7.2 Summary of resources to be included in the economic evaluation

Resource item	Unit cost	Number of units		Total cost		Incremental costs of proposed service
		Proposed service	Comparator	Proposed service	Comparator	
Costs borne by MBS						
GP attendance	\$y	A	B	$A \times \$y$	$B \times \$y$	$(A \times \$y) - (B \times \$y)$
Initial specialist attendances	\$y	A	B	$A \times \$y$	$B \times \$y$	$(A \times \$y) - (B \times \$y)$
Subsequent specialist attendances	\$y	A	B	$A \times \$y$	$B \times \$y$	$(A \times \$y) - (B \times \$y)$
Ultrasound of orbital contents	\$y	A	B	$A \times \$y$	$B \times \$y$	$(A \times \$y) - (B \times \$y)$
Total costs borne by MBS:						
Costs borne by other government agencies						
Hospitalisation for retinal procedure	\$x	A	B	$A \times \$x$	$B \times \$x$	$(A \times \$x) - (B \times \$x)$
Tobramycin eye drops	\$y	A	B	$A \times \$y$	$B \times \$y$	$(A \times \$y) - (B \times \$y)$
Tobramycin eye ointment	\$y	A	B	$A \times \$y$	$B \times \$y$	$(A \times \$y) - (B \times \$y)$
Total costs borne by other government agencies:						
Costs borne by patients						
GP attendance	\$z	A	B	$A \times \$z$	$B \times \$z$	$(A \times \$z) - (B \times \$z)$
Initial specialist attendances	\$z	A	B	$A \times \$z$	$B \times \$z$	$(A \times \$z) - (B \times \$z)$
Subsequent specialist attendances	\$z	A	B	$A \times \$z$	$B \times \$z$	$(A \times \$z) - (B \times \$z)$
Tobramycin eye drops	\$z	A	B	$A \times \$z$	$B \times \$z$	$(A \times \$z) - (B \times \$z)$
Tobramycin eye ointment	\$z	A	B	$A \times \$z$	$B \times \$z$	$(A \times \$z) - (B \times \$z)$
Initial consultation with clinical counsellor	\$z	A	B	$A \times \$z$	$B \times \$z$	$(A \times \$z) - (B \times \$z)$
Subsequent consultation with clinical counsellor	\$z	A	B	$A \times \$z$	$B \times \$z$	$(A \times \$z) - (B \times \$z)$
Total costs borne by patients:						
Costs borne by other parties (eg health insurance agencies)						
Initial consultation with clinical counsellor	\$y	A	B	$A \times \$y$	$B \times \$y$	$(A \times \$y) - (B \times \$y)$
Subsequent consultation with clinical counsellor	\$y	A	B	$A \times \$y$	$B \times \$y$	$(A \times \$y) - (B \times \$y)$
Total costs borne by other parties						
Total costs:						

Presenting production changes for MSAC assessment

A production change is the value estimated in monetary units of the potential working time gained or lost measured in time units (days, weeks, years, etc) that is realised as productive activity. It may also include realising the productive change of the potential impaired working time gained or lost by a sick patient continuing to work (measured in similar time units together with a measure of any associated change in the extent of impairment). Production changes have been called ‘indirect economic outcomes’, in recognition of the fact that subsequent decisions had to be made to realise the time gained as productive activity to the advantage of the rest of society, rather than as any other activity.

If production changes are combined with surrogate outcome indicators in an economic evaluation, the analyst should provide a strong justification, because this combination is generally inappropriate.

If production changes are to be included in a cost-utility analysis, the application or assessment report should adopt a method that avoids double-counting changes in health-related quality-of-life. Preference weights in a cost-utility analysis may already capture health-related changes because they may incorporate the utility impacts of productive capacity to the individual receiving the proposed service. These health-related changes may therefore already be appropriately included in the denominator of the cost-utility ratio.

Unlike direct health benefits, the economic benefit to society through patients’ return to, or maintenance of, productive capacity is both difficult and controversial to estimate accurately. This is because the available methods and their application remain unresolved. Therefore, although changes in production as an outcome of therapy may be included in supplementary analyses of MSAC assessments, they should not be included in the base case analysis.

There are several difficulties in estimating the net present value of production changes.

These estimates are underpinned by three assumptions:

- for short-term absence, production will be made up on the return to work
- employers usually have excess capacity in the labour force to cover absenteeism
- for long-term absence, production will be made up by a replacement worker otherwise unemployed.

Where estimation of production changes can be justified in an MSAC assessment, the application or assessment report should address each of the three underlying assumptions listed above when estimating production changes from the potential working time gained or lost (reported in time units). For example, the claim that there has been a recovery of production lost due to returning to health from an episode of illness depends on demonstrating that:

- the worker returns to work
- the worker is productive

- the work lost is not made up elsewhere by others in the company or the same worker following return to work. (Note: if the worker is highly productive, the incentives to replace him or her are stronger.)
- no temporary replacement from outside has been employed (namely that there is full employment).

As in this example, the marginal increase in society's production due to the return of healthy workers to the workplace is overestimated if the human capital method is used; that is, the workers' time regained is simply multiplied by the labour market value of the average worker (usually estimated by the average wage). It is not always likely to be zero either, but some proportion in between. The application or assessment report should provide and justify the best estimate of the true proportion based on firm evidence. Addressing the four questions in the example above would therefore help to convert the potential working time gained or lost reported in time units into production gains or losses.

11.7.2 Defining outcome variables

Outcome variables are those primarily affecting the denominator (ie estimates of incremental benefits associated with a service compared with the comparator) of the incremental cost-effectiveness ratio. Although transition variables can affect both the numerator and denominator of the cost-effectiveness ratio, MSAC prefers them to be discussed with the outcome variables.

The base-case economic evaluation should be based on the outcome measure that most closely and validly estimates the final health outcome from a patient perspective. Generally, outcomes to be considered in an analysis will be those associated with the disease under study and not those diseases which, in the fullness of time, patients might be expected to develop if they receive effective treatment for their current condition.

The application or assessment report should nominate and justify the outcome that is considered to best reflect the comparative performance of the interventions being compared. The outcome upon which the economic evaluation is based may need to reflect more than one type of intermediate outcome (eg where a variety of desired and adverse outcomes are presented in the clinical balance sheet requested in Section 11.2). The application or assessment report should indicate whether the outcome upon which the economic evaluation is based represents the final patient-relevant outcome of treatment. Where appropriate, the application or assessment report should explain and justify the linking of each measured short-term and/or surrogate outcome included in the clinical balance sheet to a modelled final outcome, including a justification for how these are quantified over time.

For medical services that cure short-term illnesses, quality of life is unlikely to be an issue. It may also be reasonable to assume that certain events, which may themselves be serious, do not have a large effect on the average quality of life of the survivors (eg pneumonia).

When considering the benefits of diagnostic tests, health benefits arising from changes in treatment that ensue as a consequence of the result of the diagnostic test need to be distinguished from non-health benefits due to value of information

(eg where a patient is given further information about their diagnosis or prognosis but this does not have any impact for management of, or outcomes for, the patient). MSAC's preference is for only health benefits to be included in the base case analysis. Non-health related benefits should not be included in the base-case analysis but may be included in a sensitivity analysis.

Where a change in health-related quality of life is the principal intended final outcome, a health-related quality of life measure should be considered. This is true for some indications (eg relief of pain, treatment of depression, treatment of some cancers) in which improved quality of life is the principal aim of delivery of the service. Alternatively, quality of life may actually be impaired by the proposed service or by the main comparator.

The requirements for evidence of changes in outcomes include the quantification of the effect of the service on the course of the condition being diagnosed, treated and/or managed, the effect on patient's health-related quality of life and the valuation of those effects in a manner that reflects the preferences of the general population. It is important that extrapolations and modelling of outcomes beyond those available from the primary evidence presented in Section 10 be distinguished from data populating an economic evaluation that are directly derived from the primary evidence. This is facilitated by presentation of a stepped economic evaluation. Where a choice is made to use data that are not consistent with data from the primary evidence, the justification for this choice should be presented.

Analyses should be based on the best evidence available; however, it is recognised that there may be deficiencies in the evidence base available to gauge the extent of difference in outcomes associated with a service compared with its comparator. For example, some parameters may be estimated with a low degree of precision, or may relate to a population that is not directly representative of the population under consideration. In these cases, the limitations of the data and details of any attempts to overcome these limitations should be stated. Appropriate sensitivity analysis should be conducted to explore the impact of uncertainty in the quantification of outcomes on the results of the economic evaluation.

Health-related quality-adjusted life years (QALYs)

The QALY is a preference-weighted measure of adjusted survival time, where the adjustment is by means of health-related quality-of-life preference weights derived for specific health states. Expected survival time in each of these health states is weighted by these preference values and then summed across the duration of survival to generate the expected QALYs.

The QALY is accepted as a valid measure of health-related quality of life and is widely used as a measure of health outcomes in the economic evaluation of medical technologies. A QALY has the following key characteristics:

- It combines extension of life and quality of life in a single index that allows comparison across health interventions.
- The index is anchored on a 0–1 scale of death to perfect health with equal intervals measured in such a way as to have equal value.

- The values or weights that underpin the QALY measure are based on a sample of individual preferences. These preferences are obtained in a way that involves a trade off between quality and quantity of life. This provides some validity to the QALY as representing societal trade-offs and therefore social values.

In principle, QALYs provide a measure of health outcomes that is comparable across interventions. Although promoting QALYs as the outcome of choice can be an attractive concept to decision makers (because this metric allows interventions in all disease areas to be directly comparable), many concerns over the estimation of QALYs have been documented. Therefore, an application or assessment report should consider the extent to which the value of extending an analysis to capture benefits in terms of QALYs will be limited by the quality of the data used to derive preference weights associated with various health states. Progression through modelling steps should continue only as long as the results generated are likely to be of value and informative to MSAC.

Obtaining utility weights for inclusion in assessments of medical services

Several approaches to obtaining utility weights to permit the estimation of QALYs are discussed in these guidelines:

1. Use of a multi-attribute utility instrument (MAUI) in a study.
2. Use of a MAUI in a sample of patients matched to study participants and the population for whom the proposed service is to be made available.
3. Direct elicitation of preference ('utility') weights in a study.
4. Creation of scenarios to indirectly elicit 'utility' weights.
5. Mapping results of other quality-of-life instruments to the utility weight anchors of a 0–1 interval of death to full (perfect) health.
6. Reporting 'utility' weights from published sources.

The generally preferred method of measuring QALYs is by the repeated application of a valid, reliable and responsive MAUI questionnaire to participants in a study, together with the application of an appropriate scoring algorithm. For MAUIs, the measurement of the health state happens in the study itself, which enables more accurate and unbiased measurement of the health states as experienced by the patients receiving the relevant treatments. The valuation step is then inferred using an acceptable scoring algorithm, which means that the valuation is conceptually and practically separated from the assessment of the particular disease or treatment, and therefore not subject to bias. The advantages and disadvantages of relying on this method are discussed in greater detail in the PBAC Guidelines, Appendix 6, section A6.3.

It is recognised that MAUI instruments are not routinely included as an outcome measure in many studies, so it is anticipated that there will be a lag time before this preference can be met routinely. It is also recognised that in many cases it will be necessary to attach utility weights to health states that are not observed within a study; for example, because they are the result of events that occur outside the study

timeframe. Accordingly, guidance is also provided on alternative approaches. In some circumstances, it is possible that an alternative approach would be preferred to the use of a study-based MAUI.

1. Multi-attribute utility instruments (MAUIs)

A MAUI can be used to collect information from study participants on predefined and prevalued health states at baseline and during the study. There are a number of MAUIs that vary in their coverage of health domains, but all of which claim to cover the main areas of health-related quality of life that patients would be willing to trade for increased survival. Acceptable MAUIs are the Health Utilities Index (HUI2 or HUI3), the EQ5D ('EuroQol'), the SF-6D (a subset of the Short Form 36, or SF-36) or the Assessment of Quality of Life (AQoL) instrument. Currently, there is insufficient basis for a preference to be expressed between these MAUIs. All are based on acceptable scaling techniques of the standard gamble (SG) or time trade-off (TTO), and some have different scoring algorithms for different countries. Studies directly comparing these MAUIs suggest that each MAUI yields different results for the same health state, so their utility weight results cannot be compared with complete confidence.

The MAUIs listed above vary in their coverage of important health domains, but they all cover the main areas of health-related quality of life that patients would be willing to trade for increased survival. HUI2 is designed for use in childhood conditions. All the MAUIs have strengths and weaknesses. For example, as a general observation, the EQ5D has fewer possible health states, which means that it has been perceived as relatively unresponsive or insensitive compared with the other MAUIs. Another feature of EQ5D is that when a difference is detected, the numerical value can appear disproportionately large compared with the more gradual increments of the other MAUIs.

The use of any other possible preference-based instrument, such as the Quality of Well-Being Scale (QWB) or the 15D (15 Dimensions), needs to be particularly justified, including with reference to the above criteria of comparability, acceptable scaling techniques and responsiveness.

Details of MAUIs that have been used in relevant studies for the purposes of reporting utility weights should be provided. The application or assessment report should justify the selection of any MAUI not listed above as acceptable by assessing:

- the validity of the instrument
- the reliability of the instrument
- the responsiveness or sensitivity of the instrument to differences in health states between individuals who are likely to be affected by the proposed service and its main comparator
- the responsiveness or sensitivity of the instrument to changes in health states over time experienced by any one individual
- the duration of the period assessed when responding to the MAUI questionnaire compared with the duration of the condition of interest

- the applicability to the general Australian population of the scoring algorithm applied to the responses reported with the MAUI questionnaire to calculate utility weights.

Include any data and references that support the selection of the MAUI in a technical document or an attachment.

2. Using a MAUI in a sample of matched patients

Conceivably, a MAUI could be administered to appropriately matched groups of patients with baseline and final study outcomes as observed in the studies. However, this population-matching approach is subject to multiple sources of bias and thus uncertainty, particularly related to how similar the sampled patients are to those in the economic evaluation and the inability to blind the sampled patients from the objectives of the study.

3. Directly eliciting weights in a study

Direct methods may be used within a study to ask patients to value their current health state at baseline (or over a recent period of time) and at points during the study. The methods commonly used are: a rating scale, a time trade off technique, a standard gamble technique, or willingness to pay. Where these methods are used, an assessment should be provided that considers the following:

- whether the patient population is likely to give a representative valuation of the condition
- whether the technique of valuation at baseline and during the study are valid and likely to be free of bias; for example, do the results correlate with clinical or other measures of health outcomes in the study; does the time frame of the hypothetical exercise affect the results
- whether the results of the exercise are reliable (is there a high variance in results or inconsistencies in responses, or a high number of missing observations)
- what attributes of health-related quality of life and other patient attributes are being valued
- are the individual responses likely to differ from the general population (eg because the severity of the condition leads to adaptation to illness and affects the utility weight at baseline).

4. Scenario-based studies of quality of life

An alternative to direct measurement of preference for health states in study patients is to gather evidence from a valuation exercise among individuals presented with hypothetical health state scenarios designed to mimic the health states associated with the intervention and the comparator. Although this may be a useful post-study supplement to the recommended method of obtaining utility weights from a study to value quality beyond the horizon of the study, it raises issues of potential bias typical of observational studies. The assessment should consider particularly:

- whether the methods by which the health state scenarios were constructed allow all of the critical changes in quality of life associated with the intervention to be captured

- whether the methods by which the health state scenarios were constructed are likely to lead to bias in the valuation of health-related quality of life associated with the intervention (eg by focusing on some aspects of health related quality of life, such as physical functioning, while excluding or minimising the impact of others, such as mental or social health).

The PBAC Guidelines provide guidance on the appropriate presentation of information relating to scenario-based utility valuation of health outcomes (PBAC Guidelines, Appendix 6, section A6.4)

5. Mapping of generic and disease-specific scales

Although some of the generic and disease-specific scales have used sophisticated psychometric techniques for instrument construction, none of these scales are capable of representing patient preferences on a life–death scale and so cannot be used to calculate QALYs without some transformation. However, a number of attempts have been made to map or transform scores in clinical studies from disease-specific or generic measures into MAUI scores. These are then used to construct QALYs. This approach varies from a simple intuitive mapping to the use of statistical techniques. This is not a well-established procedure and where it is done special attention needs to be given to establishing that results generated are plausible and unbiased, particularly where the utility estimates generated have a substantial impact on the results of the economic evaluation. Where statistical techniques have been used, tests of reliability might include the predictive value of the technique across a range of quality-of-life values and changes in quality of life within, and differences between, subjects in the relevant medical condition. Where this approach is adopted, extensive sensitive analysis around the utility estimates generated should be undertaken to examine the sensitivity of results of the economic analysis to this variable.

6. Preference weights ('utilities') sourced from the literature

'Off-the-shelf' utility estimates may sometimes be available from the literature, and have been most often used when seeking to examine the impact of quality-adjusting a survival claim estimated in terms of life-years gained. As for any presentation of secondary (or even tertiary) data or analysis, the validity of the utility estimate depends on the methods used to elicit the estimate. Accordingly, present and assess the results against the preferred characteristics of a primary utility study, including:

- how the studies were identified (eg systematic search preferred to selective reporting)
- how representative the health state in each identified study is of the health state in the presented economic evaluation (including the type and severity of symptoms and the duration of the health state)
- how the health state was captured (eg MAUI versus scenario-based)
- how the preference was determined (eg SG or TTO)
- what sample was chosen to respond to the MAUI questionnaire or scenario (eg members of the general public, patients, care givers, health care professionals)
- what assessment was made of the nature and direction of bias that might arise given the sample and methods
- how the sensitivity analyses examined variation in the identified utility options.

A particular difficulty in interpretation has occurred when a cost-utility analysis relies on combining utility weights across different sources for different health states within an economic evaluation, particularly across different sources that used different methods.

Providing evidence

Where any of the above techniques to calculate QALYs have been used, the assessment should, where possible, include supportive data and references that demonstrate the validity and reliability of the methods used.

Additional advice on the acceptability of methods for obtaining utility valuations and the presentation of evidence in relation to preference weights can be found in the PBAC Guidelines, Appendix 6.

Presenting outcome variables for MSAC assessment

The name (and description or definition as necessary) of each outcome variable included in each step of the economic evaluation should be provided. The application or assessment report should provide sufficient detail about each outcome and its measurement to enable MSAC to assess its importance. The extent of outcome and the source for this quantification should be provided. If using data or opinion that differs from the evidence provided in Section 10 for estimation of outcomes, the justification for this selection should be provided.

For each outcome included in each step of the economic analysis, the following steps should be followed:

- describe the outcomes included in the evaluation
- define a clinically important difference in the outcome
- report the magnitude of treatment effects
- quantify the degree of uncertainty around the point estimate of the outcome
- specify the source of the evidence.

These steps are described in more detail below.

Describe the outcomes (and units of measurement) included in the evaluation

The natural unit of measurement should be described. It is useful in economic evaluation if outcomes can be expressed as the time to a particular event (eg mortality can be presented as time to the event of death, as in a survival analysis). When outcomes are presented in this format, differences in outcomes across two interventions can be measured as the integral between the curves in time-to-event plots for the two interventions. If time-to-event data are not available, the number of successes or failures of treatment (eg proportion of patients achieving a target outcome at particular time points) are preferable to a mean change in physiological variables (an exception could be in the case of a cost-minimisation analysis, where the mean change to a physiological variable may be sufficiently responsive to detect small but clinically important differences).

Justification for the definition of treatment ‘success’ or ‘failure’ should be provided (eg for interventions used in the management of epilepsy, treatment success may be better defined as the proportion of patients having no epileptic seizures over a period of time compared with, for example, the proportion of patients achieving a 50% reduction in number of seizures compared to baseline).

Define a clinically important difference in the outcome

The application or assessment report should define what constitutes a clinically important difference in the outcome and justify the definition; this is particularly important in the case of continuous variables, where large studies may detect statistically significant, but clinically unimportant, differences between treated and control groups.

Report magnitude of treatment effects

The size of the effect assumed in the economic evaluation should be reported; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences; for time-to-event analysis, the hazard ratio is an equivalent statistic.

If the magnitude of the difference in treatment effect is not statistically significant or if it is not clinically important in terms of effects on health-related quality-adjusted survival, it is not appropriate to calculate an incremental cost-effectiveness ratio.

Quantify the degree of uncertainty around the point estimate of the outcome

Consideration of the degree of uncertainty around point estimates for outcomes is often more important than consideration of the point estimate itself.

The application or assessment report should provide a 95% confidence interval around the estimate of outcome. If this is not available, the *P*-value is an alternative, but less preferred measure.

Where probabilistic cost-effectiveness modelling is presented, the application or assessment report should provide the justification for the selection of a distribution around the point estimate of the outcome.

Specify the source of the evidence

The application or assessment report should specify the source and summarise the quality of the evidence upon which the economic evaluation is based. If the evidence used as a basis for the economic evaluation involves a selection of one or more sources of evidence over others, as presented in Section 10, the report should present a justification for the selection and summarise differences in outcomes (both effectiveness and safety) as reported in the selected evidence compared to the omitted evidence.

The application or assessment report should specify whether data from the study or studies were analysed on an ‘intention-to-treat’ basis. This approach is generally preferred and if other approaches are considered appropriate, justification for the alternative approach should be provided. The application or assessment report should explain how data from dropouts and withdrawals (missing data) were incorporated into the analysis.

If a study was ‘negative’ (ie failed to detect a difference in the outcome), an estimate of the power of the study to detect a clinically important difference between the treated and control groups should be provided; this can be important in the interpretation of the results of cost-minimisation analyses where the two services are claimed to have equivalent effects.

If the study measured a number of outcomes, the application or assessment report should discuss whether and how an adjustment was made for multiple comparisons in the analysis; results for many outcomes at a variety of different times resulting in a large number of hypotheses to be tested are often reported. If not adjusted for multiple comparisons, the odds will be high that through chance alone, a statistically significant difference will emerge in one of these comparisons.

The application or assessment report should provide details of the methodology used to derive values for the variables influencing the final outcome in an evaluation that are not available directly from the primary evidence provided in Section 10 (eg transition variables or utility estimates for health states). For example, the report should present the search strategy used to locate appropriate data from the literature, and inclusion and exclusion criteria applied to the results of a search of the literature.

The application or assessment report should discuss how different parameters in an economic evaluation are combined to achieve the final outcome. Where outcomes have been extrapolated over time (eg where it is assumed that an outcome measured in the study/studies will be maintained in the longer term), the underlying assumptions and rationale for the extrapolation should be discussed. It is important that the biological plausibility and validity of extrapolations be considered (eg assumption of a linear relationship between outcomes and time may not be clinically plausible for many conditions). Where QALYs, or other composite measures of outcome, are derived, the relationship between the results measured in the studies constituting the primary source of evidence and any derived results should be explicitly described.

To facilitate this, all variables influencing the final outcome in the economic evaluation must be listed and documented in a table. Variables influencing outcomes include:

- probabilities in each branch of a decision analysis, particularly probabilities that simulate a treatment effect by differing between the two arms (that represent the service under consideration and its main comparator) of the economic evaluation
- health states representing patient-relevant outcomes.

The present value of future health outcomes measured from the studies or estimated from a model should also be calculated. This means that where health outcomes are anticipated over a number of time periods (beyond one year), these should also be discounted. Discounting of future costs and benefits is a standard feature of economic evaluation. Costs or benefits are discounted at an annual rate of 5%.

11.8 Outputs from the economic evaluation

11.8.1 Presenting the results of the economic evaluation

The results of each step of the economic evaluation should be presented, firstly in disaggregated form, then in increasingly aggregated form (with discounting applied as appropriate). The appropriately aggregated and discounted results should be presented separately for outcomes and resources and separately for the proposed service and its main comparator. For cost-effectiveness and cost-utility analyses, the application or assessment report should present the incremental cost of achieving each additional unit of outcome when the proposed service is substituted for the main comparator.

Table 11.8.1 provides a suggested format for the presentation of summary results of the stepped economic evaluation. Section D.5 of Part II of the PBAC Guidelines provides suggested formats for presentation of more detailed results.

When drawing conclusions of comparative cost-effectiveness from results of cost-effectiveness analyses, the degree of uncertainty around the point estimate of the incremental cost-effectiveness ratio should be reflected in the conclusion. Thus, terms such as 'dominant' and 'dominated' should generally be avoided except in situations where one intervention costs less and is more effective than the other under a wide range of plausible assumptions.

Where the economic evaluation has used a Markov model, the application or assessment report should also present a Markov trace. For each arm in the economic evaluation (ie for the proposed service and its main comparator) and after each cycle:

- the proportions of the cohorts in each health state should be reported
- discounted outcomes (eg utilities) and the discounted costs for each cohort (both for each cycle and as cumulative results) should be summed
- the incremental cost-effectiveness should be calculated.

The application or assessment report should compare this trace with any corresponding empirical evidence (eg partitioned survival) and comment on and explain any differences.

Table 11.8.1 Assessment of the implications for the economic evaluation of translating the clinical evaluation

Outcome	Incremental costs	Incremental effectiveness	Incremental cost-effectiveness^a
For each study-based outcome relied on in the economic evaluation without further modification	Govt: HCS: Societal:		
For any study-based outcome relied on in the economic evaluation with any <i>application</i> of study results to the population and/or setting of interest over the time horizon of the study or studies only			
For any outcome relied on in the economic evaluation with any <i>extrapolation</i> from the time horizon of the study or studies ^b			
For any important outcome generated for or by the economic evaluation from the study-based outcome(s) (<i>'transformation of nature of outcome' only</i>) ^c			
For the final outcome relied on in the economic evaluation generated as a valuation of the study-based outcome(s) (<i>'value transformation' only</i>)			
For the final outcome relied on in the economic evaluation <i>combining</i> any extrapolation from the time horizon of the study or studies with any transformation of the study-based outcome(s)			

Govt = government perspective; HCS = health care sector perspective; Societal = societal perspective

- a** With sensitivity analyses substituting the upper and lower 95% confidence limits of the difference in outcomes achieved.
- b** The application or assessment report should justify and explain the methods of the approach taken to align the changes in the incremental costs with the changes in incremental effectiveness to extrapolate the evidence from the study/studies to the time horizon of the economic evaluation.
- c** Where the approach to transforming the nature of the outcome also involves extending the time horizon of the analysis, the methods of the approach taken to align the changes in the incremental costs with the changes in incremental effectiveness should be justified and explained.

Note: The application or assessment report should provide a justification if claiming a different base-case analysis from that defined above.

11.8.2 Presenting a sensitivity analysis

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis should be used to translate the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared. The most appropriate ways of presenting uncertainty are confidence ellipses and scatter plots on the cost-effectiveness plane and cost-effectiveness acceptability curves. The use of univariate, best/worst case or scenario-based sensitivity analysis to quantify the effect of parameter uncertainty in an analysis cannot incorporate the uncertainty in more than two or three parameters simultaneously.

The results of an economic evaluation should be accompanied by a sensitivity analysis examining the extent of uncertainty around the point estimate of the incremental cost-effectiveness ratio; and examining the effect of varying uncertain estimates and assumptions included in the economic evaluation on the results of the base-case economic evaluation.

One-way sensitivity analyses should be conducted on a range of variables using plausible extremes of values. The selection of the variables and their plausible extreme values should be justified. The source of the evidence supporting the choice of extreme values should be specified and the quality of that evidence summarised. Justifications might include for example the upper and lower 95% confidence limits of the relevant incremental treatment effect variables reported in studies, or the range of estimates from the available studies of the natural history of a medical condition.

The univariate sensitivity analyses can be used to highlight the variables that are important drivers of the results of the economic evaluation. Where there are multiple outcomes, the application or assessment report should consider providing a matrix with the effects of variables on various outcomes that differ across the two arms (eg in terms of health outcomes, mortality and quality of life).

The application or assessment report should present the results of multiway sensitivity analyses on variables shown to be important drivers of results in the one-way analyses. The selection of these variables and their combination should be explained. Results should be presented in tabular form and as graphs. A tornado diagram with incremental cost-effectiveness on the x-axis is a particularly efficient and informative way of presenting the results of both the univariate and multivariate sensitivity analyses.

If discounting has been necessary, the robustness of the results of the analysis on different discount rates (including a zero discount rate on nonmonetary outcomes alone and on both costs and outcomes) should be tested.

Where a probabilistic sensitivity analysis is provided (from either a Monte Carlo decision analytic model or from statistical analysis of direct evidence), also examine the sensitivity of base case estimates of incremental cost, incremental effect and incremental cost-effectiveness to changes in one variable at a time as univariate sensitivity analyses conducted on each variable, using plausible distributions. The distribution and its moments that are chosen should be justified. Where more than one

variable is adjusted, justification for the assumed correlation across variables should be presented.

A graphic presentation of the results on the cost-effectiveness plane can be a particularly informative means of presenting uncertainty around the value of parameters in the underlying model. The simulated joint cost-effectiveness density for the model can be plotted on the four quadrant cost-effectiveness plane. Interval estimation of incremental cost-effectiveness ratios should only be presented if all outcome points in the density are positive (as intervals representing points in other quadrants can be difficult to interpret). Results should also be presented diagrammatically in the form of a scatter plot on the cost-effectiveness plane and, if desired, an acceptability curve. However, acceptability curves should not be presented without presentation of the corresponding scatter plot of the cost-effectiveness plane. It may be useful to describe the simulated percentage of points in each quadrant of the cost-effectiveness plane, and to provide an ellipse indicating the space within which 95% of the points fall.

The use of probabilistic sensitivity analysis) or, where appropriate, stochastic analysis of patient-level data) allows complete characterisation of the uncertainty associated with all input parameters. This can then be reflected in terms of decision uncertainty in the cost effectiveness of the options – that is, the probability that a given technology is more cost effective than its comparator(s) if the data and model structure are accepted as valid. The most appropriate ways of presenting uncertainty are confidence ellipses and scatter plots on the cost-effectiveness plane and cost-effectiveness acceptability curves. Within a probabilistic analysis it is also helpful to present the contribution of the uncertainty in each parameter to overall decision uncertainty. This can be achieved using expected-value-of-information methods.

It may be helpful to examine the sensitivity of the model to any changes in assumptions concerning the structure of the economic evaluation which are important but debatable (eg the time horizon or the treatment algorithm). The application or assessment report should compare any aspect of the model's results against any corresponding results obtained empirically and comment on any differences. For example, the predicted number of cases and outcomes each year for the current treatment for the time horizon of the model compared to observed and predicted levels.

Section 12 Financial implications

The preceding sections (particularly Sections 10 and 11) inform the decision about whether a service should be publicly subsidised from the perspective of society as a whole. However, the Australian Government will need to make provision for the necessary funds to make a service available. Thus, a financial analysis examining financial implications from a government perspective, in particular the MBS perspective (or other relevant government program) is also required. In circumstances where it is anticipated that costs to government will exceed \$10 million, it is recommended that Section E of Part II of the PBAC Guidelines is consulted for a suggested format for presentation of information in relation to financial implications.

The application or assessment report should provide an estimate of the likely extent of use of the service under MSAC consideration and provide an estimate of the total financial costs to government (and the MBS or other relevant government program, specifically) of subsidising the service (and any associated services, such as diagnostic tests that may require to be performed with the service). The approach used to derive these estimates should be explained and justified, and the source for any data used to derive the estimates should be provided. Sufficient detail should be provided to allow the estimates to be verified and replicated. Where patient co-payments are considered in the determination of financial implications (eg for patients having reached the safety net threshold for co-payments), mean co-payments rather than median co-payments (as is applicable for the economic evaluation) should be used in the analysis.

The application or assessment report should provide estimates of changes in use of other government-subsidised services as a result of substitution of the service under MSAC consideration for the main comparator (and any associated services). The report should also provide an estimate of the financial implications for government of changes in use of other services. The approach used to derive these estimates should be explained and justified, and the source for any data used to derive the estimates should be provided. Sufficient detail should be provided for the estimates to be verified and replicated.

An estimate of the net financial costs to government (and particularly to the MBS or other relevant government program) of subsidising the service should be provided.

Section 13 Other relevant factors

Over time, a number of issues have arisen that have been important in some MSAC considerations but are not relevant in the majority of considerations. Examples include situations where:

- the service being evaluated relies on the use of capital equipment that would not be eligible for subsidy under Medicare or any other relevant government program (eg office-based procedures)
- a service has implications for creating or exacerbating workforce shortages for particular professional or craft groups
- very high capital equipment costs and relative safety of a service create incentives for over-provision of that service to recoup the capital costs of investors
- issues in relation to equity principles are important (eg if the requested listing of a service raises patient affordability considerations, if inequities are embedded into utility valuations).

Where such issues are important, the application or assessment report should provide a discussion of the issue and its implications.

Attachment A – Glossary of Terms

aggregated	Statistics based on grouped variables. For example, the relevant costs and benefits to society (calculated from economic and financial analyses), grouped according to who sustains the costs and benefits (eg government, health care system, or society).
	See also <i>Disaggregated</i> , <i>Input variable</i>
analytical plan	A written plan that explains how data are converted from a clinical perspective to an economic perspective (ie ‘translated’). The analytical plan should present the data, sources, methods and analyses for each translation issue, and explain how and where the results will be used in the economic analysis.
	See also <i>Translation</i>
application (of clinical study results)	One of the steps of ‘translation’. Predictions of clinical outcomes for the population and setting of the clinical studies are applied to the target population and setting for the proposed service, in situations where the populations and settings do not match. This approach helps to overcome the fact that the target population may have a different baseline risk profile from that of the study population and outcomes may also be affected by the setting.
	See also <i>Transform</i>
base-case economic evaluation	The results of an economic evaluation using the projected most likely values against which the results of any sensitivity analyses can be compared.
	See also <i>Sensitivity analysis</i>
co-administered intervention	An intervention (such as drug or dietary supplement) that is given at the same time as the main intervention being studied.
Cochran <i>Q</i> statistic	Statistical measure from the Cochran chi-squared test, which shows whether there is any heterogeneity between study results in a systematic review (cf the I^2 statistic which shows how much heterogeneity there is).
	See also I^2 <i>statistic</i>
comparator	For an MSAC assessment, the comparator is the service that is most likely to be replaced by the new service, should the new service be included on the MBS (or other relevant

government program) as proposed.

cost–benefit analysis An [economic evaluation](#) that compares health care services that have a common health outcome. Both costs and [benefits](#) are measured in monetary terms to calculate a net monetary gain/loss or benefit gain/loss.

cost-consequence analysis Comparison of the incremental costs of the proposed service over its main comparator with an array of outcomes measured in their natural units, rather than a single representative outcome as presented in a cost-effectiveness analysis.

See also *Cost-effectiveness analysis, Natural unit*

cost-effectiveness analysis A type of economic evaluation that compares health care services that have a common health outcome. The output is generally displayed as cost per unit of effect. That is, the costs are measured in monetary amounts and the health outcomes are measured in natural units.

cost-minimisation analysis A type of economic analysis that compares health care services that have a common health outcome, to find the least costly one. Used when the proposed service has been shown to be no worse than the comparator (noninferior).

See also *Noninferior*

cost-utility analysis A type of economic analysis that compares health care services that have a common health outcome in which costs are measured in monetary terms and outcomes are measured in terms of extension of life and the utility value of that extension (eg quality-adjusted life years).

See also *Healthy life years and Quality-adjusted life years*

disability adjusted life year (DALY) A measure of the suffering caused by an illness. Calculated as the sum of the years of potential life lost due to premature mortality, and the years lost due to disability due to a disease or health condition. One DALY represents the equivalent of the loss of one year of full health.

disaggregated Statistics based on individual (ungrouped) variables. For example, the relevant costs and benefits to society (calculated from economic and financial analyses), separated according to who sustains them.

See also *Aggregated, Input variable*

extrapolation (of clinical study results) One of the steps of ‘translation’. Predictions of clinical outcomes from the baseline risk of a disease or condition are extrapolated from the study time horizon to the target time horizon for the proposed service, in situations where the

study and target time horizons do not match.

See also *Translation*

financial analysis	A procedure for comparing only the financial costs and cost off-sets of competing options, rather than comparing their clinical and economic costs and benefits. Also called 'budgetary analysis'.
first-line treatment	The recommended treatment for a disease or a condition, used when the first signs or symptoms appear. First-line treatments are usually chosen based on evidence for their efficacy.
healthy year equivalent (HYE)	The hypothetical number of years spent in perfect health that could be considered equivalent to the actual numbers of years spent in a defined imperfect state of health.
I^2 statistic	Statistic quantifies the amount of heterogeneity between studies in a systematic review (cf Cochran Q statistic which shows whether there is heterogeneity or not). See also <i>Cochran Q statistic</i>
incremental cost-effectiveness	A measure of how much extra a proposed service costs to produce an extra unit of outcome compared to an available alternative (or management without any intervention) for a specified indication. It is calculated by dividing the difference in the net costs for the two alternatives by the difference in their net outcomes.
incremental safety	The additional level of safety that one service imposes on another. See also <i>Safety</i>
input variable	A resource provided as part of managing a disease or disorder. See also <i>Cost-effectiveness analysis, Resource and Transition probability</i>
management algorithm	The steps by which a condition is managed (eg diagnostic tests performed, first-line treatment, second-line treatment, and so on).
meta-analysis	A statistical technique for combining results from different studies to obtain a quantitative estimate of the overall effect of a service. The meta-analysis may produce a stronger conclusion than any single study.

meta-regression	An extension of meta-analysis; used to look at the differences of effects across studies. A meta-regression examines the relationship between one or more study characteristic (eg dose, length of treatment) and the sizes of the effect observed in the studies.
	See also <i>Meta-analysis</i>
modeled economic evaluation	A type of economic evaluation in which study-based variables are modified using modeling techniques ('translated') to take account of differences between the study variables and the target variables for the proposed service.
	See also <i>Translation</i>
modelling	An analytical technique using simulated processes to explain the impact of one or more factors on a number of outcomes.
multi-attribute utility instrument (MAUI)	An instrument used to collect information from trial participants on predefined and prevalued health states at baseline and during the trial.
natural unit	The base unit of measurement for a variable (eg mmHg for blood pressure, dollars for cost).
	[CHECK]
noninferior	Term used to indicate that a proposed service has equivalent (but no better) efficacy to that of the comparator.
	See also <i>Efficacy</i>
off-the-shelf utility estimate	An estimate of utility based on a premodelled example with similar characteristics to the required estimate.
	See also <i>Utility</i>
	[CHECK]
patient copayment	The amount that a patient contributes for a Pharmaceutical Benefits Scheme (PBS) medicine. This is often much less than the full cost of the medicine, or the 'dispensed price'. The Australian Government subsidy is the difference in price between the patient contribution amount and the dispensed price.
quality-adjusted life year (QALY)	A unit of health outcomes that adjusts gains (or losses) in years of life after a service, by the quality of life during those years. They provide a common unit for comparing cost-utility across different interventions and health problems.

resource	A factor of production, an input or a produced good.
safety	A judgment of the acceptability of risk (a measure of the probability of an adverse outcome and its severity) associated with using a particular service in a particular situation.
second-line treatment	The treatment used when the first-line treatment (the treatment chosen first, based on evidence of its efficacy) does not work. See also <i>First-line treatment</i>
sensitivity analysis	A method used to test whether variations in the assumptions affect the conclusion of an economic evaluation. This is done by varying the items about which there is uncertainty over a specified range.
standard gamble (SG)	A method of estimating health preferences using a choice between two options. One option has a certain outcome that is the health state to be rated; the other option is a gamble with a chance of full health and a chance of death. The chance of death is varied until the person choosing finds the options of equal value.
stepped economic analysis	Presentation of a modelled economic analysis in which each step of the translation is shown. See also <i>Modelled economic analysis, Translation</i>
study population and setting	The population and setting used in the clinical studies used to underpin an effectiveness or cost-effectiveness analysis. See also <i>Cost-effectiveness analysis</i>
summary statistic	Quantitative estimate of the overall effect of a particular intervention or service on a particular outcome obtained from a meta-analysis of all available studies.
surrogate outcome	Physiological or biochemical markers that can be measured relatively quickly and easily and that predict important clinical (patient-relevant) outcomes. Surrogate outcomes are often used when clinical outcomes are difficult to measure or require longer follow-up. They are also called 'intermediate outcomes'.
target population and setting	The population and setting of the service that is the subject of the MSAC assessment (proposed service).
time trade-off (TTO)	A method of measuring the quality of life of a patient or a group, by asking them to mark on a scale of 1–10 the answer to the following hypothetical question:

‘Imagine you have 10 years to live, and you can choose to live these in your current health state, or to give up some years to live for less time in full health. What is the number of years in full health that is of equal value to 10 years in your current health status?’

transformation
(of clinical study results)

One of the steps of ‘translation’. A process where differently measured clinical outcomes measured in clinical studies are transformed to match the target outcomes of the proposed service.

See also *Translation*

transition probability

The probability that the health of a patient will change within a given period.

translation

Collective term for the application, extrapolation and transformation of clinical study results for a modelled economic analysis where the target population, time horizon or outcomes are different from those of the clinical studies.

See also *Analytical plan, Application, Extrapolation, Transformation*

uncertainty

The reduction of confidence in a conclusion when more than one estimate is available for a variable or more than one structure is available for a model. Statistical uncertainty arises when a variable includes a range of estimates within which the true value is likely to be found. Inferential uncertainty arises when there are alternative explanations for a measured difference or when extrapolations are made from an estimate. Structural uncertainty arises in a model when all the relationships between the various components are not fully demonstrated.

utility

The desirability of a particular level of health status or health outcome, usually expressed between zero (death) and one (full health).

utility instrument

An instrument for measuring outcomes in terms of the preferences individuals express for specific health states or health outcomes; it provides a common unit that can be used to compare different types of outcomes under conditions of uncertainty.

wider population and setting

Broader population and setting in which the service is likely to be used if included on the MBS (or other relevant government program)

willingness to pay (WTP) The maximum amount that a person is willing to pay to:

- achieve a particular good health status or outcome, or to increase the probability of a good outcome

OR

- avoid a particular bad health state or outcome, or to decrease its probability.