



# Prescription for Pharmacoeconomic Analysis

Methods for cost-utility analysis

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*Investing in Health*

**PHARMAC**  
Pharmaceutical Management Agency

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*"While economic and other technical approaches do not provide a quick and easy 'technical fix' to complex social decisions, they can help to clarify the basis for decisions [and] to provide information about trade-offs that are inevitable...".*

*Devlin and Hansen, 1999*

# Foreword

I have pleasure in presenting the final version 2 of the Prescription for Pharmacoeconomic Analysis – known by many as “the PFPA”.

The PFPA has high importance to PHARMAC as it describe the approach we take when doing cost-utility analysis – the form of analysis that provides information on the relative cost-effectiveness of a pharmaceutical compared to other funding options.

We all know money is limited. The funding of pharmaceuticals is no exception – we can't fund everything, so difficult choices have to be made. Cost-utility analysis is a tool that provides us with information on what pharmaceuticals offer the most health gains from a limited budget. In this way, PHARMAC is able to make more informed choices.

I would however like to emphasise that cost-utility analysis is only a tool. It does not make the decision for us. The PHARMAC Board has nine decision criteria to weigh up when making funding decisions, of which cost-effectiveness is only one. It is however this one criterion that, in essence, is the focus of this document.

Cost-utility analyses are undertaken at PHARMAC by a small but competent team of analysts. These analysts have a range of backgrounds, including economics, pharmacology and public health medicine. Considerable time has been spent by the team reviewing all aspects of PHARMAC's methodology for economic analysis. In addition, PHARMAC consulted widely on a draft version of this document in 2006.

I would like to thank those who provided comments on the draft document. PHARMAC staff and the PHARMAC Board reviewed all responses, and as a result a number of amendments were made to the document.

PHARMAC will continue to review and update its methodology for undertaking cost-utility analysis. We welcome any further feedback.



Matthew Brougham  
Acting Chief Executive

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# Executive Summary

**Purpose:** To ensure that economic analyses performed by (and for) PHARMAC are based on the recommended methodology for cost-utility analysis for pharmaceuticals in New Zealand. This information can then be used by PHARMAC to compare the cost-effectiveness of different interventions (where cost-effectiveness is one of nine decision criteria used by PHARMAC).

This document is intended for use by PHARMAC staff, pharmaceutical companies and contracted health economists preparing economic analyses for PHARMAC.

The key recommendations to consider when undertaking cost-utility analyses for PHARMAC are summarised below.

- Recommendation 1: Most PHARMAC analyses regarding new pharmaceuticals are in the form of a cost-utility analysis (CUA), as it is practical and enables comparisons across different pharmaceuticals.
- Recommendation 2: Undertake analyses from the perspective of the funder, with respect to PHARMAC's decision criteria. Always clearly state the decision problem.
- Recommendation 3: The target population is the New Zealand population most likely to receive treatment.
- Recommendation 4: The comparator(s) used in analyses should be the treatment that most prescribers would replace in New Zealand clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace).
- Recommendation 5: Well-conducted randomised-controlled trials (RCTs) and meta-analyses are the preferred data sources when estimating relative treatment effects. In the absence of valid RCTs, evidence from the highest available level of study design should be considered.
- Recommendation 6: All trials should be critically appraised using the Graphic Appraisal Tool for Epidemiology (GATE) and grades of evidence assigned.
- Recommendation 7: Economic models should avoid unnecessary complexity and should be transparent. A lifetime horizon should be used in most CUAs.
- Recommendation 8: All statistically significant clinical events should be included in base-case analyses. For clinical events with a  $p$  value close to 0.05, consideration should be given to whether the results are likely to be clinically significant, the magnitude of the effect, the relevance and validity of composite measures, and also whether statistical significance has been demonstrated in an independent study.
- Recommendation 9: Non-compliance should be included in the model in cases where there is evidence indicating that non-compliance rates may be significant and hence the effectiveness (and cost) of treatment may be impacted.

- Recommendation 10: Convert rates to transition probabilities for use in CUA.
- Recommendation 11: Measure health-related quality of life using Quality-Adjusted Life Years (QALYs).
- Recommendation 12: The EQ-5D New Zealand Tariff 2 should be referred to first when calculating utility values, with the Global Burden of Disease (GBD) disability weights used to check for consistency.
- Recommendation 13: If subjective judgement is used to map health states, these health states should be validated either through published literature or expert clinical input.
- Recommendation 14: The range of costs included in cost-utility analyses depends on the level of analysis undertaken, with a wider range of costs included in more detailed analyses.
- Recommendation 15: Pharmaceutical costs should take into account any rebate from the Supplier, and should be based on the dose used in the key clinical trials (unless there is evidence of efficacy for different doses in clinical practice). Dispensing fees and pharmacy mark-up should be included if these are likely to differ between treatment arms. The analysis should also include the lower cost of a future generic pharmaceutical.
- Recommendation 16: Hospital inpatient costs can be calculated using Diagnostic Related Group (DRG) codes. Adjustments should be made for complexity, volume of patients and mechanical ventilation if necessary.
- Recommendation 17: Hospital outpatient costs should be included in CUAs. Terminal costs (i.e. costs incurred at the end of a person's life) should be included if these costs are likely to be significantly different between treatment arm or if they occur at significantly different times.
- Recommendation 18: Direct patient healthcare costs should be included in CUAs. These should be restricted to healthcare costs that the government partially subsidises, and should be based on the cost to government plus the additional cost to the patient. These costs include General Practitioner visits, pharmaceutical co-payments and continuing care.
- Recommendation 19: Costs to non-healthcare government departments and indirect patient costs should not be included in PHARMAC CUAs.
- Recommendation 20: Discount all costs and benefits in CUAs at a 3.5% discount rate. Include rates of 0%, 5%, and 10% in sensitivity analyses.
- Recommendation 21: The overall incremental cost per QALY result should be reported as a point estimate as well as the range over which the cost per QALY is likely to vary. In addition, information on discounted real and nominal costs, savings, life-expectancy and quality of life gains/losses resulting from treatment should be reported separately.

Recommendation 22: Sensitivity analysis should include univariate (simple) analysis, multivariate analysis and extremes (scenario) analysis. The level of sensitivity analysis undertaken should be determined by the level of analysis, with probabilistic sensitivity analysis undertaken for more detailed analyses.

# 1. Background

## 1.1 What is PHARMAC?

PHARMAC, the Pharmaceutical Management Agency, is a Crown Entity that is directly accountable to the Minister of Health. PHARMAC manages the Pharmaceutical Schedule, the list of community pharmaceuticals that are funded by the Government. It also negotiates national contracts for some medicines used by District Health Board (DHB) hospitals, and related products.

PHARMAC's primary objective is:

*'to secure for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the funding provided.'*

Further information on PHARMAC can be found at: [www.pharmac.govt.nz](http://www.pharmac.govt.nz).

## 1.2 Purpose of the PFPA

The purpose of this document, the Prescription for Pharmacoeconomic Analysis (PFPA), is to provide an overview of the methods PHARMAC uses when conducting cost-utility analysis. It does not in any way attempt to be a comprehensive academic paper or to describe the technical details of cost-utility analysis. It also does not attempt to provide a thorough description of PHARMAC's prioritisation process or to provide guidance for assessing other technology aside from pharmaceuticals. Rather, it describes the process involved and methods used when conducting cost-utility analysis. Documenting of this methodology aims to ensure that cost-utility analyses performed by (and for) PHARMAC measure costs, benefits, time preference and uncertainty in a similar fashion; hence enabling comparison between the cost-effectiveness of different interventions and ensuring that the results of analyses are meaningful for decision making.

The PFPA aims to be as free of value judgements as possible. Values not explicitly included in the cost-utility analysis (e.g. equity, acceptability, need) can then be taken into account separately during the prioritisation and decision-making process, along with any values implicitly included in an analysis.

This document is intended for use by PHARMAC staff, pharmaceutical companies and contracted health economists preparing economic analyses for PHARMAC.

## 1.3 Version 2 of the PFPA

The idea of standardising and documenting the methods PHARMAC uses when undertaking economic analyses originated in 1997. At that time, PHARMAC had undertaken a number of cost-utility analyses and considered it would be useful to formalise the approach.

PHARMAC consulted widely on the draft manual, and comments were received from lead national and international health economists, clinicians, the pharmaceutical industry, and the Health Funding Authority. Following amendments to the draft

version, the manual, labelled the 'Prescription for Pharmacoeconomic Analysis' (PFPA) was finalised and published on the PHARMAC website in September 1999.

Since then, changes have occurred within the New Zealand health system. There has also been further international debate on issues such as discounting of costs and benefits and the measurement of utility values. In 2004, PHARMAC decided to review the PFPA. The process involved in updating the PFPA is outlined in Appendix 1.

Version 2 of the PFPA is a 'living' document, and as such amendments will be made over time. Details of these amendments will be outlined in Appendix 2.

## 2. Economic Analysis at PHARMAC

### 2.1 What is Economic Analysis?

Economic analysis is the explicit consideration of the costs and benefits of a proposed course of action. Economics is based on three fundamental concepts that summarise the issues PHARMAC faces daily:

- scarcity - resources will always be insufficient to support all possible activities;
- choices - due to scarce resources, decisions must be made regarding how best to use them; and
- opportunity cost - by choosing to use resources one way, we forgo other opportunities to use the same resources.

Based on these concepts, resources are only used efficiently if the value of what is gained from their use is greater than the value of alternative options that could have been funded.

For further information on the purpose of, and techniques for undertaking economic analysis in healthcare, please refer to standard health economics texts such as:

*Drummond MF, Sculpher MJ, Torrance GW, O'Brien B, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. 3rd ed. Oxford: Oxford University Press, 2005.*

### 2.2 Why does PHARMAC use Economic Analysis?

The objective of PHARMAC is to secure the best possible health outcomes from within the funding provided. As PHARMAC must work within a fixed budget, it is impossible to fund every new pharmaceutical that may potentially benefit someone. The demand for pharmaceuticals will always exceed our ability to pay for these pharmaceuticals. In short, choices are inevitable.

Economic analysis provides a valid, replicable and scientific tool for PHARMAC to use in order to maximise total health gains from the budget available.

Economic analysis is not a technical fix for complex decisions, but merely a tool designed to bring greater rationality to often complex decisions, and shed light on the logic behind choices. It is used to inform decision-making rather than replace it.

### 2.3 Does PHARMAC Consider Other Criteria when making Funding Decisions?

All pharmaceuticals awaiting funding are prioritised against other expenditure options (either listing of other new pharmaceuticals or expanding access to existing pharmaceuticals).

Cost-effectiveness is one of nine criteria used when making decisions regarding the funding of new pharmaceuticals (i.e. cost-effectiveness by itself does not determine the outcome). Other criteria are taken into account when making funding decisions for community pharmaceuticals, as outlined in PHARMAC's Operating Policies and Procedures:

[http://www.pharmac.govt.nz/operational\\_policies\\_and\\_procedures.asp](http://www.pharmac.govt.nz/operational_policies_and_procedures.asp)

PHARMAC's decision criteria are:

- the health needs of all eligible people within New Zealand;
- the particular needs of Maori and Pacific peoples;
- the availability and suitability of existing medicines, therapeutic medical devices and related products and related things;
- the clinical benefits and risks of pharmaceuticals;
- the cost-effectiveness of meeting health needs by funding pharmaceuticals; rather than by using other publicly funded health and disability support services;
- the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule;
- the direct cost to health service users;
- the Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere; and
- any other criteria that PHARMAC thinks are relevant. PHARMAC will carry out the necessary consultation whenever it intends to take any 'other criteria' into account.

## 2.4 Types of Economic Analysis

**Key Recommendations:** Most analyses undertaken by PHARMAC staff are in the form of Cost-Utility Analysis (CUA) as it is practical and enables comparisons across different pharmaceuticals. This enables PHARMAC to prioritise pharmaceuticals for investment decisions.

Several forms of economic analysis are available including:

- **Cost-Minimisation Analysis (CMA)**  
CMA assumes that there is no net health change involved in moving from one treatment to another, hence the decision can be made on the basis of the difference in total cost alone. CMA is appropriate when the clinical outcomes of the drug and the comparator are equivalent.
- **Cost-Effectiveness Analysis (CEA)**  
In CEA the incremental costs are compared with the incremental outcomes, as measured in physical units (e.g. life-years saved, heart attacks prevented). A disadvantage of CEA is that it does not enable direct comparison of interventions treating different conditions.
- **Cost-Utility Analysis (CUA)**  
CUA is a variation of CEA in which outcomes are weighted in common currency, usually quality-adjusted life years (QALYs). QALYs combine changes in quantity and quality of life (mortality and morbidity) into one composite measure. CUA enables comparison between the cost-effectiveness of interventions treating different conditions, and also takes into account benefits resulting from both decreases in mortality and decreases in morbidity.
- **Cost-Benefit Analysis (CBA)**  
In CBA incremental outcomes are expressed in monetary terms, usually using the willingness-to-pay approach. The results of CBA are expressed as one figure, representing the difference between benefits and costs ( $B-C > 0$ ), or as a ratio ( $B/C$ ). Disadvantages of CBA include the difficulty in comparing treatments that improve quality of life with those that save lives, and the difficulty associated with placing a dollar value on health benefits. There are also ethical objections to placing a monetary value on health, particularly with respect to valuing a human life.

Table 1 summarises the differences between the forms of economic analysis.

**Table 1: Differences Between Types of Economic Analysis**

Type of Analysis	Measurement of Benefits
Cost-Minimisation	Benefits found to be equivalent
Cost-Effectiveness	Physical units (e.g. life years gained)
Cost-Utility	Healthy years (e.g. quality-adjusted life years)
Cost-Benefit	Monetary terms

## 2.5 What is the Process for Undertaking and Reviewing Cost-Utility Analyses at PHARMAC?

Cost-utility analyses, commonly referred to as CUAs, are generally done 'in-house' by the Technology Assessment Group (TAG). However, PHARMAC staff also review and comment on CUAs submitted by Pharmaceutical Suppliers.

### 2.5.1 PHARMAC Process for Undertaking Cost-Utility Analysis

Most CUAs are done internally by the TAG due to the short timeframes within which analyses are required. It also ensures continuity of methods and quality control. In addition, analyses often need to be updated at short notice following the receipt of further clinical advice or proposed price reductions - the process thus has to be flexible. PHARMAC analyses are based on the methods outlined in this document.

As PHARMAC must work in a pragmatic public policy/purchasing environment with constrained analytical capacity, there are inevitable trade-offs between precision and timeliness of CUAs. Assessments are therefore conducted at four levels – rapid, preliminary, indicative, and detailed. The levels of analysis are outlined in Table 2.

**Table 2: Levels of PHARMAC Analyses**

Type	Description	FTE Required
Detailed	Includes a detailed and systematic identification and synthesis of relative clinical effectiveness, prognosis, health-related quality of life, and cost data. Evidence critically appraised using full Graphic Appraisal Tool for Epidemiology (GATE). Costs and savings to other government organisations considered in the report in a qualitative manner. Probabilistic sensitivity analysis undertaken. Reviewed internally (clinical assumptions reviewed by the Pharmacology and Therapeutic Committee (PTAC)) and externally.	2-6 months
Indicative	An interim assessment using some opportunistic data, but more detailed than a preliminary analysis. Evidence critically appraised using GATE Lite. Reviewed internally and by PTAC.	4-6 weeks
Preliminary	A rapid assessment largely using opportunistic data. Evidence critically appraised using GATE Lite. Statistically non-significant events and costs only included if they are likely to change the results of analyses. Reviewed internally.	1-2 weeks
Rapid	A very rapid assessment using opportunistic data.	1-2 days

FTE = Full-Time Equivalent. Note that these are indicative timeframes, and that actual timeframes vary depending on experience and workload.

Very few proposals receive a full assessment as these take around 2-6 months to complete and hence can be too slow in the policy context. The process is usually iterative, meaning that rapid assessments are conducted first; then preliminary assessments; then if this is insufficient to make a recommendation, an indicative or detailed analysis is undertaken.

The level of analysis undertaken depends on the factors outlined in Table 3.

**Table 3: Determinants of Level of Analysis Undertaken by PHARMAC**

Determinants of level of analysis	Details
Timeframes	In some cases a CUA result may be required within a week; hence a more detailed analysis cannot be undertaken.
Impact on pharmaceutical budget	A high expenditure pharmaceutical is more likely to require a detailed CUA, especially if the pharmaceutical is highly effective.
Reliability of results	If the results of a CUA are very sensitive to key assumptions a higher level of analysis may be required.
Extent of information available for analysis	Pharmaceuticals for rare conditions are more likely to undergo rapid analysis due to unavailability of data.
Impact of CUA on funding decision	In some cases the pharmaceutical may be funded based on other decision criteria, hence a detailed analysis may not be required.
Availability of analyst resources	Given limited analyst resources, it may not be cost-effective to undertake a detailed analysis when a number of other CUAs are also required.

Over a period of six years PHARMAC has undertaken 120 funding analyses (approximately 20 per year), of which 38% were rapid, 21% preliminary, 28% indicative, and 13% detailed. These analyses were done by one to two full-time equivalents (FTEs).

Most CUAs are written up as 'Technology Assessment Reports' following a set template. CUAs are then peer-reviewed by colleagues who examine the economic methodology. Analyses may also be clinically reviewed by the Pharmacology and Therapeutic Advisory Committee (PTAC)<sup>1</sup>; a specialist PTAC subcommittee; or clinical experts.

A more detailed outline of the process involved in undertaking cost-utility analysis at PHARMAC is outlined in Appendix 3.

### **2.5.2 PHARMAC Process for Reviewing Supplier Cost-Utility Analyses**

PHARMAC encourage Pharmaceutical Suppliers to provide a CUA when submitting a significant funding proposal. The provision of a good quality analysis, following the methods outlined in the PFFPA, may expedite the proposal review and information acquisition process, enabling the proposal to be prioritised.

When PHARMAC receives a CUA from a Pharmaceutical Supplier it is reviewed, and often amended, by PHARMAC analysts. The guidelines PHARMAC uses to review analyses are attached in Appendix 4.

In order for analysts to be able to review CUAs more efficiently, a CD with a copy of the TreeAge model and/or Microsoft Excel spreadsheet should be provided. If amendments have been made to the analysis, PTAC will usually be supplied a copy of the supplier CUA and PHARMAC's amended CUA, with the differences between the CUAs clearly explained.

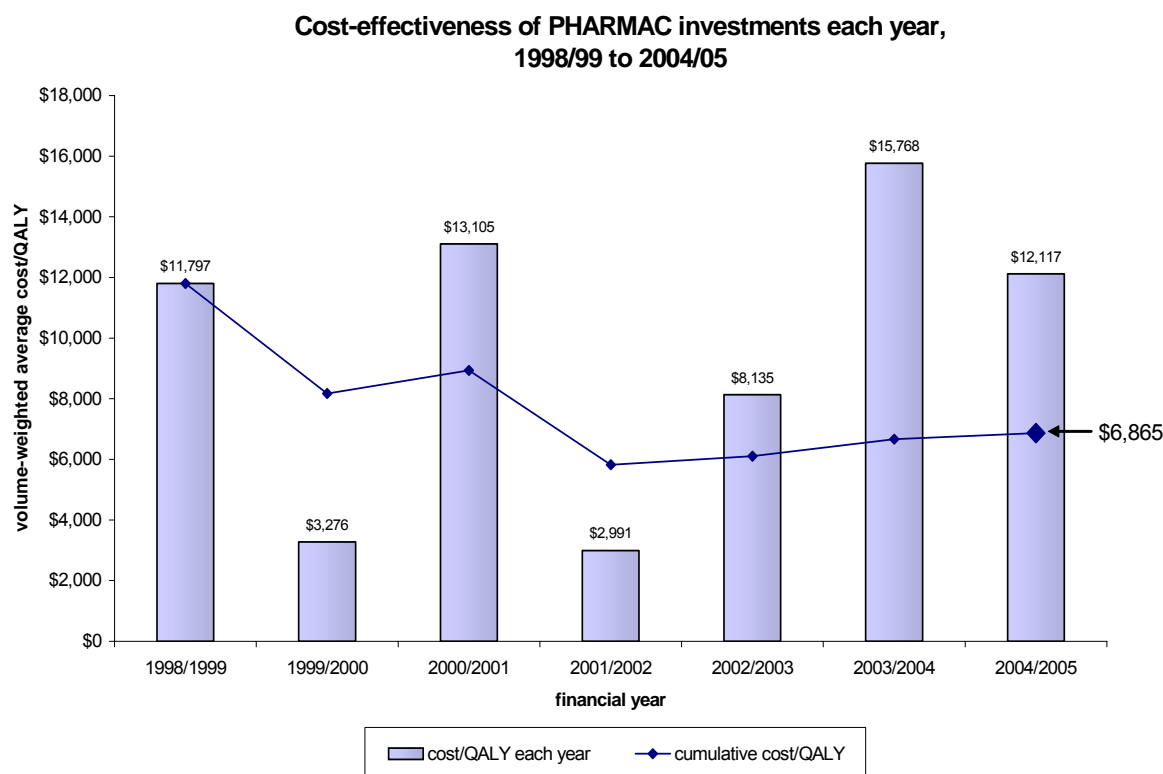
<sup>1</sup> Further details on PTAC can found at <http://www.pharmac.govt.nz/ptac.asp>

## 2.6 When is a Pharmaceutical Considered to be 'Cost-Effective'?

A proposal to invest in a pharmaceutical can be considered “cost-effective” only in comparison with another proposal. At PHARMAC, there is no threshold below which a pharmaceutical is considered “cost-effective”. The main reason for this is that cost-effectiveness is only one decision criterion used by PHARMAC. One proposal may be more cost effective than another but rate poorly on other decision criteria and therefore may not be funded (hence, on ‘successfulness grounds’, it will not be considered cost effective).

Another reason for not having a threshold value is that the spending on community pharmaceuticals is required to be kept within a fixed budget. Given the binding nature of this constraint and all things being equal, what is and is not considered “cost effective” will vary with the amount of funding available (not just in terms of the total budget each year, but the available budget at any point in time).

The following data show that what is and is not considered cost effective changes over time<sup>2</sup>. Between the 1998 and 2005 financial years, new investments made by PHARMAC have cost around \$6,900 per QALY (cumulative volume-weighted average<sup>3</sup>). However, the cost-effectiveness of new investments has varied widely each year – reflecting both the mix of investment opportunities and the funding available at the time. These features are illustrated in the graph below:

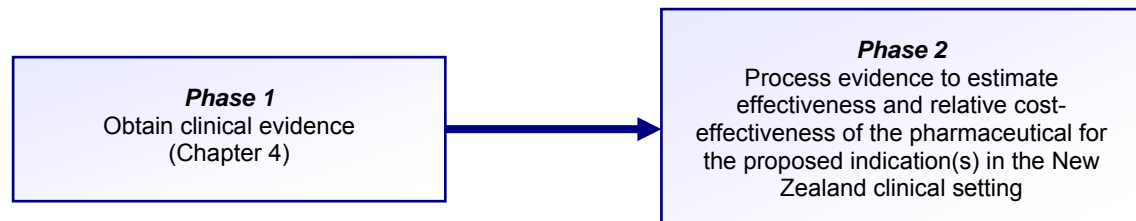


<sup>2</sup> Data derived from PHARMAC’s Annual Reports to Parliament.

<sup>3</sup> The cumulative cost/QALY each year is the sum of the net costs to DHBs of all PHARMAC’s pharmaceutical annualised investments (where cost/QALYs were estimated) up to and including that year, divided by the sum of the estimated annualised QALYs gained by those patients who used those pharmaceuticals up to and including that year. Annualised measures are calculated so that individual investment decisions are directly comparable to each other. Further information on annualised costs and QALYs is available from PHARMAC.

## 3. Scope of Analysis

Cost-utility analysis at PHARMAC has two distinct phases:



### 3.1 Decision Problem and Perspective

**Key Recommendation:** Undertake analyses from the perspective of the funder, with regards to the PHARMAC decision criteria. Costs and savings to other (non-healthcare) government departments should be discussed in the report. Always clearly state the decision problem.

#### 3.1.1 Perspective

PHARMAC analyses are undertaken from the perspective of the funder (with regards to PHARMAC's decision criteria), for the following reasons:

- PHARMAC's decision criteria include the impact to the health budget and direct patient healthcare costs, therefore these are included in the analysis.
- PHARMAC has a separate budget from other government sectors (e.g. social welfare); hence any patient benefits and/or costs that accrue beyond individual health outcomes are outside the scope of PHARMAC's control.

PHARMAC acknowledges that in some cases a funding decision may have an appreciable impact on other (non-healthcare) parts of the government sector. PHARMAC therefore recommends that for detailed analyses, any costs or savings to other non-healthcare government sectors that may result from funding a pharmaceutical should be considered in a qualitative manner, with discussion on how these costs/savings may impact on the overall cost-effectiveness of the pharmaceutical. This recommendation will be reviewed.

#### 3.1.2 Decision Problem

All analyses should include a clear statement about the decision problem that prompted the analysis. This should include information about the disease, patient population, and treatment options available.

## 3.2 Target Population

**Key Recommendations:** The target population is the New Zealand population most likely to receive treatment. It may be necessary to use subgroup analyses if treatment can be targeted to those most likely to benefit. However, subgroup analyses should not be used when there is no overall treatment effect in the intention-to-treat population or primary endpoint. In cases where the subgroup was defined retrospectively in the clinical trial(s), the data should be used cautiously and evidence of statistical heterogeneity reported.

The target population is the New Zealand population most likely to receive treatment. Any differences between the population in the key clinical trials and the target population should be discussed in the report.

### 3.2.1 Subgroup Analyses

If treatment can be targeted to those who are most likely to benefit (e.g. through Special Authority criteria), the use of subgroup analyses may be necessary.<sup>4</sup>

Subgroup analyses comprise of two inter-related elements:

#### 1. Variability in absolute baseline risk

Variability in baseline risk occurs due to differences between patients in aspects such as disease severity causing differences in treatment outcomes. This relatively common effect is best summarised as a constant relative reduction in treatment effects across the trial population of varying baseline (expected) risks. This enables application of the overall trial data to specific subgroups with greater expected absolute risks of future events (i.e. poorer prognosis) and hence greater likelihood of benefiting from a new treatment. The absolute or incremental treatment effect can then be calculated by multiplying the expected absolute risks across the eligible population by the estimated overall relative treatment effect [57]<sup>5</sup>.

#### 2. Variability in relative treatment effects

Variability in relative treatment effects occurs due to differing characteristics of the patient, the intervention(s), or the disease causing varying relative reductions in the risk of clinical outcomes (across and overlying the trial population, which in turn contains varying absolute baseline risks).<sup>6</sup> In this case, which is far less common, analysis is required to identify statistically significant heterogeneity (variation) in the treatment effects across the subgroups. Such evidence is needed to help justify any calculations of absolute treatment effect that apply the estimated relative treatment effect for the subgroup to the expected risk for the subgroup [57].<sup>5</sup>

When examining variability in treatment effects, in order for the results of subgroup analyses to be reliable, the subgroups in the clinical trial (or meta-analysis of clinical trials) should be defined *a priori* on the basis of known biological mechanisms or in

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<sup>4</sup> Patient subgroups may have different responses to treatment or magnitudes of benefit. These subgroups may be defined by age, gender, other demographic factors, disease-related factors (symptom complexes, severities), comorbidities, or intractability and factors affecting treatment effectiveness. The degree of breakdown depends upon the complexity of the targeting decisions to be made. Some situations will require many subgroups, others just the overall group.

<sup>5</sup> PBAC guidelines, Part II: Guidelines for preparing the main body of a major submission Section C Translating the clinical evaluation to the listing requested for inclusion in the economic evaluation.  
[http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacguidelines-index~pbacguidelines-part2~pbacguidelines-part2\\_c](http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacguidelines-index~pbacguidelines-part2~pbacguidelines-part2_c)

<sup>6</sup> In general, an estimate of treatment effect is interpretable with respect only to the whole population of a randomised trial (or whole population of randomised trials within a meta-analysis) rather than by testing within each individual subgroup. [57]

response to findings in previous studies. The choice of subgroup and expected direction of difference should ideally have been justified in the trial protocol [54].

Where subgroups are defined retrospectively, information should be interpreted cautiously. This is because it is more likely that differences in effect in subgroups of patients are due to chance, given the smaller patient numbers. There is also an increased probability of either falsely ascribing 'significant differences' due to over-testing or producing false-negative results [48]. Due to these concerns, it may be more appropriate to use data from a retrospective subgroup of patients in the sensitivity analysis rather than the base-case analysis.

In addition, statistical tests of interaction [50, 60]<sup>7</sup> should be used to assess whether a treatment effect differs among subgroups (i.e. evidence of heterogeneity)<sup>8</sup>. However, even when there is heterogeneity between subgroups, results of subgroup analyses should still be interpreted with caution. The outcomes of subgroup analyses should be checked to ensure that they were pre-specified and that treatment effects are both plausible (pharmacological, biological and clinical) and statistically strong [48].

When examining variability in treatment effects, subgroup analysis can be acceptable if justified by a formal and reliable subgroup analysis [57]<sup>5</sup> that adequately considers the above elements of plausibility, timing of the underlying hypothesis (*a priori*) and statistical heterogeneity.<sup>9</sup> Otherwise, subgroup analysis should generally not be used when a trial reports statistically significant treatment effect(s) in subgroup(s) or secondary endpoint(s) yet there is no overall treatment effect in the intention-to-treat population<sup>10</sup> or primary endpoint [48,56].

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<sup>7</sup> Relevant statistical tests of interaction include the chi-square test using the Q statistic in an individual trial or the Cochran Q statistic across the pooled result, and the I<sup>2</sup> statistic with its 95% uncertainty interval.

<sup>8</sup> Statistical tests of interaction are preferred to individual tests within each subgroup – individual tests often overestimate the extent of true differences.

<sup>9</sup> For a complete checklist for assessing and interpreting subgroup analysis, refer to both Cook et al 2004 [59] [http://www.mja.com.au/public/issues/180\\_06\\_150304/coo10086\\_fm.pdf](http://www.mja.com.au/public/issues/180_06_150304/coo10086_fm.pdf) and Part II Section C of the PBAC guidelines [http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacguidelines-index~pbacguidelines-part2~pbacguidelines-part2\\_c](http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacguidelines-index~pbacguidelines-part2~pbacguidelines-part2_c)

<sup>10</sup> Subgroup treatment effects in a trial with no overall treatment effect are said to be usually superfluous subgroup salvages of otherwise indeterminate (negative) trials [48].

### 3.2.2 Comparator(s)

**Key Recommendation:** The comparator(s) used in analyses should be the treatment that most prescribers would replace in New Zealand clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace).

The comparator(s) used in PHARMAC analyses should be:

1. the treatment that most prescribers would replace in New Zealand clinical practice; and
2. the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace).

The analysis should consider both current clinical practice and likely future practice (i.e. treatment regimen at the time the pharmaceutical is likely to be funded). This allows for any changes that may occur in treatment regimens over time.

In cases where treatment regimens differ substantially throughout New Zealand, it is recommended that a range of comparators be used in the analysis. The results of the analysis using the different comparators should be reported separately, as well as reporting a weighted-average (weighted by patients numbers prescribed comparator treatment) of the cost per QALY result.

If there is any uncertainty regarding the most appropriate comparator to use in the CUA, clinical experts should be asked. The Pharmacology and Therapeutic Advisory Committee (PTAC) often performs this role for analyses conducted by PHARMAC.

The comparator used in the model should not be constrained by data availability. In cases where the key clinical trials have not used the appropriate comparator(s), it may be necessary to perform an indirect comparison based on published data (further information on this is in the modelling section).

## 4. Evidence for Relative Clinical Effect

This section outlines what sources of evidence are preferred when calculating clinical effect for inclusion in an economic model. This section does not cover sources of evidence for estimating baseline risk of disease, health-related quality of life, or resource use.

All appropriate evidence relating to the pharmaceutical(s) and population under assessment should be identified, described, and quality-assessed. The level of clinical evidence may vary depending on the level of analysis and time available to systematically review the evidence – for less detailed analyses, more opportunistic data may need to be used and less comprehensive literature searches undertaken.

For a complete overview of the use of clinical evidence, please refer to PHARMAC's 'Recommended methods to derive clinical inputs for proposals to PHARMAC', available at <http://www.pharmac.govt.nz/pdf/62465.pdf>. This document describes how relevant clinical inputs are systematically identified and then synthesised.

### 4.1 Data Sources

**Key Recommendations:** All appropriate levels of evidence should be identified; however well-conducted randomised controlled trials (RCTs) and meta-analyses are the preferred data sources when estimating relative treatment effects. In the absence of valid RCTs, evidence from the highest available level of study design should be considered with reference to the limitations of the study design.

#### 4.1.1 Key Data Sources

Key clinical data sources to be used when estimating relative treatment effects include published randomised controlled trials (RCTs), meta-analyses, and observational studies. Other possible sources include unpublished trial data, expert opinion, case reports, and data from medical records [1,2,3,4].

Details on the advantages and disadvantages of these data sources, including their recommended use, are outlined in the Table 4.

**Table 4: Data Sources**

Data Source	Advantages	Disadvantages	Recommended Use
Randomised controlled trials (RCTs)	External influences minimised through randomisation, patient selection, and double-blinding. This ensures that the effect is attributable to the intervention alone.	Selected patients, investigators and comparator treatments may result in poor external validity. Often short time spans. May be subject to publication bias.	All else being equal, published trials are preferred to unpublished trials as the latter have not been formally peer reviewed. If the use of unpublished trials is necessary, these should be subject to the same quality assessment as published studies, hence if there is insufficient information to assess quality such data should be used with caution.  If published trials are available, data from unpublished trials

Data Source	Advantages	Disadvantages	Recommended Use
			should only be included in the sensitivity analysis (so as to determine contribution of the trial).
Meta-analysis <sup>11</sup>	<p>A single trial may be insufficiently powered to detect treatment effects.</p> <p>Useful when results conflict between trials; when inappropriate comparators are used; or when a trial consists of only one treatment arm.</p>	<p>Publication and inclusion biases (i.e. choice of trials included).</p> <p>May be difficult to assess validity.</p> <p>Incompatible trials may be included.</p>	<p>Meta-analysis may be useful when there is more than one key trial or when results conflict between trials.</p> <p>With more detailed analyses it may be necessary for the analyst to undertake a meta-analysis if there are no published meta-analyses available.</p>
Observational studies <sup>12</sup>	<p>High real-world relevance.</p> <p>Allow observation of a new treatment on compliance and treatment switching patterns.</p>	<p>Lack of control over confounding factors.</p> <p>Underlying biases.</p> <p>Lack of control groups.</p>	<p>Use to compare with the results of a clinical trial.</p> <p>Observational studies are most useful when estimating baseline risk and modelling non-compliance.</p> <p>More than one independent source should be examined in order to gain confidence in the validity of the conclusions.</p>
Expert opinion	<p>Clarification of unreliable, conflicting or insufficient clinical information in the literature.</p>	<p>Subject to selection bias.</p>	<p>It is not recommended that expert opinion be used as the primary source for assessment of effectiveness. PHARMAC mainly uses expert opinion to review an economic model, in particular any clinical assumptions.</p>
Case reports and medical records	<p>High real-world relevance.</p>	<p>High risk of bias.</p> <p>Small patient numbers.</p>	<p>Generally not recommended that these be included in CUAs.</p>

<sup>11</sup> Meta-analysis systematically combines the results of trials in order to draw overall conclusions regarding the efficacy and/or safety of the treatment.

<sup>12</sup> Observational studies register outcomes of groups of patients treated in ordinary clinical practice.

## 4.2 Obtaining Data

### 4.2.1 Data Sources

Potentially useful information sources on clinical efficacy and event rates include:

- MEDLINE: <http://www.ncbi.nlm.nih.gov/pubmed/>
- TRIP: <http://www.tripdatabase.com>
- EMBASE: <http://www.embase.com>
- Cochrane: <http://www.thecochranelibrary.com>
- Centre for Reviews and Dissemination: <http://www.york.ac.uk/inst/crd/crddatabases.htm>
- BMJ Clinical Evidence: <http://www.clinicalevidence.com/ceweb/conditions/index.jsp>
- FDA: <http://www.fda.com>
- WHOSIS Evidence for Health Policy: <http://www3.who.int/whosis/menu.cfm>

Database searches should be supplemented by scanning references in articles and hand searching key journals. A useful listing of key journals that are available on the internet is at: <http://www.york.ac.uk/res/herc/journal.htm>

General journals include:

- British Medical Journal (BMJ): <http://bmj.com/index.dtl>
- The Lancet: <http://www.thelancet.com/>
- Journal of the American Medical Association (JAMA): <http://jama.ama-assn.org/>
- New England Journal of Medicine (NEJM): <http://content.nejm.org/>
- New Zealand Medical Journal (NZMJ): [www.nzma.org.nz/journal](http://www.nzma.org.nz/journal)

Information on drug safety can be found at:

- Medsafe: <http://www.medsafe.govt.nz>
- TOXLINE: <http://toxnet.nlm.nih.gov/>

It is also useful to check international health technology organisations' assessments of the evidence. These include:

- National Institute for Health and Clinical Excellence (UK): <http://www.nice.org.uk/>
- Canadian Agency for Drugs and Technology in Health: <http://www.cadth.ca/>
- Scottish Medicines Consortium: <http://www.scottishmedicines.org.uk/>
- Australian Pharmaceutical Benefits Scheme: <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/public-summary-documents>

### 4.2.2 Search Strategy

All evidence should be obtained systematically. Details of the search strategy used to retrieve clinical studies should be described, including:

- medium used to conduct search and by whom;
- databases searched;
- time period in which the search was undertaken; and
- search strategy and keywords used.

If any evidence is excluded when obtaining data inputs for the CUA, this should be justified.

## 4.3 Assessing Data Quality

**Key Recommendations:** All trials should be critically appraised using the Graphic Appraisal Tool for Epidemiology (GATE) and grades of evidence assigned. PHARMAC recommends that when high-quality studies are available, these should be the preferred data source when estimating relative treatment effects.

### 4.3.1 Critical Appraisal of Trials

PHARMAC recommends that the full Graphic Appraisal Tool for Epidemiology (GATE) [58] be used when critically appraising clinical trials for detailed analyses. For indicative and preliminary analyses GATE LITE should be used.

The GATE framework involves the following five steps:

1. asking focused questions based on PECOT (population, exposure, comparison, outcome, time);
2. searching the literature for best available evidence;
3. appraising the study by 'hanging' on the GATE frame;
4. assessing study quality;
5. application of evidence in practice.

Details on the GATE framework, including critical appraisal spreadsheets, are available at: [www.epiq.co.nz](http://www.epiq.co.nz) and <http://ebm.bmj.com/cgi/content/full/11/2/35>.

The following table outlines a number of issues to consider when critically appraising a clinical trial.

**Table 5: Factors to Consider in Critical Appraisal of Trials**

Factors for appraisal	Questions to consider
Availability of data	Was the trial published in a peer-reviewed journal?
Patient population	Was the patient population in the trial similar to those considered for funding?
Number of patients	Was the sample size large enough to indicate efficacy (i.e. that the results did not occur due to chance)? Or was the effect large enough to be statistically significant even in a small sample size?
Comparator	Was the comparator consistent with current clinical practice in New Zealand?
Dose, formulation and administration regimen	Were these consistent with recommended treatment regimes in New Zealand?
Method of randomisation, including adequate concealment	Was there likely to be any selection bias or confounding? Were patients, clinicians and assessors blinded?
Length and completeness of follow-up	Were patients followed for an adequate time period? How often were patients assessed? Was analysis undertaken on the intention-to-treat population?
Selection of endpoints	Was the selection of endpoints relevant?

The quality of studies tends to vary between therapeutic groups. For example, for cardiovascular drugs, a large number of RCTs are often undertaken involving large

numbers of patients. However, for mental health drugs, in some cases it is more difficult to conduct good quality RCTs due to poorer compliance rates and difficulties with recruitment. PHARMAC therefore recommends that the quality of the clinical evidence should be assessed relative to the ability to conduct good-quality RCTs within the therapeutic group, in order to reduce biases against pharmaceuticals where it may be difficult to conduct high-quality RCTs.

It is also recommended that poor quality data be explicitly highlighted, especially for therapeutic groups where high-quality, double-blinded trials are able to (and should) be conducted.

### 4.3.2 Grading the Evidence

Assigning levels of evidence to studies is useful for determining the weighting that should be placed on the results of an analysis when making a decision. Although the final scores are only guides, if a study rates poorly it is likely that the study is subject to significant biases, and hence caution should be taken when interpreting the results.

There are many different methods of assigning levels of evidence, and there has been considerable debate regarding which method is best.

A commonly used checklist is that developed by the Scottish Intercollegiate Guidelines Network (SIGN), outlined below:

**Table 6: SIGN Checklist**

Level of Evidence	Type of Evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	High-quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.
2+	Well conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic uncontrolled observational studies (cross sectional studies, prospective longitudinal follow-up studies, retrospective follow-up case series, case reports)
4	Expert opinion and/or modelling in absence of empirical data.

PHARMAC recommends that in cases where there are well-conducted RCTs, systematic reviews and meta-analyses available (i.e. grade of evidence 1+ or 1++), these should be the preferred data source when estimating relative treatment effects. In such cases, studies with a grade of evidence below 1+ should be rejected. These studies should, however, be included in evidence tables of the report for discussion.

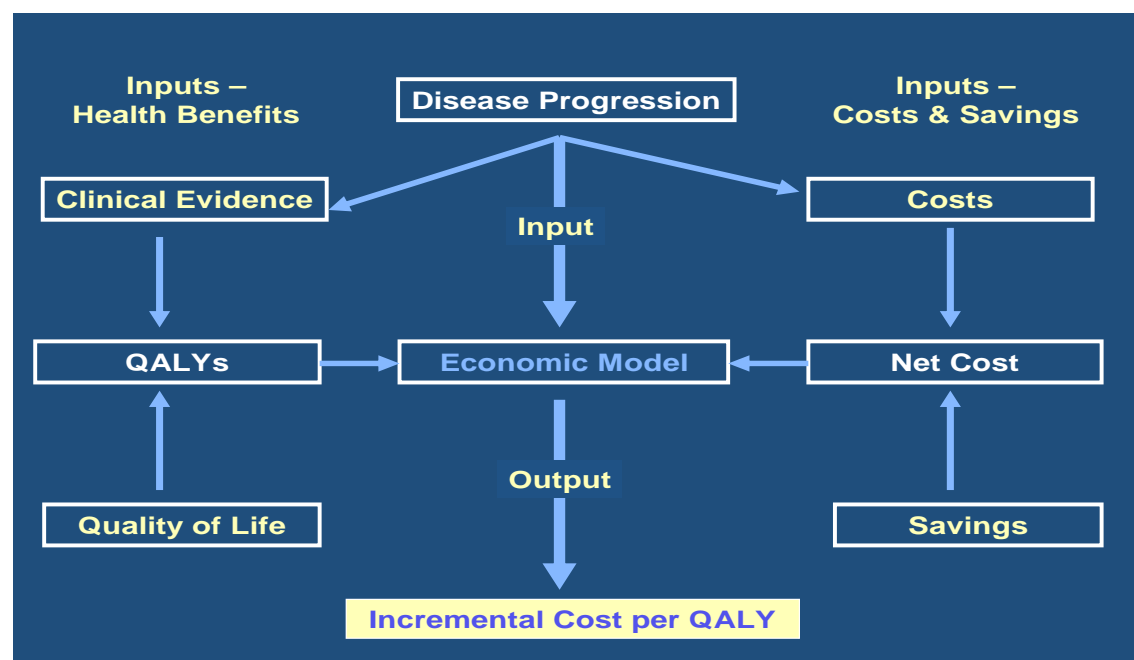
In cases where the clinical evidence on relative treatment effect is limited to RCTs with a high risk of bias (i.e. grade of evidence of 1-), good quality observational studies (cohort studies and case-control studies) should also be considered.

PHARMAC acknowledges that in some cases it may be necessary to use lower levels of evidence if this is all there is available (for example, pharmaceuticals for rare diseases where data may be limited to case studies).

## 5. Economic Modelling

Decisions have to be made regardless of data availability. Modelling in economic analysis is necessary in order to inform decision-making at a particular point in time.

Cost-effectiveness models combine information about disease progression, the relative clinical effectiveness of a pharmaceutical (usually obtained from RCTs), and the costs and savings associated with the funding of a pharmaceutical. This is outlined in the diagram below:



### 5.1 Models

**Key Recommendations:** Models should avoid unnecessary complexity and should be transparent, well described and reproducible.

Models consist of a series of branches, representing the expected health outcomes of different treatments.

#### 5.1.1 Scope of Model

The simplest model type should be chosen providing it captures the essential features of the disease and interventions, and all relevant data are incorporated.

Model types include [3,8,10,11,12]:

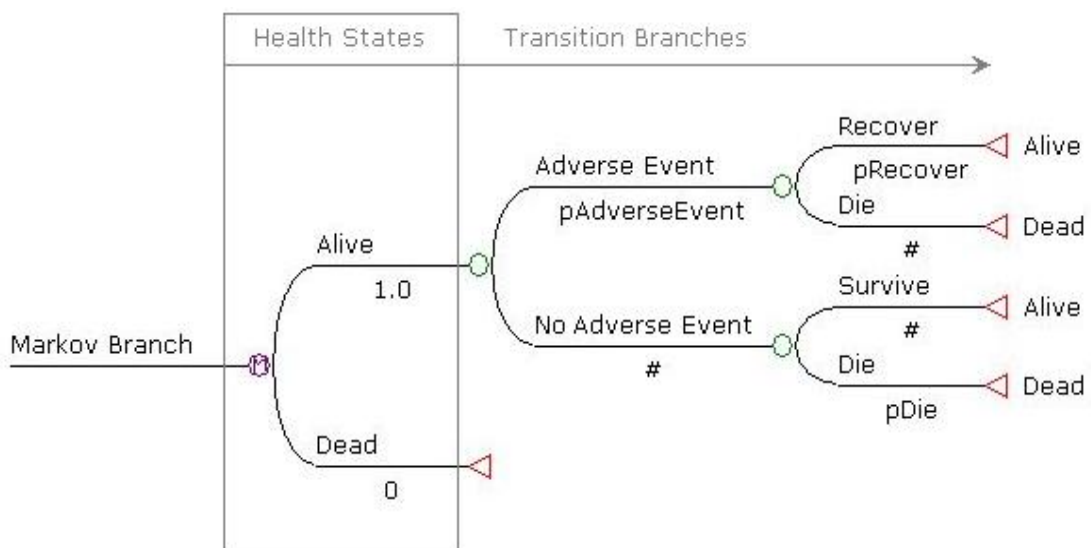
- **Simple Decision Trees**

Simple decision trees can be used in cases where an event may happen only once, during a discrete period, and the patients are not at continuous risk of recurrence (e.g. acute episode of illness leading to either full recovery or death).

- **Markov Models**

Markov models assume that an infinite cohort of patients is always in one of a finite number of health states. The whole cohort usually begins in an initial health state (or Markov state), and moves between states at defined recurring intervals (Markov cycles), as determined by the transition probabilities.

A branch of a Markov Model is shown below. In this example, all patients begin in the 'Alive' health state, and are then at risk of having an adverse event, which they may recover or die from. The model would also incorporate the disease-specific mortality rate of the target population. The model is usually run for enough cycles so that the entire cohort is in the 'Dead' state.



Each of the Markov states is assigned a utility (i.e. quality of life score). The contribution of this utility to the overall prognosis depends on the length of time spent in the health state. Summing QALYs across all cycles gives the QALY estimate for each treatment arm.

Markov models are necessary when the time horizon spans more than a few discrete time periods, when events can recur, or when the timing of events is uncertain or varies (for example, chronic diseases).

Markov models can be evaluated using first-order Monte Carlo simulation. This involves tracking large numbers of patients (e.g. 10,000) through a Markov model individually, and provides information on the variability within the patient population.

### 5.1.2 Transparency

Models should be transparent and the structure, data and process of building the model should be detailed enough to enable competent analysts who are not familiar with the model to reproduce it.

### 5.1.3 Health States

Health states included in a model should correspond to the underlying disease progression and/or health status.

## 5.2 Time Horizon and Cycle Length

**Key Recommendations:** In the majority of CUAs a lifetime horizon should be used and half-cycle adjustment applied.

The time horizon should extend far enough into the future to capture all the major clinical and economic outcomes of the alternatives under assessment.

In general, a lifetime horizon should be used in order to estimate differences in expected survival duration. However, for conditions that are unlikely to exist over a lifetime, or where there is uncertainty around whether survival benefits will persist, the choice of a shorter time horizon (e.g. until recovery or death) can be justified, providing there are no differences in mortality, long-term morbidity and cost between the alternative options.

### 5.2.1 Cycle Length

The cycle length should be the minimum time period over which pathology and/or symptoms in patients is expected to alter, and should be based on the nature of the disease rather than the availability of data [10]. For example, if clinical events are likely to occur frequently, a short cycle length should be used.

### 5.2.2 Half-Cycle Adjustment

Markov models assume that a patient's time in a state is constant for the duration of the cycle, and that transitions between states occur at discrete points of time (at the beginning or end of the cycle). However, most transition probabilities (e.g mortality), are estimated on the mean (i.e. assuming transitions occur on average half-way through the cycle). These unaligned transitions and mean probabilities may result in over or under-estimating health outcomes. An unbiased estimate must therefore ensure that, on average, patients move between states halfway through the cycle. A half-cycle correction can achieve this adjustment [10,11].

## 5.3 Clinical Data Inputs

**Key Recommendation:** All statistically significant clinical events should be included in base-case analyses. For clinical events with a  $p$  value close to 0.05, consideration should be given to the magnitude of effect; whether the results are likely to be clinically significant; the relevance and validity of composite measures; and also whether statistical significance has been demonstrated in an independent study. The exclusion of any event from an analysis should be justified.

It is important to make sure that the most relevant outcomes to the condition are included in the CUA and that they reflect the perspective and scope of the model. This will often require incorporating information on relative treatment effects (usually obtained from clinical trials) with baseline health events.

Outcomes included in the model may include (but are not limited to):

- probability of success or failure,
- relapse,
- adverse events,
- discontinuation / loss to follow-up, or
- death.

These outcomes should be well-defined, mutually exclusive, and generally long-term or final outcomes.

### 5.3.1 Relative Clinical Effectiveness Data

Clinical trials should be analysed using data from the intention-to-treat (ITT) population in order to take into account outcomes of all patients irrespective of whether they received treatment (for further information on data sources to be used when estimating relative treatment effects, refer to Section 4).

PHARMAC recommends that all statistically significant clinical events be included in the base-case analysis of CUAs (where statistical significance is defined here as the  $p$  value being less than 0.05)<sup>13</sup>.

For clinical events with a  $p$  value close to (but still larger than) 0.05 (i.e. the event is close to but does not reach conventional statistical significance), the following should be considered.

**Table 7: Issues to Consider when Evaluating Statistically Insignificant Events**

Issue	Question
Magnitude of effect	Is the treatment effect size substantial given size of study? <sup>14</sup>
Clinical significance	Is the outcome patient-focused with clinically meaningful effects on longevity or quality of life and with good evidence for causality? <sup>15</sup>
Independent study	Has statistical significance been demonstrated in more than one independent study (or in a meta-analysis of relevant studies), with no evidence of statistical heterogeneity?
Composite events	Are similar events statistically significant when combined? <sup>16</sup>

<sup>13</sup> The  $p$  value is the probability that an observed effect is due to chance; it therefore provides a measure of the strength of an association. This section uses  $p$  values to notionally define statistical significance, however it is noted that confidence intervals may better summarise the strength and precision of the effect estimate.

<sup>14</sup> Effect sizes with  $p$  values close to but not reaching statistical significance will be due to either one of two circumstances: (1) the effect is strong but the confidence interval is wide, because numbers of events etc. are small; or (2) the effect is weaker but the confidence interval is narrower. In either case the  $p$  value being close to 0.05 means that the 95% confidence interval will only just include the value of 1.0 (i.e. a small but statistically significant chance that there is no effect). When deciding whether to still include such clinical events, a strong effect (1) will take presence over a weaker effect (2). A strong effect (with wide confidence limits) means that the effect is likely to be clinically important, being limited by insufficient power (where 'absence of evidence is not evidence of absence') [64]. Conversely, a weak effect with narrower confidence limits is unlikely to be clinically important (i.e. greater confidence but a negligible effect on outcomes).

<sup>15</sup> To help determine whether events are clinically significant, outcomes should be examined to determine whether their association with treatment is likely to be causal. Key criteria for determining causal associations include [52]: temporality (i.e. the cause must precede the effect); strength of association; consistency between different populations and different study designs; and a dose-response relationship (i.e. increased exposure is associated with an increased biological effect).

<sup>16</sup> In order for composite endpoints to be valid, the results of the individual endpoints of composite measures reported by clinical trials should be reported [62], with the number of individual end points being minimised to preferably no more than 3 or 4 [63]. Component nonfatal end points should be measured appropriately, with the use of a blinded end points committee, a core laboratory, or both [63], and analysis of nonfatal events should take into account competing risks. For information on the assessment of composite outcomes, please refer to the PBAC guidelines for preparing a major submission [57]:

Accounting for clinical factors and magnitude of effect means that, in some cases, a result considered to be 'statistically non-significant' (i.e.  $p$  value equal to or greater than 0.05) should still be used. This is because the magnitude of clinical relevance overrides the statistical aspects. Likewise, in some cases a result considered to be statistically significant ( $p$  value less than 0.05) should not be used, because it has no meaningful clinical effects.

When analysing multiple events without significant effects individually, preferably raw data should be used and suitable statistical tests should be conducted (e.g. F-test). When only summary data are available, it is important to also take into account the likelihood of the same patient being included in multiple groups.

A clear exception, where events that are not significantly different between groups can be omitted, is when there is no difference in survival and any difference in the mean (point estimate) of events favours the comparator (e.g. if the new intervention has fewer adverse events but statistical significance is not reached).

In general, the exclusion of any event from an analysis should be justified, and the impact of a decision to include or exclude certain parameters should be included and tested in the sensitivity analysis. However, for rapid analyses, statistically non-significant events should only be included if they are likely to change the results of the analysis.

### **5.3.2 Incorporation of Relative Treatment Effects with Baseline Events**

A common approach is to model risk factors or interventions as having an additive or multiplicative effect on baseline probabilities, mortality or disease incidence. This is done by deriving relative risks (or odds ratios) between treatment options in clinical trials, and then 'superimposing' these estimates onto baseline probabilities derived from other sources (usually population-based) [8,45].

For example, the use of disease-specific mortality with all-cause mortality. All-cause mortality should be derived from NZ life tables,<sup>17</sup> unless an alternative source can be justified. In general, it is not necessary to correct for the fact that all-cause mortality includes disease-specific mortality in the general population, unless the disease represents a major cause of death in the population [45]. The choice of functional form for disease-specific mortality should be specified and justified.

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<sup>17</sup> <http://www.stats.govt.nz/datasets/population/life-tables.htm>

## 5.4 Modelling

**Key Recommendations:** Non-compliance should be included in the model in cases where there is evidence indicating that non-compliance rates may be significant and hence may impact the effectiveness (and cost) of treatment. The methodology, limitations, and any possible biases associated with extrapolating data should be clearly described in the report.

Data from clinical trials and other sources needs to be translated into an appropriate form for incorporation into a model.

Modelling may require:

- extrapolating data to the longer term;
- extrapolating intermediate endpoints to obtain final outcomes;
- generalising results from clinical trials to the New Zealand clinical setting; and
- synthesising head-to-head comparisons where the relevant trials do not exist.

The methodology, limitations, and any possible biases associated with extrapolating and incorporating data should be clearly described in the report and explored through sensitivity analysis.

### 5.4.1 Extrapolation to Longer Terms or Final Outcomes

Many trials have endpoints that may be too early. It may therefore be necessary to use intermediate outcomes to obtain final endpoints by extrapolating data beyond the period observed in the clinical trials, and comparing the extrapolated outcomes with expected long-term outcomes from observation studies (or any clinical trials in other settings with long-term outcomes that are relevant). This often requires explicit assumptions regarding the continuation of treatment effect once treatment has ceased [3,9].

### 5.4.2 Extrapolation of Clinical Trial Data to New Zealand Clinical Practice

Clinical practice in New Zealand may differ from that in clinical trials in terms of the level of resources available (e.g. staffing), patient management (e.g. frequency of consultation), and type of patient. These may in turn impact on compliance rates, hence affecting the effectiveness of treatment in clinical practice [3,9,10].

Types of treatment non-compliance (a.k.a. non-adherence) are included in Table 8.

**Table 8: Types of non-compliance**

Types of Non-Compliance	Details
Primary non-compliance	Failing to initiate treatment – equivalent to no treatment.
Drug regimen non-compliance	Treatment 'holidays', inadequate treatment dose, administration timing variations, treatment withdrawal.
Premature discontinuation	Failing to complete a recommended course of treatment, and/or non-redemption of repeat prescriptions.

PHARMAC recommends that non-compliance be included in the model in cases where there is evidence indicating that non-compliance rates may be material and hence may impact the effectiveness (and cost) of treatment. This can be achieved by incorporating different discontinuation rates into the model, and the subsequent probability of treatment success for non-compliant and compliant patients.

Observational data can be used to estimate levels of non-compliance. Similarly, any additional costs associated with non-compliance (e.g. hospitalisation, co-morbidities), should be incorporated in the analysis.

In cases where there is no strong evidence of non-compliance with treatment (yet non-compliance is likely), this should be tested in the sensitivity analysis by varying both effectiveness data and costs.

#### **5.4.3 Synthesising Head-to-Head Comparisons**

Many trials may not use the most relevant treatment comparator for the New Zealand clinical setting, or a CUA may require comparisons against more than one alternative treatment. In such cases, it may be necessary to synthesise a head-to-head comparison [14]. For example, a difference in clinical effect between Drug A and Drug B can be modelled by obtaining separate estimates from trials comparing Drug A versus placebo, and Drug B versus placebo.

For information regarding how results from trials should be synthesised, please refer to the revised PBAC guidelines [57].<sup>18</sup>

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<sup>18</sup> PBAC guidelines, Section B(i) Clinical evaluation for the main indication: Presenting an indirect comparison of randomised trials.  
<http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacguidelines-index~pbacguidelines-part3>

## 5.5 Transition Probabilities

**Key Recommendation:** Convert rates to transition probabilities for use in CUA.

### 5.5.1 Point Estimates vs. Probability Distributions

In most cases the use of point estimates in CUAs is sufficient. PHARMAC is currently reviewing the usefulness of probability distributions, and a recommendation will be made at a later date regarding whether they should be routinely used. It is currently recommended that probability distributions be used only in detailed analyses.

### 5.5.2 Converting Rates to Probabilities to Transition Probabilities

A rate is defined as an instantaneous likelihood of transition at any point of time, whereas a probability is the proportion of the population at risk that makes a transition over a specified period of time. As Markov models concern transitions over specified time periods, it is the transition probabilities that are relevant to Markov modelling [53].

A rate can be converted to a probability using the following formula:

$$p = 1 - e^{-rt}$$

where p = probability of an event;  
r = constant rate;  
t = time

The probabilities included in the model must correspond to the relevant cycle length. If the Markov cycle length is changed (e.g. from yearly to monthly), one cannot simply divide the probability by the number of cycles (e.g. 12) to obtain the transition probability for the shorter cycle. Rather the above formula should be used – i.e.  $p = 1 - e^{-r/12}$ .

If there is no information available on rates (e.g. if information is only available on yearly transition probabilities rather than monthly), transition probabilities can be converted to rates using the following formula, and the calculated rate used to recalculate the relevant transition probability:

$$r = - \frac{\ln(1 - p)}{t}$$

where r = constant rate;  
p = probability of an event;  
t = time.

## 6. Health-Related Quality of Life

In 1948 the World Health Organisation defined health as being not only the absence of disease and infirmity, but also the presence of physical, mental and social well-being [33]. Quality of life issues have become increasingly recognised as important in health care, particularly with the treatment of chronic conditions with long-term effects on quality of life.

### 6.1 Measures of Health-Related Quality of Life

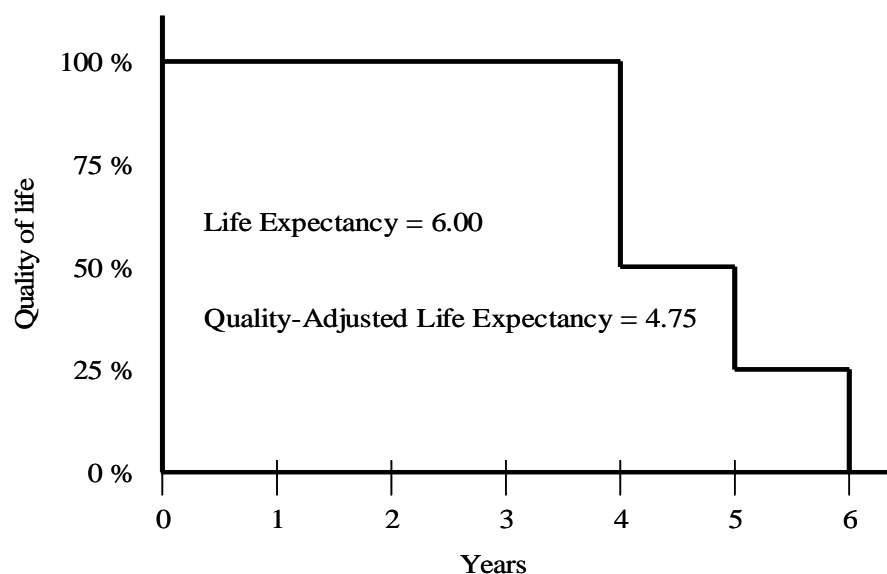
**Key Recommendations:** Health-related quality of life (HR-QOL) should be measured using Quality-Adjusted Life Years (QALYs) as they are simple to calculate, universally used, and have face validity.

Health measures that incorporate both the quality and the length of life into a common currency include quality-adjusted life years (QALYs), disability-adjusted life years (DALYs)<sup>19</sup> and healthy year equivalents (HYES)<sup>20</sup>.

#### 6.1.1 Quality-Adjusted Life Years (QALYs)

QALYs have been used since the 1960s and remain the most widely used measure for integrating effects of treatments on length and quality of life.

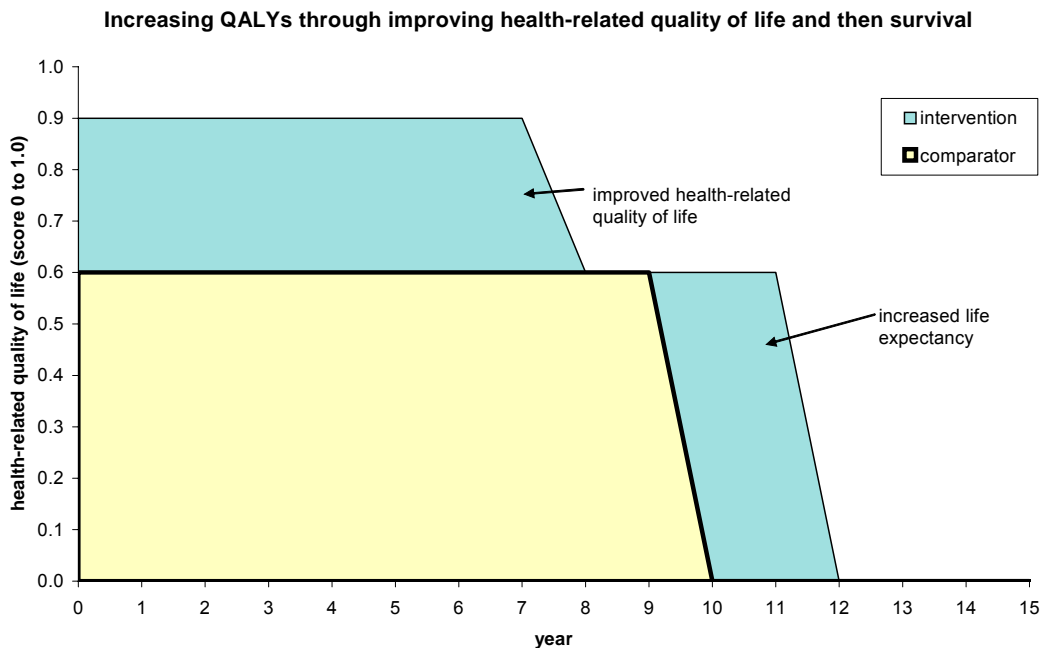
Under the QALY framework, one QALY is equivalent to living one year in perfect health, or two years at half of perfect health, and so on. This is illustrated in the following figure. Here, life expectancy (the number of years left before death) is 6.00. Quality-adjusted life expectancy (the number of QALYs left before death) is 4.75. This is calculated by multiplying each life year by the average quality of life experienced in that year  $((4 \times 1) + (1 \times 0.5) + (1 \times 0.25))$ . This is equivalent to the area under the curve.



<sup>19</sup> DALYs are expressed in terms of years of life lost due to premature death and years lived with a disability of specific severity and duration.

<sup>20</sup> HYES incorporate individual preference structures over a complete path of health states (rather than discrete health states).

The diagram below illustrates how a theoretical intervention may gain QALYs through both improving patient quality of life and life extension:



QALYs have been criticised on ethical, conceptual and operational grounds. A key criticism is that QALYs assume uniform preferences (i.e. each QALY has equal value regardless to whom it accrues). This criticism is based on the results of CUAs often being applied within a utilitarian framework. However, CUA is capable of being applied to achieve any desired distribution of QALYs through attaching weights to the estimated QALY gains [55]. One such alternative distributional theory is, for instance, Rawls' Theory of Justice, where groups with relatively poor health are favoured over groups with better health.

PHARMAC recommends that QALYs be used in CUAs as they are simple to calculate, have face validity, enable CUA to be performed, and there are substantial empirical data available on the preferences people place on various combinations of suffering and limits on activities.

It is also recommended that value-judgement weightings not be included when calculating QALYs, as it is considered important to keep the results of CUAs as value-free as possible. Also cost-effectiveness is only one of nine decision criteria that PHARMAC uses, and other values may be addressed under other decision criteria.

## 6.2 Health-Related Quality of Life Instruments

**Key Recommendations:** The New Zealand EQ-5D Tariff 2 should be referred to first when measuring health-related quality of life, and should be used to describe the health states. The Global Burden of Disease disability weights should be used to check for consistency with the estimated EQ-5D values. The New Zealand EQ-5D Tariff 1 should be included in the sensitivity analysis.

A number of instruments have been developed to measure health state preferences [35]. These instruments provide a utility rating in the form of a single number representing the net aggregate impact of physical, emotional, and social functioning on quality of life.

There has been much debate in the literature regarding the most appropriate tool for measuring preferences in health gains. Given the multidimensional nature of HR-QOL, no single measure has been (or is likely to be) accepted as the gold standard [15]. The Washington Panel on Cost-Effectiveness in Health and Medicine reviewed these instruments in 1996, and chose not to endorse one instrument above another [2]. They note that each instrument has different properties, and each member of the Panel valued these properties differently.

Instruments available include (but are not limited to) the EuroQol 5D (EQ-5D); Health Utility Index (HUI); Short-Form 36 (SF-36); Short-Form 6D (SF-6D); Quality of Well Being index (QWB); Quality of Life and Health Questionnaire (QLHQ); Rosser-Kind Index; Assessment of Quality of Life instrument (AQOL); Sickness Impact Profile (SIP); and Index of Health Related Quality of Life (IHRQOL).

### 6.2.1 Recommended Instrument - EuroQol 5D

The EQ-5D is one of the most widely used and adapted instruments internationally. It consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and three levels (no problems, some problems and extreme problems), resulting in 245 unique health states (including Unconscious and Dead). Health states worse than death (i.e. negative values) are possible.

In order to derive generic utility weights specific to the New Zealand population, Devlin et al. undertook a survey of the New Zealand population in 1999 using the Euroqol Group's EQ-5D questionnaire [16]. The survey was mailed to 3000 randomly selected New Zealanders, and was completed by 1360 (approximately 45% response rate). Each respondent rated their health on the five EQ-5D dimensions and assigned a global score to their profile. Valuations for a subset of the 245 EQ-5D states were collected from respondents using the Visual Analogue Scale (VAS). Regression analysis was used to interpolate values over the 245 possible EQ-5D states [16].

As discussed in a key article by Devlin and Hansen et al., almost two-thirds of the survey responses had to be rejected due to missing, implausible or otherwise unusable valuations [16]. This resulted in two tariffs being produced – one ('Tariff 1') that included the 'logical inconsistencies'<sup>22</sup> (and hence may be more representative of the population's views), and the other ('Tariff 2') that excluded these inconsistencies (and hence may more accurately reflect underlying preferences) [16].

The validity and reliability of the EQ-5D health state valuations have also been examined in the Maori population. Perkins et al. [46] surveyed 66 Maori people to investigate the

<sup>22</sup> Logical inconsistency was defined as "when a state that 'in logical terms' is unambiguously less severe than another is assigned a lower value" [16].

content validity and reliability of the EQ-5D in this population. They reported that approximately three-quarters of respondents considered the EQ-5D representation of health to be adequate, suggesting the instrument has content validity. However, a high prevalence of missing valuations (particularly for the health state 'dead') and logical inconsistencies suggested that it lacked construct validity in this population.

As it is likely that health state preferences of New Zealanders differ from those of people from other countries, it is preferable to use the weights derived from the New Zealand population. The EQ-5D is widely used internationally and utility weights have been derived from the New Zealand population. It is therefore recommended that the EQ-5D Tariff 2 be referred to first and should be used to describe the health states. Other instruments can be used, however their use should be well justified.

In addition, it is recommended that Tariff 1 of the EQ-5D be used in the sensitivity analysis.

## 6.3 Obtaining Utility Values

<b>Key Recommendations:</b> If subjective judgement is used to map health states, these health states should be validated either through published literature or expert clinical input.
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### 6.3.1 Mapping

Mapping health states to health status classification instruments requires subjective judgements; however the estimates can be further validated by input from clinicians and the literature.

Mapping can involve both relating the baseline characteristics of the target patient population to relevant generic health states in the quality of life instrument(s) used for the CUA, and then estimating the extent that treatment alters baseline health status.

### 6.3.2 Literature

Existing utility values available in the literature can be used to check for consistency with the EQ-5D weights, providing similar health states and patients are used, and that the measurement instrument is credible.

Data on HR-QOL can also be obtained from the following information sources:

- MEDLINE: <http://www.ncbi.nlm.nih.gov/pubmed/>
- EMBASE: <http://www.embase.com>
- CEA Registry: <http://www.tufts-nemc.org/cearegistry/>
- QOL Instruments Database: <http://www.qolid.org/>
- Health Related Quality of Life: <http://www.cdc.gov/hrqol/>
- Australian Centre on QOL: <http://acqol.deakin.edu.au/index.htm>
- PBAC Australian Product Information Datasheets: <http://www.pbs.gov.au/html/healthpro/home>

### **6.3.3 Disability Weights – Global Burden of Disease (GBD) Study**

The Global Burden of Disease (GBD) study [36] estimated the burden of 483 separate sequelae of 107 diseases and injuries by gender and age (five-year age groups) for all regions of the world. DALYs were used to measure the impact of mortality and non-fatal health outcomes for a wide range of diseases and illnesses.

The results of a GBD study in the Australian population were published in 1999 [18]. This study provided estimates of the incidence, prevalence, duration, mortality and morbidity for more than 175 disease and injury categories. A smaller study was undertaken for the New Zealand population by the Ministry of Health in 2001 [47].

In order to estimate DALYs, the Australian study used the disability weights derived from the Dutch population for conditions common in developed countries [37], and supplemented this with weights used in the GBD study for other conditions. Note that in general the Dutch and GBD weights are reasonably consistent. Both set of weights were derived using the Person Trade-Off (PTO) method. However, the Dutch weights also defined each disease stage based on a modified version of the EuroQol instrument. In total, weights were obtained for 54 disease and injury categories [18].

It is recommended that the GBD weights be used to check for consistency with the EQ-5D weights, but should not be used as the main source of utility value.

### **6.3.4 Direct Measurement**

Utility values may be obtained through questioning the general public, patients, physicians, and/or related health professionals and caregivers. This can be done using the Standard Gamble (SG), Time Trade-Off (TTO) or VAS techniques. However time constraints mean this is often not a feasible option at PHARMAC.

## 7. Estimating Costs

To every extent possible, the agreed costing methods should be used to enable comparisons across analyses. However alternative cost values should be used in sensitivity analyses.

### 7.1 Costs Included in PHARMAC Analyses

**Key Recommendations:** The range of costs included in cost-utility analyses depends on the level of analysis undertaken, with a wider range of costs included in more detailed analyses.

Costs included in PHARMAC CUAs are outlined in Table 9.

**Table 9: Costs included in PHARMAC cost-utility analysis**

Cost	Details	Source(s)
Pharmaceutical	Community and hospital pharmaceuticals	Pharmaceutical Schedule Pharmaceutical Suppliers (pharmaceutical patent information) Clinical trials (doses) DHB hospitals
Hospital inpatient	Diagnostic Related Group (DRG) prices for inpatient diagnosis, treatment and/or procedures	New Zealand Health Information Service (NZHIS)
Hospital outpatient	Healthcare professional costs DRG prices Laboratory and diagnostics	DHB hospitals NZHIS
Direct patient healthcare	General practitioner visits Pharmaceutical co-payments Home or continuing care	Ministry of Health

The reporting of costs should state how units were measured, resources were valued, and how final cost figures were derived (further guidance on the presentation of cost data is included in Section 11).

With more rapid analyses, it may not be necessary to include a wider range of costs or very small costs that merely confirm the result that may be obtained from considering the basic costs. In such cases, calculation of additional costs may require considerable time and may complicate the analysis unnecessarily without making any material difference to the result. Justification should be given for the exclusion of costs.

Costs that are the same in both treatment arms can be validly excluded if there is no significant difference in mortality rates or time periods between treatments.

## 7.2 Pharmaceutical Costs

**Key Recommendations:** Pharmaceutical costs should take into account any rebate from the pharmaceutical supplier, be based on the dose used in the key clinical trials (unless there is evidence of efficacy for different doses in clinical practice), and take into account the lower price of a future generic pharmaceutical. Dispensing fees and pharmacy mark-up should be included if this is likely to differ between treatment arms. The cost of co-administered pharmaceuticals and any significant costs with administering the pharmaceutical should also be taken into account.

### 7.2.1 Price of Pharmaceutical(s)

Pharmaceutical costs included in CUAs should be restricted to pharmaceuticals listed (or considered for listing) on the Pharmaceutical Schedule or funded by DHB hospitals. In addition, the total pharmaceutical cost should be included irrespective of whether it is paid by the patient or government.

For pharmaceuticals listed on the Pharmaceutical Schedule<sup>23</sup>, the price of the pharmaceutical should include any rebate that has been negotiated with the Supplier. The analysis should state whether the price is confidential.

For pharmaceuticals used in hospitals that are not listed on the Pharmaceutical Schedule, the price should be estimated as the price hospitals are likely to pay.

When calculating pharmaceutical costs, consideration should also be given to the length of the pharmaceutical patent and time until a generic pharmaceutical is likely to become available. It is recommended that in cases where the patent expiry is within 10 years from expected date of pharmaceutical funding, the expected time and price reduction from a likely generic pharmaceutical should be included in the analysis. If the patent expiry is after 10 years from expected date of funding, a conservative proxy should be used for the estimated time until the introduction of a generic pharmaceutical and subsequent price reduction (e.g. 25 years until expiry and 70% price reduction with introduction of generic).

Pharmaceutical costs included in the analysis should not only include the cost of pharmaceuticals used to treat the disease or condition, but also the cost of pharmaceuticals used to treat any significant side-effects of treatment.

It is recommended that pharmaceutical prices be deflated by two percent per year in the sensitivity analysis (not the base-case analysis) as a proxy for inflation in other prices<sup>24</sup>.

### 7.2.2 Dose of Pharmaceutical(s)

The dose of the pharmaceutical used in CUAs should be the dose used in the key clinical trials. In cases where the dose in the clinical trials does not reflect current clinical practice in New Zealand, the dose should be based on that used in clinical practice providing there is some evidence of efficacy at the proposed dose. In cases where there is no evidence available, CUAs should consider different scenarios where the dose (but not the effectiveness) is varied.

Any dose adjustments over time should also be taken into account.

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<sup>23</sup> <http://www.pharmac.govt.nz/schedule.asp>

<sup>24</sup> The reason inflation needs to be included in the analysis is because pharmaceutical prices tend to either decrease or remain fixed over time, where all other costs tend to increase.

The dose of the pharmaceutical may depend on the weight or surface area of the patient. The average weight of adults in New Zealand is currently approximately 75.9 kg. However, it may be necessary to adjust this according to the age and/or gender of the population treated.

In some cases it is necessary to take into account any drug wastage that may occur if infusions cannot be stored once prepared.

### **7.2.3 Dispensing Fees and Pharmacy Mark-Up**

Dispensing fees should be included in the following circumstances:

1. if the comparator is placebo;
2. if the comparator is a controlled drug and hence associated with a different dispensing fee;
3. if one pharmaceutical is dispensed stat (i.e. every three months) and the comparator is dispensed on a monthly basis or under close control;
4. if there is a significant difference in mortality between treatment arms during the treatment period.

Note that for pharmaceuticals dispensed in hospital pharmacies, a dispensing fee should only be included if the pharmaceuticals are dispensed for outpatient use.

Details on the current dispensing fee and pharmacy mark-up are provided in Appendix 5.

### **7.2.4 Administration of Pharmaceutical(s)**

The cost of administering a pharmaceutical should be included in the analysis, except in cases where these costs are very small and make no difference to the results of the analysis.

Further information on pharmaceutical administration costs in New Zealand is included in Appendix 5.

### **7.2.5 Co-Administered Pharmaceutical(s)**

The cost of any pharmaceuticals that need to be co-administered with the treatment should be included in the analysis.

## **7.3 Hospital Inpatient Costs**

<b>Key Recommendations:</b> Hospital inpatient costs can be calculated using DRG codes, and should be categorised as real cost-savings, nominal cost-savings and additional costs.
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It is argued by some that cost offsets do not need to be taken into account as often these are not realised. For example, a new treatment may prevent or shorten hospital stays but the beds freed up will be occupied by another patient. Thus, DHBs may not gain direct financial savings, but rather more people with other conditions will receive treatment.

However, hospital cost offsets are part of the net resource use of a drug intervention, and measuring net resource use is the goal of CUA. Hence, any savings to DHBs will manifest either as discrete savings through services no longer being used, or through those resources being deployed elsewhere.

### 7.3.1 Calculation of Hospital Costs

Hospital costs can be calculated using Diagnostic Related Group (DRG) prices. DRGs are a hospital patient classification system that provides data relating the number and types of patients treated in a hospital to the resources required by the hospital.<sup>25</sup> To a certain extent DRG prices are able to capture the resources used by a particular group of patients and severity of conditions, and hence are useful when estimating hospitalisation costs.

However, a disadvantage of DRG prices is that they do not distinguish between the “fixed” costs necessary to run a service regardless of patient numbers (e.g. overheads, minimum staffing levels, etc.) and the marginal costs (i.e. the extra costs incurred treating each new patient). They are therefore average prices, and as such they do not provide an accurate estimate of the opportunity cost of resources.

Even though it is preferable to use marginal costs to estimate the cost of hospitalisation, data on average costs are more readily available and in most cases is sufficient. Average costs are, however, likely to overestimate the opportunity cost of hospitalisation.

In cases where the cost of hospitalisation is the main driver of the results of the analysis, further work should be undertaken to determine the marginal cost. Any adjustments to DRG prices should be justified in the report. It is however recommended that international prices and costs not be used in analyses due to differences in resource use in New Zealand (even after exchange rate adjustments).

Adjustments that may need to be made to DRG prices are outlined in Table 10.

**Table 10: DRG Adjustments**

DRG Adjustment	Details
Complexity	DRG prices should be adjusted for more severe conditions.
Volume of patients	In cases where more than one DRG code needs to be used, the cost per admission should be weighted by the number of discharges under each DRG code.
Mechanical ventilation	DRG prices should be adjusted for mechanical ventilation co-payments when relevant.
Tertiary and rural	Tertiary and rural adjusters do not need to be included as decisions regarding the funding of community pharmaceuticals are made at a national level.

### 7.3.2 Reporting of Hospital Costs

In order to manage DHB expectations regarding cost savings that result from the funding of a new pharmaceutical, it is recommended that hospital costs and savings be separated into the following categories:

1. real cost savings to DHBs (i.e. cases where the funding of a new pharmaceutical will result in actual cost savings);
2. nominal cost savings to DHBs (i.e. cases where the funding of a new pharmaceutical is likely to result in reducing waiting lists and other non-monetary benefits); and
3. additional costs (i.e. where the funding of a new pharmaceutical results in additional tests, specialist consultations, hospitalisations, etc.).

<sup>25</sup> Further information and data at: <http://www.nzhis.govt.nz/documentation/wies/index.html>

## 7.4 Other Health Sector Costs

**Key Recommendations:** Hospital outpatient costs should be included in CUAs. Terminal costs associated with the primary condition being treated should be included in CUAs if these costs are likely to be significantly different between treatment arms or if they occur at significantly different times.

### 7.4.1 Hospital Outpatient Costs

Hospital outpatient costs may include:

- outpatient clinic appointments/services;
- laboratory and diagnostic tests;
- nursing services provided by the hospital; and
- hospital-based outpatient programmes.

The cost of outpatient hospital visits should be estimated using the hourly consultation cost or same-day DRG costs. This cost is particularly relevant when subsidies for pharmaceuticals are only available when prescribed by specialists.

Laboratory and diagnostic tests can be costed as per test/procedure. Care should be taken to ensure that these costs are not included in the DRG costs, in order to avoid double-counting.

### 7.4.2 Terminal Care Costs

A large proportion of costs occur in the last couple of years of a person's life, which can affect the cost-effectiveness of a treatment. These costs should be included in CUAs if they are likely to significantly impact the results. This is most likely to occur in cases where patients are receiving palliative care in their final few months of life and a new treatment improves survival, or if the costs occur at significantly different times.

In cases where patients die in hospital, terminal care costs can be calculated from DRG prices. In cases where patients receive palliative care until death (e.g. terminal cancer patients), terminal care costs can be calculated as the cost of home visits (nurse and specialist) and/or hospice care.

The cost of terminal care should, however, be restricted to the terminal costs associated with the primary condition being treated.

## 7.5 Direct Patient Healthcare Costs

**Key Recommendations:** Include direct patient healthcare costs in CUAs. These should be restricted to healthcare costs that government partially subsidises, and should be based on the cost to government plus the additional cost to the patient. These costs include General Practitioner visits, pharmaceutical co-payments, and home or continuing care.

Direct patient healthcare costs included in CUAs should be restricted to healthcare costs that the Government partially subsidises through the health sector budget. The cost included in the CUA should be the cost to government plus the additional cost to the patient.

Direct patient healthcare costs include:

- General Practitioner visits;
- pharmaceutical co-payments;
- home or continuing care.

Direct patient healthcare costs do not include:

- lost wages as a result of sickness;
- cost of premature mortality;
- non-government subsidised costs such as private hospital, physiotherapy, unsubsidised pharmaceuticals.

### 7.5.1 GP Visits

The cost of a General Practitioner (GP) visit should be based on the average cost to the patient plus any government subsidy (if applicable). Details are provided in Appendix 5.

### 7.5.2 Pharmaceutical Co-payments

For CUAs, it is recommended that the total pharmaceutical cost be included, irrespective of whether it is paid by the patient or the government. As outlined previously, pharmaceutical costs included in CUAs should be restricted to pharmaceuticals listed (or considered for listing) on the Pharmaceutical Schedule or funded by DHB hospitals.

### 7.5.3 Cost of Home or Continuing Care

The cost of home care or continuing care (rest home or private geriatric/psychogeriatric care) should be included in CUAs, independent of who is paying for these services (i.e. the family, DHB, Accident Compensation Commission (ACC), or Ministry of Social Development). The inclusion of these costs also provides a proxy for the disutility associated with the requirement for additional care. Cost details are provided in Appendix 5.

## 7.6 Direct Non-Healthcare Costs

**Key Recommendations:** Costs to non-healthcare government departments should not be included in CUAs.

### 7.6.1 Costs to Other Government Departments

Costs to other non-healthcare government departments that occur as a result of pharmaceutical funding decision, but are not paid for out of the health budget (i.e. Vote:Health), should not be included in CUAs. These costs are not part of PHARMAC's decision criteria or legislative objective, and there is often insufficient information regarding the actual financial impact of pharmaceutical funding decisions on other government departments. Also, decisions made in other departments may be based on very different assumptions and levels of analysis, so it becomes very difficult to incorporate these data in a consistent manner. These costs may, however, be considered qualitatively in the report.

### 7.6.2 Direct and Indirect Taxes and Transfer Payments

Direct and indirect taxes and transfer payments should not be included in CUAs, as such taxes and transfer payments merely represent the shifting of funds from one sector of the economy to another. These are also difficult to calculate correctly and may result in double counting.

## 7.7 Indirect Healthcare Costs

### 7.7.1 Future Healthcare Costs

Even though in theory future healthcare costs (i.e. costs associated with patients living longer and hence consuming health care resources) should be included in CUAs<sup>26</sup>, these are very difficult to calculate as in most cases there is limited data available, and obtaining data may be time-consuming. However, these costs should be considered in more detailed analyses.

### 7.7.2 Capital Costs, Depreciation, and Overhead Costs

Capital and overhead costs are generally included in DRG prices, and do not need to be estimated separately in the majority of CUAs. However, these costs should be included if significant.

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<sup>26</sup> To exclude these costs would favour interventions that increase length of life at the expense of those that improve quality of life.

## 7.8 Indirect Patient Costs

**Key Recommendations:** Indirect patient costs should not be included in CUAs.

Indirect costs are those costs relating to lost productivity of a patient due to treatment, illness or death, or that of family members if they attend to patients.

Indirect patient costs include:

- cost of patient time off work (i.e. lost wages) and reduced productivity costs,
- cost of premature mortality; and
- intangible costs (e.g. pain and suffering experienced as a consequence of a treatment).

The arguments (and counter-arguments) for including indirect costs are outlined in Table 11.

**Table 11: Arguments (and Counter-Arguments) for the Inclusion of Indirect Costs**

Arguments for Inclusion of Indirect Costs	Counter-Arguments
Sickness or treatment that results in inability for the patient or caregiver to work incurs a cost to individuals and employers in terms of replacement of sick workers, training the replacement, and lower levels of productivity.	<p>The actual production loss for society from sickness is likely to be much smaller than the estimated value of potential production lost. For short-term absences a person's work may be covered by others or made up by the sick person on his/her return to work. For long-term absences, an individual's work can be covered by someone drawn from the unemployed. Therefore, while absence from work may cost the individual or employer, it may not cost society very much.</p> <p>There are also ethical concerns with including the cost of lost productivity in analyses, as these costs tend to bias against those who are not in the labour force - particularly children, homemakers, retired people, the unemployed, and those unable to work. Incorporating differential earning levels will also result in valuing one group of individuals more than another, which is politically and ethically contrary to society's values. It would also result in healthcare interventions being more likely to be directed towards well-paid working people.</p>
There are costs associated with premature mortality in terms of loss of potential income; and savings in terms of future health care spending that would likely have occurred if the patient survived.	Similar ethical issues as with the inclusion of lost productivity costs (i.e. biases against those not working).
Intangible costs, such as pain and suffering experienced as a consequence of a treatment, may be significant.	<p>Intangible costs are particularly difficult to measure and value. There are also ethical concerns with placing a monetary value on patient pain.</p> <p>The impact of treatment on pain and suffering is often taken into account when estimating quality of life. To also include a monetary cost would result in double-counting.</p>

### 7.8.1 PHARMAC Perspective

PHARMAC recommends that indirect costs not be included in CUAs, for the following reasons:

- including indirect costs would result in double-counting, as the impact of treatment on pain, suffering and inability to work is taken into account when estimating health-related quality of life;
- these costs are often difficult to quantify correctly and require unrealistic assumptions (e.g. a zero rate of unemployment) which may invalidate CUA results (this is particularly important when working in a pragmatic public policy environment where cost-effectiveness is part of the decision criteria);
- incorporating differential earning levels will result in valuing one group of individuals more than another (for example, they tend to bias against those who are not in the labour force which may result in treatments for women or the elderly being less cost-effective);
- the actual production loss for society from sickness is likely to be significantly lower than indicated by *a priori* estimates (for example, work can be covered by the unemployed);
- PHARMAC's objective is to maximise health gains from health sector funds. If societal costs were included in analyses, this could result in PHARMAC considering issues it has no control over (for example, an analysis including indirect costs could favour those with high incomes and hence suggest that it would be cost-effective to further subsidise primary education);
- it would be time-consuming and thus inefficient to include these costs in CUAs, as it would result in significant opportunity costs in terms of staff time. Given fixed analytical capacity at PHARMAC, by increasing the complexity of analyses there would be a trade-off in terms of numbers and timeliness of assessments. This in turn may cause delays to the listing of beneficial pharmaceuticals.

It is however recommended that 'indirect patient costs' be incorporated in the QALY estimates through the utility values.

## 7.9 Sourcing of Cost Data

It is not recommended that cost data from overseas or clinical trials be used in CUAs due to potential differences in clinical practice, absolute and relative prices, and also the opportunities to redeploy resources. Obtaining New Zealand data may require approaching a variety of sources including PHARMAC, the New Zealand Health Information Service (NZHIS), Ministry of Health, and DHBs.

Expert clinical opinion should be sought regarding likely treatment patterns and applicability of resource use.

## 8. Discounting

Discounting is necessary to correctly compare treatments that have costs and benefits that occur at different times.

The extent to which future benefits and costs are discounted in comparison with the present is reflected in the discount rate. As the discount rate increases, future benefits and costs become less important when compared with benefits and costs occurring in the present.

PHARMAC recommends that both costs and benefits be discounted at the same rate for the following reasons:

- health and money can be exchanged at the margin at a rate that remains constant over time. If different rates are used for costs and benefits, inconsistencies may appear over time in the relativity of money and health;
- if benefits are discounted at a lower rate than costs, future programmes always look better (high benefit, low cost) than current programmes, and the cost-effectiveness ratio will always improve on delay (as the cost numerator decreases more quickly than the benefit denominator);
- individuals can only be treated equally over time if the same discount rate is used for benefits and costs. If health benefits are not discounted, benefits for future patients would be considered better;
- if a lower rate was used for benefits compared with costs, a treatment with high annual payments but minimal benefits per year would appear highly cost-effective due to the fact that costs are discounted more broadly than future benefits.

### 8.1 Approaches to Determining the Discount Rate

The appropriate rate of discount is controversial, and no precise gold standard exists. Most countries base their discount rate on the long-term rate of government bonds or a rate recommended by other countries in order to allow comparisons in the results of analyses. In the past PHARMAC has used the risk-adjusted long-term cost of capital to government to discount future costs and benefits when undertaking CUA.

There are six key approaches to determining a discount rate:

- rate used in other countries;
- the social rate of time preference;
- the social opportunity cost;
- a weighted average social discount rate;
- the shadow price of capital; and
- 'bottom up' approach.

#### 8.1.1 Discount Rate used in Other Countries

Some argue that the discount rate used in New Zealand should be more consistent with that used in other countries. However, there are several reasons why this argument does not hold:

- New Zealand's economic performance is not identical to other economies hence the use of an international discount rate may not reflect societal or individual preferences in New Zealand.
- Economic analyses cannot be directly transferred and compared between countries.
- The risk-free bond rate and resources available in New Zealand are not identical to that in other countries.

### 8.1.2 Social Rate of Time Preference

The social rate of time preference is the rate at which society is willing to exchange present for future consumption.

It is frequently argued that the after-tax interest rate of a risk-free investment (e.g. long-term government bonds) represents an individual investor's willingness to forgo present consumption for the future, and that this rate reflects the individual's rate of time preference. Then if society's collective rate of time preference is an aggregate of individual rates, the required rate is given by the rate of return on long-term government bonds.

### 8.1.3 Social Opportunity Cost Rate

The social opportunity cost rate of discount is the real rate of return forgone in the private sector (i.e. the cost in financial market terms if government projects were undertaken in the private sector). The basic notion behind this is that public investments can displace or crowd out private investments or consumption. This can be estimated using a number of different models which aim to work out what the market would expect to receive for a particular project. However, it is likely that the discount rate in the public sector is lower than that in the private sector (if it was not there would be no need for government provision of health care and private health insurance markets would be more dominant).

### 8.1.4 Weighted Average Social Discount Rates

The social discount rate is a weighted average of the social rate of time preference and social opportunity cost rate, and hence reflects both the loss in private investment and cost of forgone consumption. This is based on the risk-free rate of capital, a market risk premium, and an adjustment for risk.

### 8.1.5 Shadow Price of Capital

The shadow price of capital seeks to establish the loss to society that occurs when a dollar that would otherwise have gone to private investment is displaced. This is based on the principle that the ultimate purpose of investment is consumption, hence if money is not spent on new pharmaceuticals the funds would remain in the economy for private consumption or investment.

Funds that would otherwise have been used for consumption are discounted at the consumption (or market) rate of interest – the rate at which individuals are willing to exchange present for future consumption. As consumer preferences should dictate government policy, the consumption (or market) rate should equal the social rate of time preference [22,23].

### 8.1.6 'Bottom Up' Approach

In the 'bottom up' approach it is assumed that government spending should finance projects with the highest rate of return first and then in order of return rankings. Therefore, the opportunity cost is the rate of return of the last project funded (i.e. rate of return of the marginal project). Problems with this approach relate to the problems

with Internal Rate of Return (IRR) calculations, and level at which government spending is scrutinised.

## 8.2 Recommended Discount Rate

**Key Recommendations:** Discount all costs and benefits in CUAs using the 5 year average real risk-free long-term government bond rate (3.5%). Include rates of 0%, 5%, and 10% in sensitivity analyses.

PHARMAC considers that the social rate of time preference is the most relevant approach for PHARMAC to use when determining the discount rate as it reflects society preferences. This requires the use of the long-term government bond rate.

The following issues also need to be considered:

### 8.2.1 Should the Risk-Free or Risk-Adjusted Rate be Used?

The risk-free rate of return is the rate at which the New Zealand Government can borrow (government bond rate). Some however argue that this rate should be adjusted for the risk of the investment and the compensation for covering this risk (e.g. risk of uncertain future). Others argue that this risk could be taken into account by including higher costs and/or lower benefits in the sensitivity analysis, and that it is inappropriate to use the discount rate to compensate for this risk.

In the past PHARMAC has used the risk-adjusted government bond rate (currently 8%), upon direction from the PHARMAC Board. This was recently reviewed, and the Board decided that the discount rate used in CUAs would be based on the five-year average real risk-free long-term government bond rate.

### 8.2.2 Should the Discount Rate be Adjusted for Inflation?

In order to ensure consistency, the use of a real or nominal discount rate should depend on whether costs included in the analysis have been adjusted for inflation. In general it is simpler to adjust the discount rate. As PHARMAC uses real costs, the long-term cost of capital rate should be adjusted for inflation.

$$\text{Real cost of capital} = [(1 + \text{nominal rate}) / (1 + \text{inflation})] - 1$$

This can be approximated as the nominal rate minus inflation.

### 8.2.3 Should Long-Term or Short-Term Government Bond Rates be Used?

As it is preferable to use stable long-term government bond rate, the rate used should be long enough to avoid fluctuations (e.g. five years).

### 8.2.4 Recommendations

All costs and benefits in CUAs should be discounted based on the five-year average real risk-free long-term government bond rate. It is therefore recommended that a rate of 3.5% be the base rate used over the next five to ten years.

Rates of 0%, 5%, 10% should be included (without exception) in sensitivity analyses<sup>27</sup>.

The impact of reducing the discount rate to 3.5% will be that the present value of future costs and benefits will increase, and hence encourage a longer-term perspective.

### 8.3 Exemptions

The above discount rate does not apply when undertaking budget impact analysis (BIA), which serves a very different purpose. BIA focuses on the financial aspects of proposals within a limited timeframe (usually 1-5 years) and is used to determine if PHARMAC can afford to fund a treatment given the current budget. Investment decisions are often associated with substantial uncertainty even in the short term – within the next few years pharmaceutical prices may decrease, or PHARMAC's budget may change. With an uncertain future (and the associated risks), it is therefore reasonable that a higher discount rate be used. This is particularly the case when forecasts indicate that PHARMAC has very tight budget constraints.

Cost-utility analysis differs in that it is not used to make an investment decision, but rather to determine the relative ranking of pharmaceuticals. It is therefore not considered necessary to capture the risk in the discount rate. In addition, CUA is not purely a financial analysis, but also involves the quantification of health benefits. In some cases significant health benefits occur in the future (for example, with childhood immunisation), in which case a lower discount rate is necessary.

Equally, while CUA evaluates real costs and benefits, BIA focuses on actual (i.e. nominal) expenditure. Furthermore, the capital costs have no obvious relationship to benefits, but a strong significance to any budget decision. In practice this would mean that while the investment ranking would be decided by a discount rate of 3.5%, the impact on the budget would be evaluated using a discount rate of 8%. Assuming that no other decision criteria were relevant, this method would ensure that the investments that offer the highest health gain within the available funding path would then be funded.

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<sup>27</sup> Rates of 0%, 5%, and 10% enable comparison with analyses undertaken in other countries (5%), past PHARMAC analyses (10%), and the impact of the discount rate (0%).

## 9. Cost-Effectiveness Results

Cost-utility ratios should be based on incremental results (i.e. the difference in costs and QALYs gained between the new pharmaceutical compared with current treatment) rather than on totals or averages, as this provides us with information on the amount of additional benefit that would be gained from the additional costs. This is calculated by taking the difference between the costs of the two treatments, divided by the difference in their effectiveness.





The incremental cost per QALY is calculated as follows:

$$\begin{aligned} \text{Incremental cost/QALY} &= \text{discounted incremental costs} / \text{discounted QALYs} \\ &= \frac{(\text{net costs of intervention}) - (\text{net costs of alternative}), \text{ discounted}}{(\text{net QALYs of intervention}) - (\text{net QALYs of alternative}), \text{ discounted}} \end{aligned}$$

The results of the model should be reported as conditional on their input data.

### 9.1 Interpretation of Results

In general if:

$\Delta C < 0; \Delta E > 0$		dominant (more effective and less costly)
$\Delta C > 0; \Delta E < 0$		dominated (less effective and more costly)
$\Delta C > 0; \Delta E > 0$		trade-off
$\Delta C < 0; \Delta E < 0$		trade-off

where:  $\Delta$  = change; C=costs; E=effectiveness.

When presenting the results of the analysis, the overall incremental cost per QALY result should be reported as a point estimate as well as the range over which the cost per QALY is likely to vary.

In addition, cost and QALY information should be reported as outlined in Table 12. Costs and savings should be reported separately, and estimates should be based on the time horizon of the analysis (usually lifetime).

**Table 12: Reporting of Cost-Effectiveness Results**

	Reporting Details
Costs and savings	Discounted costs and savings to the Pharmaceutical Schedule of a funding decision
	Discounted real costs and savings to DHBs (over lifetime and 5 years)
	Discounted nominal costs and savings to DHBs (over lifetime and 5 years)
	Discounted direct costs and savings to patients
	Discounted total and net costs of both regimen and comparator
Quality-Adjusted Life Years	Discounted normal life expectancy of target population without the proposed intervention
	Discounted increase in expected life expectancy from proposed intervention
	Discounted expected quality of life gain from proposed intervention
	Discounted expected quality of life loss from proposed intervention (e.g. due to adverse events)
	Discounted total quality-adjusted life expectancy of proposed intervention and comparator, with net QALY gains

An outline of how the results should be presented is included in Section 10. An outline of how PHARMAC uses these results is presented in Section 2.

# 10. Sensitivity Analysis

Sensitivity analysis is the process by which the robustness of a CUA is assessed by examining the changes in the results of the analysis when key variables are varied.

In general, uncertainty can be characterised as either parameter-related or modelling-related.

## 10.1 Parameter Uncertainty

**Key Recommendations:** Sensitivity analysis should include univariate (simple) analysis, multivariate analysis, and/or extremes (scenario) analysis. The level of sensitivity analysis undertaken should be determined by the impact the results of the analysis could have on the funding, and the level of analysis. When undertaking detailed analysis, probabilistic sensitivity analysis may be necessary.

The following steps should be undertaken to test the level of uncertainty of a parameter [8,13]:

### 10.1.1 Identify the Parameters

Parameters to consider include those with the greatest level of uncertainty (e.g. those derived from opinion), and those with the greatest influence on model outcomes (e.g. key clinical variables and costs).

### 10.1.2 Specify the Plausible Range over which the Parameters may Vary

The range over which parameters should be varied in the sensitivity analyses should be based on the available scientific literature, expert opinions, or a scale that is regarded as plausible.

### 10.1.3 Calculate Results

The level of sensitivity analysis undertaken should be determined by the impact the results of the analysis could have on the funding decision (e.g. if a pharmaceutical has a cost/QALY of \$10,000, but may be sensitive to several parameters, more extensive sensitivity analysis should be undertaken than for a pharmaceutical with a cost/QALY of over \$100,000).

PHARMAC recommends the following approaches be considered when undertaking sensitivity analysis [27,28,29]:

**Table 13: Sensitivity Analysis Methods**

Method	Description	Advantages	Disadvantages
Univariate (simple)	Assesses the impact on the results of changing one variable.	Quick, simple, and easy to communicate results. Is sufficient if each of the uncertain variables is independent of the others.	There is a risk of ignoring interactions between parameters, hence underestimating overall uncertainty. This method also does not allow for the calculation of confidence intervals.
Multivariate	Evaluates the uncertainty related to multiple parameters by varying	Generates more realistic results than univariate sensitivity analysis.	If there are a large number of uncertain variables it may be

	more than one parameter at once.		difficult to present and interpret the results, particularly if parameters are correlated.
Threshold	Calculates the value a variable would need to reach in order to change the outcome of the analysis.	Useful when a parameter is indeterminate, such as the price of the pharmaceutical.	Requires a 'cost-effectiveness threshold', which PHARMAC does not have.
Extremes (scenario or 'worst/best case analysis')	Assesses the impact of moving one or more variables to its potential extremes.	This approach is especially useful when there is little information available on the efficacy of a pharmaceutical (for example, treatments for rare diseases).	May overestimate the uncertainty associated with the results.
Probabilistic	Based on Monte Carlo simulations. Examines the impact on the results of the analysis when variables are varied simultaneously according to predefined distributions.	Permits varying all parameters in the model simultaneously and enables calculation of the expected value and variance of decision variables.	Can only handle uncertainty in data inputs. It has also been criticised on the basis that it introduces further assumptions into the model - in particular, the choice of distribution to represent uncertainty.

At a minimum, the analysis should include univariate, multivariate and extremes sensitivity analyses. When undertaking detailed analyses, probabilistic sensitivity analysis should be considered.

#### 10.1.4 Interpret Results

PHARMAC recommends that sensitivity be interpreted by comparing the percentage change in input value with the percentage change in outcome value (i.e. the elasticity of the variable).

$$\text{Sensitivity} = (\Delta \text{ outcome} / \Delta \text{ input}) \times (\text{average input} / \text{average outcome})$$

or:

$$\epsilon = (\% \Delta \text{ outcome} / \% \Delta \text{ input})$$

This provides us with information on what degree the results of the CUA change when inputs are varied (i.e. by changing a parameter by x%, the results of the analysis change by y%).

The use of elasticity allows for a more objective judgement to be made regarding the sensitivity of variables in the model. The higher the elasticity, the more sensitive the outcome is to a change in the input variable. Elasticities approaching (or greater than) 1 indicate that the outcome is very sensitive to changes in the input variable. The direction of the relationship determines the sign of the elasticity [30].

For example, for a pharmaceutical that has a cost per QALY of \$190,000, a sensitivity analysis may be undertaken to test how the results of the CUA change if

the price of the pharmaceutical is reduced by 50%. If the cost/QALY subsequently decreased to \$98,000, the elasticity is calculated by taking the percentage change in cost/QALY after the price decrease (i.e. 0.48) and dividing by the percentage change in price (i.e. 0.5). The resulting elasticity is 0.97, indicating that the results are sensitive to the price of the pharmaceutical.

However, it should be noted that individual judgement is still required, particularly for parameters varied over a small range.

## 10.2 Model Structure Uncertainty

Modelling-related uncertainty can be characterised as depending on the structure of the chosen model or related to the overall process for modelling. This can be tested by running repeated analyses using alternative model structures, and examining the appropriateness of the results [8,31].

Modelling-related uncertainty includes [8,31]:

- choice of functional forms for extrapolating outcomes (e.g. constant benefits, linear extrapolation, etc.);
- choice of health states; and
- inclusion of a particular study in a meta-analysis (analysis could be re-run excluding the study).

It is recommended that structure uncertainty be formally examined in sensitivity analysis.

# 11. Presentation of Data and Results

It is important that CUAs are transparent so that quality and validity can be assessed. Table 14 outlines what information should be included when reporting detailed CUAs. Lower levels of analysis undertaken by PHARMAC may be less descriptive<sup>28</sup>.

**Table 14: Information to Include in Report for Detailed Cost-Utility Analyses**

Section	Details	Description
Context	Statement of objective and perspective of analysis	Decision problem that prompted the analysis
	Statement of type, scope and level of analysis	Levels of analysis include rapid, preliminary, indicative, and detailed
Disease and Patient Population	Description of disease	Symptoms Stage of disease Disease progression Prognosis
	Description of target population	Age Gender Risk factors Prevalence Incidence Ethnicity
	Description of treatment options available	Aim of treatment Indications Contraindications Dose Administration Length of treatment Adverse events Pharmaceutical Schedule listing criteria Any likely amendments to treatment over time
Study drug	Description of pharmaceutical	Indications Contraindications Formulation Strength Dose Administration Length of treatment Adverse events
	Description of indication(s)	Registered and funded indication(s) Indication for which funding is sought (including any restrictions)
Clinical evidence	Description of literature search strategy	Database searched Time period search undertaken Search strategy used Keywords Refinements

<sup>28</sup> PHARMAC staff are currently drafting internal templates for rapid and preliminary cost-utility analyses.

Section	Details	Description
		Justification for excluding any citations.
	Description of key clinical studies	Design Study population Follow-up period Withdrawals from treatment Clinical endpoints
	Critical review of clinical studies	Grade of evidence (GATE, SIGN) Possible sources of bias Methods of randomisation
	Discussion of relevance of trial results to New Zealand clinical practice	Efficacy compared with effectiveness
Model	Comparator(s)	Rational for choice of main comparator
	Description of model	Model type Transition states Markov states Copy of decision tree or branch of decision tree
	Time horizon and cycle length	Justification for time horizon and cycle length
	Discount rate	Description of discount rate used for costs and benefits
Outcome measures	Description of relevant outcomes and how they were measured	Adverse events, disease progression, mortality, etc.
	List of parameter values	Including confidence intervals
	List of assumptions	Assumptions regarding the structure of the model and data (including any extrapolation)
Health-related quality of life	Description of how HR-QOL was measured	For example, methods for mapping to generic health state instruments, use of expert opinion, etc.
	Utility values used	The health state and corresponding utility value
Costs	Description of costs	Units of resources, unitary costs
	Description of realisation of hospital costs	Information on whether a new treatment results in real savings to DHBs, nominal savings, or additional costs
	Description of data sources	Including any strengths or weaknesses of data sources
Results	Results derived from the model	Disaggregation of costs, savings, life-expectancy and quality of life gains/losses; as outlined in Section 9. Discounted incremental cost/QALY (point estimate and range)
	Interpretation and discussion of results	Discussion on likely relative cost-effectiveness of pharmaceutical
Sensitivity analysis	Results of sensitivity analysis	Use of elasticity
	Discussion of sensitivity to modelling assumptions and data inputs	Direction of bias and magnitude of effect
Discussion	Discussion of results and other issues that should be considered under	For example, health need and Maori

Section	Details	Description
	PHARMAC's decision criteria	health
Validation	Description of validation method and result	For example, pharmacoeconomic review, and/or clinical review
	Comparison with published analyses	Explanation of any differences in results
Conclusions	Description of setting to which the results of analysis can be applied	List of factors that could limit applicability in clinical practice
	Description of any research in progress	Description of how new data may alter results of analysis.

## 11.1 Checklist

Table 15 contains a checklist of information to include in PHARMAC base-case analyses and sensitivity analyses.

**Table 15: Checklist of Information to Include in Base-Case Analyses and Sensitivity Analyses**

Section	Base-Case Analysis	Sensitivity Analysis
Perspective	PHARMACs decision criteria.	-
Target population	Population most likely to receive treatment.	May consider inclusion of retrospective subgroup analyses if these data were of inadequate quality to include in base-case analysis.
Comparator	Current clinical practice in New Zealand.	May consider inclusion of placebo and/or most effective treatment (if different from current clinical practice).
Clinical outcomes	Statistically and clinically significant outcomes obtained from high-quality RCTs, systematic reviews or meta-analyses (grade of evidence of 1+ or 1++). Include impact of non-compliance if significant.	Include statistically insignificant outcomes. May consider impact of including additional sources of clinical evidence (e.g. unpublished trials). Test all modelling assumptions, including any extrapolation of data.
HR-QOL	Base of NZ EQ-5D Tariff 2. Use of GBD weights to check for consistency.	NZ EQ-5D Tariff 1.
Pharmaceutical Costs	Proposed price of pharmaceutical	Deflate price by 2% per year as a proxy for inflation in other costs.
Other Costs	Hospital, outpatient and patient costs.	Vary costs over likely ranges.
Discount rate	3.5%	0%, 5%, 10%

## Glossary

This glossary includes a list of terms that may be used in cost-utility analyses.

Term	Definition
Absolute Risk Reduction (ARR) or Absolute Risk Increase (ARI)	The absolute difference in event rates between an intervention and its comparator.
Adherence	Continuation and consistency with recommended treatment regimen.
Average cost	Total cost divided by total number of units.
Budget impact analysis	Estimate of planned resource use and impact on budget over a period of time.
Confidence interval	Numerical measure of the range within which the true treatment effect is likely to lie.
Cost/QALY gained	Result of cost-utility analysis. Monetary cost per quality-adjusted life year (QALY).
Cost-benefit analysis (CBA)	Cost-benefit analysis (CBA) measures costs and benefits in monetary terms, and expresses the results as one figure representing the difference between benefits and costs ( $B-C > 0$ ), or as a ratio ( $B/C$ ).
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis (CEA) compares the relative costs of interventions against some clearly definable outcome; such an outcome may be, for example, hospitalisation days avoided, strokes prevented or hip fractures averted. The final result is a value called the incremental cost-effectiveness ratio (ICER).
Cost-minimisation analysis (CMA)	Cost-minimisation analysis (CMA) assumes that there is no net health change between different treatment options (i.e. there is no significant difference in the effectiveness of the treatments). In this case the analysis is essentially a search for the least cost alternative.
Cost-utility analysis (CUA)	Cost-utility analysis (CUA) is similar to CEA, but health outcomes are measured using a common denominator - quality-adjusted life-years (QALYs) gained. The incremental cost-utility ratio (ICUR) is defined as the change in the costs and benefits (where benefits are measured in terms of quality-adjusted life years) resulting from substituting one treatment for another.
Decision tree	Graphical representation of alternative treatments for use under conditions of uncertainty.
Diagnosis Related Group (DRG)	Patient classification scheme which provides a clinically meaningful way of relating the number and types of patients treated in a hospital to the resources required by the hospital.

Direct cost	Fixed and variable costs (medical and non-medical) directly related to the treatment.
Disability-adjusted life years (DALYs)	An indicator that assesses the global burden of disease. These are calculated by adjusting age-specific life expectancy for loss of life due to disability.
Discount rate	Rate used to convert future costs and benefits into present values (current dollars and benefits have greater value than future dollars and benefits).
Disinvestment	May involve reduction in eligibility to a treatment (i.e. tightening of access), or cessation of treatment.
Dominant	Treatment is more effective and less costly than alternative.
Health-related quality of life	Physical, social and emotional aspects of patient's well-being.
Healthy-years equivalent (HYE)	Number of years of perfect health that is equivalent to the lifetime path of health states under consideration.
Effectiveness	Benefit of treatment in 'real world' setting.
Efficacy	Benefit of treatment in defined population in controlled or ideal circumstances (e.g. randomised controlled trials).
Extrapolation	Predicted parameter values outside of measured range, or inference of value of parameter of related outcome.
Incremental cost	The difference between the cost of an intervention and the cost of the comparator.
Indirect cost	Productivity gains or losses related to illness or death.
Intangible cost	Cost of pain and suffering as a result of illness or treatment.
Health status measure	Instrument such as the EQ-5D, which measures different aspects of quality of life on a scale of 0 (dead) to 1 (perfect health).
Marginal cost	The additional cost of one extra unit of product or treating one additional patient.
Markov model	A statistical representation of discrete, recurrent events over time in which the probability of transition from one to another depends on the current state.
Meta-analysis	A systematic process for finding, evaluating and combining the results of data from independent sources.

Monte Carlo simulation	Simulation modelling that uses random numbers to capture effects of uncertainty.
Number needed to harm (NNH)	The number of patients who are treated that would lead to one additional person being harmed compared with patients who receive the control treatment. NNH=1/ARI
Number needed to treat (NNT)	The number of patients who need to be treated in order to prevent or create one additional event occurring over a predefined period of time. NNT=1/ARR
Opportunity cost	Value of the alternative options that could be undertaken with the same resources.
Perspective	Viewpoint of analysis (e.g. funder, society, government, individual).
Probabilistic sensitivity analysis	Method of sensitivity analysis where probability distributions are specified for uncertain parameters and a Monte Carlo simulation is performed to obtain a probability distribution of expected outcomes and costs.
Quality-adjusted life years (QALY)	<p>A QALY ('quality adjusted life year') is a standard economic measure, which combines the effects of changes in the length and quality of life that result from treatment. Quality-adjusted life-years help compare gains in the quality of life with gains in the quantity (length) of life, in a simple and direct manner.</p> <p>Quality of life weightings (or utilities) are typically measured on a scale of 0 to 1, where 0 is equivalent to death and 1 to perfect health. These weights can then be summed over life expectancy in order to calculate the total number of QALYs.</p> <p>The difference in QALYs and overall costs gained between two treatments informs the relative cost-effectiveness of an intervention.</p>
Relative risk	Ratio of incidence of disease in exposed group divided by incidence of disease in non-exposed group.
Relative Risk Increase (RRI)	Proportional increase in rates of events between the experimental group and control group.
Relative Risk Reduction (RRR)	Difference in events between two treatment groups, expressed as a proportion of the event rate in the untreated group.
Sensitivity analysis	Process through which the robustness of an economic model is assessed by examining the changes in the result of the analysis when key variables are varied over a specified range.
Standard gamble	A technique for assessing preferences in which individuals are asked to choose between the certainty of an intermediate health state and the uncertainty of a treatment with two possible outcomes, usually full health (utility of 1) and death (utility of 0). The probabilities are then systematically altered until the individual is indifferent between the choice of the certainty of continued life in the health state of interest and the gamble.

Time trade-off	A technique for assessing preferences in which an individual is asked to choose between living for a defined period of time in a poor health state and living for a shorter period of time in full health, in order to determine what amount of time they would be willing to give up to be in a better health state. The time in full health is varied until the individual is indifferent between the two alternatives.
Utility	Values of the strength of preferences for, or desirability of, a specific level of health status or a specific health outcome.
Utilitarianism	Theory of social justice that considers that social welfare is improved through policies that produce the greatest good for the greatest number of people.
Value for money	Refers to whether the benefits of a pharmaceutical are significant enough to compensate for the higher cost.
Visual analogue scale	A technique for assessing preferences in which individuals are asked to indicate where on a line between the best and worst imaginable state (usually represented by 0 and 100) they would rate a certain health state. The health state valuation is then derived by measuring the distances between healthy (generally assigned 1) and dead (generally assigned 0) and the indicated health state on the line.

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## Appendix 1 - Process in Updating PFPA

Version 1 of the PFPA was developed and produced by Scott Metcalfe, Peter Sharplin, and Matthew Brougham between 1997 and 1999.

A Technology Assessment Group (TAG) was formed in late 2004 to review the methodology used in conducting economic analysis and the content of the PFPA. The project group was led by Rachel Grocott and the group currently consists of Rico Schoeler, Scott Metcalfe, Ginny Priest, Cameron Hall and Matthew Poynton.

The review of the PFPA involved the following process:

1. review of literature on economic methodology and international guidelines;
2. drafting of discussion documents;
3. technology assessment group meetings;
4. expert advice;
5. consultation; and
6. final revision and publication.

### **Literature Review**

The aim of the literature review was to identify and summarise consensus statements, internal guidelines, and published debates regarding the construction and use of economic models. References in articles were checked and recent pharmacoeconomic journals and health economic journals were hand-searched.

The methodology of this document drew heavily from health economic guidelines and consensus statements, with variations relating to the PHARMAC operating environment and New Zealand health system.

### **Discussion Documents**

Discussion documents were drafted summarising the information obtained from the literature review and PHARMAC's current practices. Topics included:

- reviewing clinical evidence;
- economic modelling;
- measurement of quality of life;
- measurement of costs;
- sensitivity analysis and reporting of results;
- discounting and discount rate;
- prioritisation, social issues, processes, etc.

### **Internal Discussion**

A series of meetings was organised for the Technology Assessment Group (TAG) to discuss the information in these documents. At the completion of each series of meeting, a consensus document was drafted, outlining the decisions reached.

### **Expert Advice**

Expert advice on the draft PFPA was obtained from six national and international economists. The draft PFPA was also reviewed by PTAC and the PHARMAC Consumer Advisory Committee (CAC). TAG tabulated all of the issues raised and discussed the reviews in detail, and a number of amendments were subsequently made to the document.

### **Consultation**

PHARMAC staff consulted widely on version 2 of the PFPA. Consultation letters were sent to consumer groups, medical groups, government organisations, pharmaceutical

suppliers, and national and international health economists. In addition, a letter was published in the New Zealand Medical Journal (NZMJ) alerting readers to the document and inviting consultation responses. Presentations were also held in Wellington and Auckland to discuss the revised PFPA with key stakeholders.

**Final Document**

All consultations were collated and discussed in detail by the Technology Assessment Group, and subsequent amendments were made to the PFPA. The final document was approved by the PHARMAC Board in April 2007, and published in June 2007.



## Appendix 3 – PHARMAC Assessment Process

### **Receipt of Proposals**

Proposals for the funding of new pharmaceuticals or for expanding access to pharmaceuticals may be initiated by anyone or any company (suppliers, patients, doctors, minister, public sector staff). PHARMAC receives about thirty new applications for funding each year (not including those initiated by PHARMAC).

When a proposal is received, the basic details of the proposal (such as chemical name, brand name, therapeutic group, indication, pharmaceutical supplier) are documented in a database.

### **Review of Clinical Evidence**

Following receipt of the proposal, the clinical evidence is reviewed by the Pharmacology and Therapeutics Advisory Committee (PTAC). This committee provides independent and objective advice to PHARMAC and consists of a group of medical practitioners with broad general experience and a particular interest in pharmaceuticals. There are also a number of PTAC subcommittees which comprise of experts in specialist clinical fields, such as cardiology and cancer. The PTAC often seeks advice from the expert subcommittees.

The PTAC uses the same decision criteria as PHARMAC when evaluating pharmaceuticals. The PTAC makes recommendations to PHARMAC for the assignment of high, medium or low priorities for proposals, or that a proposal be declined or referred back to the supplier for further information. This priority rating is used both to inform PHARMAC on the use of analyst resources in conducting technology assessments and in prioritising spending.

The PTAC also reviews PHARMAC CUAs (including reviewing the clinical assumptions in the analysis). These reviews may be undertaken formally at the PTAC meetings, or by individual members of the PTAC.

### **Economic Assessment and Budgetary Impact**

Economic analyses are generally done 'in-house' by the Technology Assessment Group (TAG). Most analyses to date have been undertaken by one to two FTEs. These analyses are based on the methods outlined in the PFFPA, and are usually in the form of a cost-utility analysis. The level of analysis undertaken depends on timeframes and the risk involved in making the wrong decision (i.e. high expenditure pharmaceuticals are more likely to require a detailed economic analysis). Most economic analyses are written up as 'Technology Assessment Reports' following a set template.

The budgetary impact of listing the pharmaceutical on the Pharmaceutical Schedule is also estimated, usually over a period of five years.

### **Economic Review of Economic Assessment**

It is important that models are reviewed by colleagues who are able to examine the inner workings of the model. The guidelines used for these reviews are included in Appendix 4.

The purpose of these guidelines is to:

- encourage the internal review of pharmacoeconomic analyses,
- facilitate a consistent approach to these reviews, and
- ensure that analyses follow the agreed methodology as outlined in the PFFPA.

The guidelines include a series of questions regarding the structure of the model, data inputs, modelling, quality of life, costs, results, sensitivity analysis and overview.

### **Clinical Review of Economic Assessment**

The model should make sense to people with knowledge of the disease. This includes ensuring that the right factors are included, the mathematical relationships are intuitive, and the data sources reasonable. This also ensures that the model reflects local clinical behaviour.

The PTAC, and its subcommittees, are used to review the clinical aspect of analyses. Clinical experts may also be contracted to review an assessment.

### **Collation of Information**

All information on a proposal is collated and the details are entered into a database. This includes information on PTAC priority, cost per QALY, and budget impact.

### **Prioritisation**

All pharmaceuticals awaiting funding are prioritised against other expenditure options (either listing of other new pharmaceuticals or expanding access to existing pharmaceuticals). This is based on PHARMAC's decision criteria, including affordability, health need and cost-effectiveness.

### **Negotiations with Pharmaceutical Suppliers**

The Therapeutic Group Manager is responsible for negotiating funding applications with the pharmaceutical supplier(s).

### **Interest Group Involvement**

PHARMAC consciously seeks the views, and tries to work together with, the health sector to improve its decision-making processes and improve health outcomes. Once PHARMAC reaches a provisional agreement with the Pharmaceutical Supplier(s), PHARMAC staff consult with interested parties on the proposal. Consultation responses are considered and amendments made before presenting the proposal to the PHARMAC Board.

### **Decision**

The PHARMAC Board makes the final decision regarding any amendments to the Pharmaceutical Schedule.

## Appendix 4 – PHARMAC Guidelines for Reviewing CUAs

The following guidelines are used when reviewing in-house CUAs, or CUAs provided by Pharmaceutical Suppliers.

Section	Questions
<b>Comparator(s)</b>	Have the appropriate comparator(s) been used in the analysis?
<b>Time horizon</b>	What is the time horizon of the analysis? Is this appropriate and justified in terms of the underlying disease and the effect of interventions?
<b>Cycle length</b>	What is the cycle length of the model? Is this appropriate and justified?
<b>Health states</b>	Does the report describe all relevant treatment paths? Is a justification of the choice of health states within the model provided? Have any important health states been omitted from the model, and if so, have justification for the omissions been provided?
<b>Structure</b>	Does the analysis outline the assumptions relating to the structure of the model? Are these assumptions reasonable and justified (e.g. rates of discontinuation of treatment)? Are these tested in the sensitivity analysis?
<b>Data inputs</b>	<p>Is the model based on the best quality data available?</p> <p>Were the sources of data used in the model clearly stated? Is there any evidence to suggest selective use of data?</p> <p>Have the probability values been calculated accurately given cycle length?</p>
<b>Modelling</b>	<p>Is there a clear and reasonable explanation of how data have been incorporated into the model (i.e. the methodology used in the calculation of probability values)?</p> <p>Has a half-cycle correction been included?</p> <p>Have data from different sources been combined? If so, is the data compatible and combined using appropriate methodology?</p> <p>Did the analysis extrapolate data to the longer term, or extrapolate intermediate clinical endpoints to final outcomes? If so, was this appropriate, justified, and modelled using the correct methodology? Was this tested in the sensitivity analysis?</p> <p>Does the model appear to be unnecessarily complicated or overly simplified?</p>
<b>Health-related quality of life</b>	<p>Were the estimated quality of life scores reasonable?</p> <p>How was quality of life measured? Was this method justified? If subjective values were used, were these tested in the sensitivity analysis?</p> <p>Were utility values adjusted for cycle length?</p> <p>Were utility values discounted using the appropriate discount rate?</p>

<b>Costs</b>	<p>Were pharmaceutical costs calculated correctly? What dose was used in the cost calculations and where was this information sourced? Is there any reason to believe that the dose used would be different from that used in key clinical trials, and is there evidence to indicate that the pharmaceutical has the same level of efficacy at that dose? Are there likely to be dose adjustments over time? If relevant, was the correct bodyweight used in the calculation of pharmaceutical cost? Do dispensing fees or costs of compounding need to be included? Was information provided on likely patent expiry? Was the price of generic pharmaceuticals included?</p> <p>How is the pharmaceutical administered? Have all costs associated with administration been taken into account?</p> <p>Have hospital costs been calculated correctly? Were these volume-adjusted? Are any adjustments necessary (e.g. adjustment for mechanical ventilation, complexity). Are you aware of any costs that appear to be inaccurate?</p> <p>Have any important and relevant costs that been excluded?</p> <p>Were costs discounted using the appropriate discount rate?</p>
<b>Results</b>	<p>Were there any important factors that have been excluded from the analysis that could have an impact on the results?</p> <p>In your opinion, are the conclusions of the analysis justified?</p>
<b>Sensitivity Analysis</b>	<p>Were the range and choice of variables used in the sensitivity analysis justified?</p> <p>Were the results of the sensitivity analysis interpreted correctly?</p>
<b>Overview</b>	<p>Did the report list any factors that could limit the applicability of the results (e.g. differences in patient population)?</p> <p>How could the analysis be improved? Describe the overall quality of the report.</p>

## Appendix 5 – Costs

These costs were as at June 2006. Please note that these costs may change. PHARMAC staff plan on publishing a more detailed document of costs at a later date. Until then, the costs included in this Appendix will be periodically updated.

### Dispensing Fee

The current dispensing fee is \$5.16 per prescription. The dispensing fee differs for the following groups of pharmaceuticals:

Group of Pharmaceuticals	Dispensing Fee (\$)
Class B pharmaceuticals	\$6.71
Monitored Therapy Medicines Services [HP4]	\$10.32
Complex Medicines Services [HP1]	\$7.74
Exceptional Circumstances Services (pharmaceuticals not on the Pharmaceutical Schedule)	\$7.74
Aseptic Pharmacy Services	\$15.48
Nicotine Replacement Therapy	\$5.72
Emergency Contraception Pharmaceutical Services	\$7.74

### Pharmacy Mark-Up

The pharmacy mark-up for pharmaceuticals with a value of less than \$150 is 4%. For pharmaceuticals with a values of \$150 or greater (and for all Special Foods and Nicotine Replacement Therapy), the pharmacy mark-up is 5%.

### Administration Costs

Pharmaceutical administration costs may include:

- laboratory/diagnostic tests or procedures required prior to the initial administration or each administration;
- pre-medication to prevent any potential side-effects;
- pharmacist time to prepare infusion at approximately \$25 per hour (this cost only needs to be included in cases where the preparation of the infusion has a relatively significant impact on pharmacist time);
- material costs required to deliver infusion (e.g. infusion line, saline, filter, alcohol swabs, etc.);
- nurse or specialist time required to administer treatment (approximately \$20-\$30 per hour for nurses and \$80-\$250 for specialists);
- post-administration monitoring by nurse;
- probability of attending appointment to have pharmaceutical administered (this may be necessary in cases where compliance is low, such as with intravenous typical antipsychotics);
- cost of home visits for administration.

### Cost of General Practitioner

The cost of a General Practitioner (GP) visit should be based on the average cost to the patient plus any government subsidy (if applicable). On average, this results in a cost per GP visit of approximately \$50.

### Cost of Home and Rest Home Care

The cost of home care is approximately \$11-\$16 per hour for a carer, and \$20-\$30 per hour for a registered nurse. The cost of rest home care is approximately \$650-\$750 per week. The cost of hospice care is approximately \$300-\$550 per day.