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Prescription for Pharmacoeconomic Analysis

Methods for cost-utility analysis

Version 2.1 - 2012

Foreword

PHARMAC, the Pharmaceutical Management Agency, is primarily responsible for managing the funding of pharmaceuticals for New Zealanders, on behalf of District Health Boards. PHARMAC's 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 amount of funding provided.

In New Zealand, pharmaceutical funding occurs within a limited budget. No matter the size of the budget, we can't fund everything, so difficult choices have to be made. Cost-utility analysis provides us with information on what pharmaceuticals offer the most health gains from the available budget. In this way, PHARMAC is able to make better informed choices.

Cost-utility analysis is however 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. However, it is this one criterion that, in essence, is the focus of this document, the Prescription for Pharmacoeconomic Analysis (PFPA).

The PFPA is important to PHARMAC as it describes the approach we take when doing cost-utility analysis. It is also a guide for pharmaceutical suppliers when undertaking their own economic analyses to support new funding applications. PHARMAC uses cost-utility analysis to compare the cost-effectiveness of a pharmaceutical with other pharmaceuticals that could be funded instead. In this relative assessment context, it is critical that each analysis is undertaken in the same way so that comparisons are valid and the results meaningful for decision-making. Cost-utility analyses provided to PHARMAC therefore need to be clear and based on the methodology outlined in this document.

The PFPA was first drafted in 1999 (version 1), and was revised in 2007 (version 2). This update includes minor changes to version 2.

PHARMAC will continue to review and update its methodology for undertaking cost-utility analysis, and if needed, incorporate changes to this document over time.

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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

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 points to consider when undertaking cost-utility analyses for PHARMAC are summarised below.

Input / Output	Recommendation
Type of analysis	Cost-utility analysis (or cost-minimisation analysis if appropriate).
Perspective	PHARMAC's decision criteria.
Target population	New Zealand population most likely to receive treatment.
Comparator	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).
Clinical outcomes	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. All trials should be critically appraised and analysed using data from the intention-to-treat (ITT) population.
Economic modelling	Economic models should avoid unnecessary complexity; be transparent; and include all statistically significant clinical events. The methodology, limitations, and any possible bias associated with extrapolating data should be clearly described in the report and explored through sensitivity analysis. This includes extrapolating data from clinical trials to the longer term (or to final outcomes); generalising results from clinical trials to the New Zealand clinical setting by taking into account non-compliance; and undertaking indirect comparisons of trials.
HR-QOL	Health-related quality of life (HR-QoL) should be measured using quality-adjusted life years (QALYs) based on NZ EQ-5D Tariff 2. The Global Burden of Disease (GBD) disability weights and published utility values should be used to check for consistency.
Pharmaceutical Costs	Pharmaceutical costs should take into account any proposed rebate, 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. The analysis should also include the lower cost of a future generic pharmaceutical.
Other Costs	Hospital, outpatient and direct patient costs should be included. Direct patient costs 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. Costs to non-healthcare government departments and indirect patient costs should not be included in CUAs for PHARMAC.

Input / Output	Recommendation
Discount rate	Discount all costs and benefits in CUAs at a 3.5% discount rate. Include rates of 0% and 5% in the sensitivity analyses.
Results	<p>The results of cost-utility analyses should be reported as incremental utility cost ratios (IUCRs), i.e. incremental QALY gains per unit net costs. IUCRs are expressed as incremental QALYs per \$1 million of the total budget invested.</p> <p>The overall incremental QALYs per \$1 million result should be reported as a point estimate as well as the range over which the cost per QALY is likely to vary. The cost per QALY result should be reported alongside the IUCR.</p>
Sensitivity Analysis	Sensitivity analysis should include univariate (simple) analysis and multivariate analysis.

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. Our functions are set out in section 48 of the New Zealand Public Health and Disability Act 2000 (NZPHD Act).

One of PHARMAC's functions is to manage the Pharmaceutical Schedule, which is the list of pharmaceuticals that are publicly funded. We also negotiate national contracts for some pharmaceuticals and products used by District Health Board (DHB) hospitals and these are also listed in the Pharmaceutical Schedule (section H).

PHARMAC's statutory 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.' Section 47(a) of the NZPHD Act

Further information on PHARMAC can be found at: 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 2.1 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 and standardise approaches.

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.

In 2004, PHARMAC decided to review and revise the PFPA. A literature search was undertaken and internal sessions were held to review each section of the PFPA. The draft new version of the PFPA was subsequently reviewed by international and New Zealand experts in cost-utility analysis. PHARMAC staff consulted widely on the new draft of the PFPA. All consultation responses were considered, and a number of amendments were subsequently made to the document. The final document was approved by the PHARMAC Board in April 2007, and version 2 of the PFPA was published in June 2007.

In 2010 PHARMAC staff considered that version 2 of the PFPA should be reviewed and updated. This 2012 update (version 2.1) includes minor changes to version 2 (outlined in Appendix 1).

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?

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, as outlined in PHARMAC's Operating Policies and Procedures:

<http://www.pharmac.govt.nz/procedures>

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 aids PHARMAC in prioritising 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 undertaken 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 – thus the process 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. Therefore, assessments are conducted at four levels – rapid, preliminary, indicative, and detailed. The levels of analysis are outlined in Table 2. Note that these are a summary of what may be included. Any given analysis may include or exclude any of the criteria listed.

Table 2: Levels of PHARMAC Analyses

Type	General Description	FTE Required
Rapid	<p>Basic economic model constructed, largely based on opportunistic data. The analysis is undertaken over a time horizon that sufficiently captures the majority of incremental costs and benefits.</p> <p>Testing undertaken to ensure extent of analysis is sufficient.</p> <p>Brief documentation of CUA (but still detailed enough to allow reproduction of the CUA by others).</p> <p>Reviewed internally.</p> <p>May include reviews and basic amendments to external analyses.</p>	<2 weeks

Type	General Description	FTE Required
Preliminary	Assessment largely using opportunistic data. Rapid systematic review of evidence undertaken. May require further modelling compared with a rapid CUA (due to disease complexity, risk, or uncertainty of results). Reviewed internally.	2-4 weeks
Indicative	An interim assessment using some opportunistic data, but more detailed than a preliminary analysis. Evidence critically appraised. Often involves more complex economic modelling. Full assessment undertaken on whether statistically insignificant events are likely to be clinically significant. Further investigation into health-related quality of life scores, including a systematic review of the literature. Full multivariate sensitivity analysis may be undertaken with detailed discussion of results Detailed documentation of critical appraisal and economic analysis. Reviewed internally and by the Pharmacology and Therapeutic Advisory Committee (PTAC).	1-2 months
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 the Graphic Appraisal Tool for Epidemiology (GATE) framework (or other similar tools). Detailed Markov model. All potential health states and clinical events included. The use of probability distributions considered. Detailed extrapolation of the clinical evidence, and statistically non-significant events tested. Further validation of utility mapping exercise, including obtaining expert clinical input. Probabilistic sensitivity analysis may be undertaken. Reviewed internally and externally (clinical assumptions reviewed by PTAC).	>2 months

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

Very few proposals receive a detailed assessment as these take one FTE around 2-6 months to complete, which can be too slow and resource-intensive for a purchasing environment. While detailed analysis may improve the academic rigour of the assessment, we have found that increased levels of complexity often does not further inform the funding decision or impact on the relative cost-effectiveness of the pharmaceutical. Undertaking detailed CUAs when not strictly needed also ties up resources, thereby impinging on the ability to undertake other analyses or funding work generally. In addition, at PHARMAC the CUA result is not critical to the setting of a subsidy, so perfecting the CUA is seldom necessary. What is most important is that the CUA is sufficient to inform PHARMAC of where the pharmaceutical should be placed on the priority list.

The process is usually iterative. If a rapid assessment indicates there is very large uncertainty in the result of the analysis (to the extent that the relative priority of the pharmaceutical is uncertain), further analysis will be undertaken. The level of analysis largely depends on the ability to prioritise the pharmaceutical with sufficient certainty.

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 more 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.

Since 2007 PHARMAC has undertaken over 50 economic assessments per year. These analyses were done by approximately 4 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)¹; a specialist PTAC subcommittee; or clinical experts.

A more detailed outline of the process involved in assessing an application at PHARMAC is outlined in Appendix 2.

2.5.2 PHARMAC Process for Reviewing Supplier Cost-Utility Analyses

PHARMAC encourages 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 PFPA, may expedite the proposal review and information acquisition process, enabling the proposal to be prioritised earlier.

When PHARMAC receives a CUA from an applicant, our health economists review it, and amend it if required. The guidelines PHARMAC uses to review analyses are attached in Appendix 3.

In order for health economists to be able to review CUAs more efficiently, an electronic version 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.

¹ 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”. Proposals are only considered in relation to other funding proposals at the time. Also, 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 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. This is not just in terms of the total budget each year, but also the available budget that we anticipate in the future.

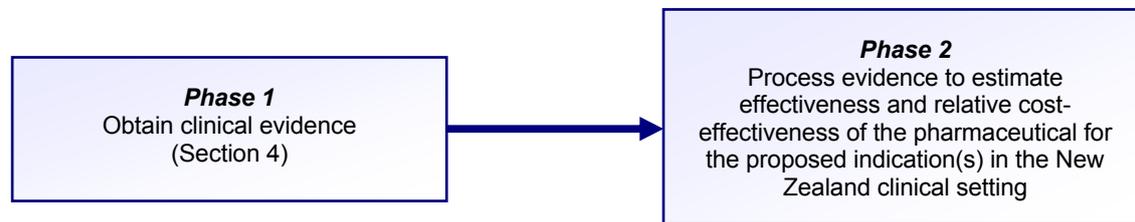
What may be considered ‘cost-effective’ therefore changes over time, with both wide variations in any year and between years.² For example, between the 1998 and 2007 financial years, individual new investments made by PHARMAC varied between 25 QALYs gained for every \$1 million saved by the NZ health sector (i.e. cost savings with health gains) and less than 5 QALYs gained for every \$1 million spent. Expressed as costs per QALYs, investments varied between saving \$40,000 per QALY gained (\$-40,000/QALY) and spending over \$+200,000 per QALY. Investments varied widely each year – reflecting the mix of investment opportunities, the funding available at the time, and the impacts of other decision criteria.³

² Data derived from PHARMAC’s Annual Reports to Parliament at <http://www.pharmac.govt.nz/AnnualReport>.

³ Grocott R. Applying Programme Budgeting Marginal Analysis in the health sector: 12 years of experience. *Exp Rev Pharmacoecon* 2009;9:181-7 <http://www.expert-reviews.com/doi/abs/10.1586/erp.09.2>

3. Scope of Analysis

Cost-utility analysis at PHARMAC has two distinct phases:



3.1 Perspective and Decision Problem

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 if significant. 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 in cases where funding a pharmaceutical may result in significant costs or savings to other non-healthcare government sectors, that these should be considered in a qualitative manner, with discussion on how these costs/savings may impact on the overall cost-effectiveness of the pharmaceutical.

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 available⁴.

⁴ Refer to Table 14 (Presentation of Data and Results) in Section 11 for further details on information to include in a CUA report when describing the disease, patient population and treatment options.

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.⁵

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].⁶

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).⁷ 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].⁶

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

⁵ 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.

⁶ 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

⁷ 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]

trials) should be defined *a priori* on the basis of known biological mechanisms or in 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]⁸ should be used to assess whether a treatment effect differs among subgroups (i.e. evidence of heterogeneity)⁹. 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]⁶ that adequately considers the above elements of plausibility, timing of the underlying hypothesis (*a priori*) and statistical heterogeneity.¹⁰ 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 population¹¹ or primary endpoint [48,56].

⁸ 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 I2 statistic with its 95% uncertainty interval.

⁹ Statistical tests of interaction are preferred to individual tests within each subgroup – individual tests often overestimate the extent of true differences.

¹⁰ 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 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

¹¹ 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].

3.3 Comparator(s)

Key Recommendation: The comparator(s) used in analyses should be the funded treatment (available on the Pharmaceutical Schedule or by DHB hospitals) that most prescribers or clinicians 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 funded in New Zealand and:

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

The analysis should consider both current clinical practice and likely future practice (i.e. the 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.

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

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 of the QALY per \$1 million invested result. The result should be weighted by the estimated patient numbers prescribed the comparator treatments.

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.

4. Evidence for Relative Clinical Effect

This section outlines what sources of evidence are preferred when calculating relative clinical effect (i.e. treatment efficacy and adverse effects) 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 critical appraisal undertaken.

For further details on how relevant clinical inputs are systematically identified and synthesised, please refer to the Guidelines for Funding Applications to PHARMAC, available at <http://www.pharmac.govt.nz/suppliers/fundingapps>.

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, post-surveillance studies, and case reports. [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	Recommended Use	Advantages	Disadvantages
Randomised controlled trials (RCTs)	<p>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 or abstracts/posters 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.</p> <p>If published trials are available, data from unpublished trials should only be included as supplementary information, which could include clinical study reports (CSRs) from the pivotal trials.</p>	External influences minimised through randomisation, patient selection, and double-blinding. This ensures that the effect is attributable to the intervention alone.	<p>Selected patients, investigators and comparator treatments may result in poor external validity.</p> <p>Often short time spans.</p> <p>May be subject to publication bias.</p>

Data Source	Recommended Use	Advantages	Disadvantages
Meta-analysis ¹²	<p>Meta-analysis may be useful when there is more than one key study or when results conflict between studies.</p> <p>With more detailed analyses it may be necessary to undertake a meta-analysis if there are no published meta-analyses available.</p>	<p>A single study may be insufficiently powered to detect treatment effects.</p> <p>Useful when results conflict between studies; when inappropriate comparators are used; or when a study consists of only one treatment arm.</p>	<p>Publication and inclusion biases (i.e. choice of studies included).</p> <p>May be difficult to assess validity.</p> <p>Incompatible studies may be included.</p>
Observational studies ¹³	<p>Used 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>	<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 (selection bias, measurement bias, etc.).</p> <p>Lack of control groups.</p>
Expert opinion	<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/extrapolations.</p>	<p>Clarification of unreliable, conflicting or insufficient clinical information in the literature.</p>	<p>Subject to selection bias.</p>
Case reports	<p>Generally not recommended that these be included in CUAs.</p>	<p>High real-world relevance.</p>	<p>High risk of bias.</p> <p>Small patient numbers.</p>
Post - surveillance studies	<p>Post-surveillance studies may provide useful information on the incidence and descriptions of adverse drug reactions.</p>	<p>High real-world relevance.</p>	<p>Lack of control groups.</p> <p>Underlying biases.</p>

¹² Meta-analysis systematically combines the results of studies in order to draw overall conclusions regarding the efficacy and/or safety of the treatment.

¹³ 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.cochrane.org/>
- National Electronic Library for Medicines (UK): <http://www.nelm.nhs.uk/en/>
- Evidence-Based Medicine (BMJ Journals): <http://ebm.bmj.com/>
- BMJ Clinical Evidence: <http://www.clinicalevidence.com/ceweb/conditions/index.jsp>
- Prescrire International: <http://www.prescrire.org/>

Database searches should be supplemented by scanning references in articles and hand searching key journals.

Information on drug safety and international regulatory authorities can be found at:

- Medsafe: <http://www.medsafe.govt.nz/>
- FDA: <http://www.fda.com/>
- European Medicines Agency: <http://www.ema.europa.eu/>

Information on international registries of clinical trials can be found at:

- ClinicalTrial.gov: <http://www.clinicaltrial.gov/>

It may also be useful to check the reviews of clinical evidence undertaken by international Health Technology Assessment organisations. These include (but are not limited to):

- National Institute for Health and Clinical Excellence (UK): <http://www.nice.org.uk/>
- NIHR Health Technology Assessment programme (UK): <http://www.hta.ac.uk/>
- Canadian Agency for Drugs and Technology in Health: <http://www.cadth.ca/>
- Scottish Medicines Consortium: <http://www.scottishmedicines.org.uk>
- Australian Pharmaceuticals Benefits Scheme: <http://pbs.gov.au/>
- Belgian Health Care Knowledge Centre: <http://kce.fgov.be/>
- The Swedish Council on Technology Assessment in Health Care: <http://www.sbu.se/en/>
- All Wales Medicines Strategy Group: <http://www.wales.nhs.uk/sites3/home.cfm?orgid=371>
- CEA Registry: <http://www.tufts-nemc.org/cearegistry/>

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/MeSH headings used.

Published errata, corrections, retractions, editorials, commentaries, and journal correspondence relating to individual trials should be included in the search strategy.

The pre-defined inclusion and exclusion criteria used for selecting relevant studies should be clearly specified. The report should clearly state the reasons for excluding any studies.

4.3 Presentation of Evidence

For key trials, the following details should be included in the report:

- (i) objective of trial;
- (ii) study design including eligibility criteria, sample size, interventions (including dose and treatment duration), methods for randomisation and blinding, duration of follow-up, and outcomes measures and methods;
- (iii) results including number of withdrawals and dropouts; and results for prospectively-defined primary outcomes, secondary outcomes and adverse effects for the intention-to-treat (ITT) population.

Further details on analysing clinical trial data are included in Section 5.4 (Transformation of Clinical Evidence).

4.4 Assessing Data Quality

Key Recommendations: Trials should be critically appraised using the Graphic Appraisal Tool for Epidemiology (GATE) framework (or other similar frameworks), with consideration given to the internal and external validity of the trials. Grades of evidence should be assigned, and assessment undertaken on the applicability of the trials to the New Zealand health sector. PHARMAC recommends that when high-quality studies are available, these should be the preferred data source when estimating relative treatment effects.

4.4.1 Critical Appraisal of Trials

PHARMAC recommends that clinical trials be critically appraised using the Graphic Appraisal Tool for Epidemiology (GATE) framework [58] (or other similar frameworks).

The GATE framework involves the following five steps:

1. asking focused questions based on PECOT (Population, Exposure, Comparison, Outcome, Time) and RAMMbo (fair Recruitment, fair Allocation, fair Maintenance, fair Measurement of Outcomes);
2. searching the literature for best available evidence;
3. appraising the study by 'hanging' on the GATE frame;
4. assessing study quality; and
5. applying the evidence in practice.

Details on the GATE framework, including critical appraisal spreadsheets, are available at: <http://www.fmhs.auckland.ac.nz/soph/depts/epi/epiq/ebp.aspx>.

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

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

Factors for appraisal	Questions to consider
<i>Internal validity – How reliable are the trial results?</i>	
Availability of data	Were all available trial data used? Were there quality controls (e.g. was the trial published in a peer-reviewed journal)?
Number of patients	Was the sample size large enough to rule out effects due to chance (i.e. false negatives and false positives)? Or was the effect large enough to be statistically significant even in a small sample size?
Method of randomisation, including adequate concealment	Was there likely to be any selection bias or confounding? Was there adequate reporting of appropriate randomisation and how this was kept concealed? 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 by Intention-to-treat (including drop-outs and deaths)?
Selection of endpoints	Were the endpoint/outcome measures relevant?
<i>External validity – How relevant are the trial results?</i>	
Patient population	Was the patient population in the trial similar to those considered for funding?
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?

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.

4.4.2 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, 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).

It should be noted that the SIGN checklist relates to the internal validity of the study and is used for assessing quality of evidence and risk of study bias. However, in assessing the effectiveness of the pharmaceutical, real-world relevance and clinical

practice are also important. The patient population and treatment regimen used in the trial should be consistent with how the treatment will be used in New Zealand clinical practice.

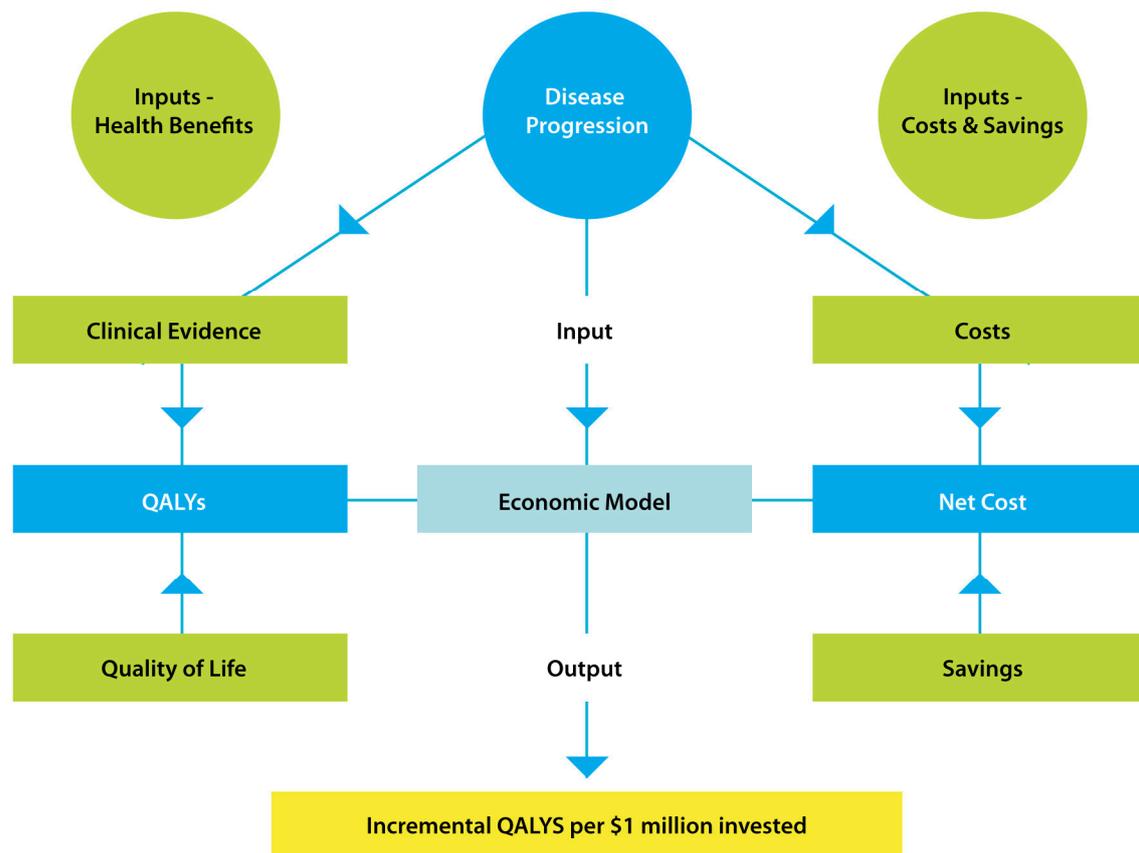
The following questions should be considered when assessing the applicability of the studies to the New Zealand health sector:

1. Are there any known biological factors that may alter the effect of the pharmaceutical?
2. What effects does the time of taking the pharmaceutical have?
3. What effects do variations in the nature and severity of the disease have?
4. Does the effectiveness of the pharmaceutical depend on the way it is administered and/or by whom (e.g. by a nurse rather than by the patients)?
5. Is the giving or taking of the pharmaceutical part of a complex procedure with many components?
6. Is any infrastructure required/available, such as monitoring with regular blood tests?
7. Are there any other factors that may affect transferability of study results to the New Zealand clinical setting?

5. Economic Modelling in CUA

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.

Economic models for CUA combine information about disease progression, the relative clinical effectiveness of a pharmaceutical (obtained from the best available evidence), 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. It is important these models capture all the appropriate additional benefits and costs.

5.1.1 Model Transparency

Model inputs and assumptions need to be clearly stated and the rationale for the inputs and assumptions need to be documented and explained. 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. Unnecessary complexity in economic models should be avoided.

5.1.2 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]:

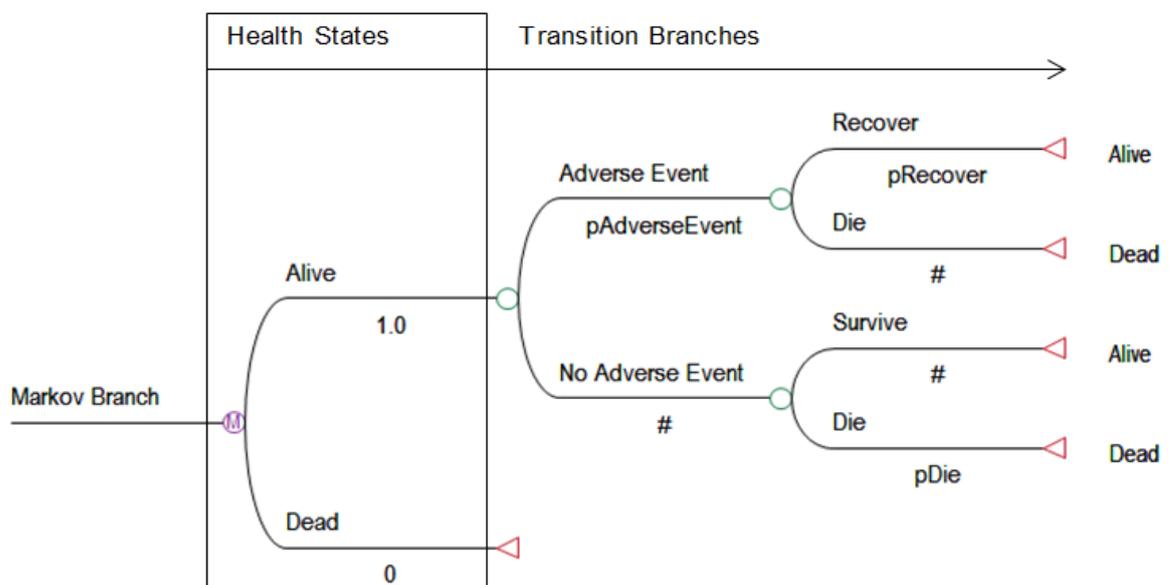
- **Simple Decision Trees**

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. For example, a simple decision tree could be used to model an 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.



When undertaking a CUA, 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).

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. The report should always justify the time horizon used in the analysis.

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. The chosen cycle length should not have an impact on the results of the analysis.

5.2.2 Half-Cycle Correction

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. Therefore an unbiased estimate should ensure that, on average, patients move between states halfway through the cycle. A half-cycle correction can achieve this adjustment [10, 11].

If a half-cycle correction is not applied, an explanation needs to be provided as to why the model does not require half-cycle correction.

5.3 Transformation of Clinical Evidence

Key Recommendation: Clinical trials should be analysed using data from the intention-to-treat (ITT) population. 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 Use of Surrogate versus Clinically-Important Outcome Measures

Economic analysis should ideally be based on studies that report clinically-important outcome measures. These are valid outcomes that are of importance to the health of the patient.

In some cases only surrogate outcomes may be available. These are a substitute for a clinically meaningful endpoint; and measure how a patient feels, functions or survives.

Surrogate measures should only be used in CUAs where there are no alternative health outcome data available. Caution must be used when using surrogate measures, as these may not necessarily translate into clinically-relevant and effective outcomes.

5.3.2 Analysing Data from Clinical Trials

Clinical trials should be analysed using data from the intention-to-treat (ITT) population, rather than per protocol (PP), 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.

Where ITT analysis has not been reported, the effectiveness rates should ideally be recalculated by adding to the “on treatment” participant population for the group (i.e. the denominator) all of the patients who withdrew, dropped-out, or were otherwise lost to follow-up. This is the group’s true ITT starting participant population.

CUAs should not include last-observation-carried-forward (LOCF) analysis due to the large bias this incorporates in economic models. LOCF assumes that a patient who drops out of the study will continue to be in the same state as the last time they were assessed. In studies where patients' health is deteriorating, this may overestimate the effects of a treatment [66].

5.3.3 Relative Clinical Effectiveness Data to be Included in CUA

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)¹⁴.

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 issues 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? ¹⁵
Clinical significance	Is the outcome patient-focused with clinically meaningful effects on longevity or quality of life and with good evidence for causality? ¹⁶
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? ¹⁷

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

¹⁴ The p value is the probability that an observed effect is due to chance; therefore it 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.

¹⁵ 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).

¹⁶ 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).

¹⁷ 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].

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 statistically significant 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.

5.3.4 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 hazard 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].

Once the baseline probabilities have been determined, a relative risk can be applied to the proposed treatment group. This may include a relative risk reduction if the proposed treatment reduces the risk of exacerbation, risk of relapse, mortality etc.

For example, disease-specific mortality can be used with all-cause mortality. All-cause mortality should be derived from NZ life tables,¹⁸ 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.

More detailed information regarding the incorporation of relative treatment effects can be found at <http://www.pbs.gov.au/info/industry/listing/elements/pbac-guidelines>.

¹⁸ <http://www.stats.govt.nz/datasets/population/life-tables.htm>

5.4 Extrapolation of Data

Key Recommendations: The methodology, limitations, and any possible bias associated with extrapolating data should be clearly described in the report and explored through sensitivity analysis. This includes extrapolating data from clinical trials to the longer term (or to final outcomes); generalising results from clinical trials to the New Zealand clinical setting by taking into account non-compliance; and undertaking indirect comparisons of trials. It is recommended that in the absence of conclusive data, conservative assumptions be used in the analysis.

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;
- translating surrogate (intermediate) endpoints to obtain final outcomes affecting disease progression, overall survival and/or quality of life;
- generalising results from clinical trials to the New Zealand clinical setting; and
- indirect 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

Many trials have endpoints that may be too early to show the full impact of the treatment. Therefore, it may 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 observational 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].

If there is any uncertainty regarding long-term benefit, it is recommended that conservative assumptions be applied in the analysis. Alternative scenarios should also be included to compare the implications of different assumptions around extrapolation beyond the clinical trial. For example, scenarios where the treatment benefit in the extrapolated phase is nil, the same as during treatment phase, or diminishes in the long term.

5.4.2 Translating surrogate endpoints to final outcomes

Available evidence may be limited to surrogate endpoints rather than clinically-important outcome measures that affect disease progression, overall survival and quality of life. Therefore, it may be necessary to translate surrogate endpoints to clinically important outcomes, using data from observational studies that relate the surrogate outcome to the clinically-important endpoints (or any clinical trials in other settings with clinically-important outcomes that are relevant).

If there is uncertainty regarding the clinical significance of endpoints or the correlation between surrogate measure and clinical outcomes, conservative assumptions should be applied in the analysis regarding their impact (short and/or long-term) on survival

and/or health-related quality of life. In the absence of conclusive data, conservative assumptions should be included in the analysis.

5.4.3 Extrapolation of Clinical Trial Data to the New Zealand Clinical Setting

It is important that the effectiveness and cost data included in the economic model are applicable to the New Zealand health sector. 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, 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.

5.4.4 Indirect Comparisons of trials

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 comparator 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.

When undertaking indirect comparisons there is greater uncertainty in the effectiveness of one treatment over the other. This is because the trials that are being compared may contain very different groups of patients, which may alter the overall treatment effect. The assumptions that are used when undertaking indirect comparisons need to be clearly stated.

For information regarding how results from trials should be synthesised, please refer to the PBAC and CADTH guidelines [57,65].^{19 20}

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. 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.

¹⁹ 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>

²⁰ CADTH report, Indirect Evidence: Indirect Treatment Comparisons in Meta-Analysis
http://www.cadth.ca/media/pdf/H0462_itc_tr_e.pdf

6. Estimating Health Benefits

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 Benefit

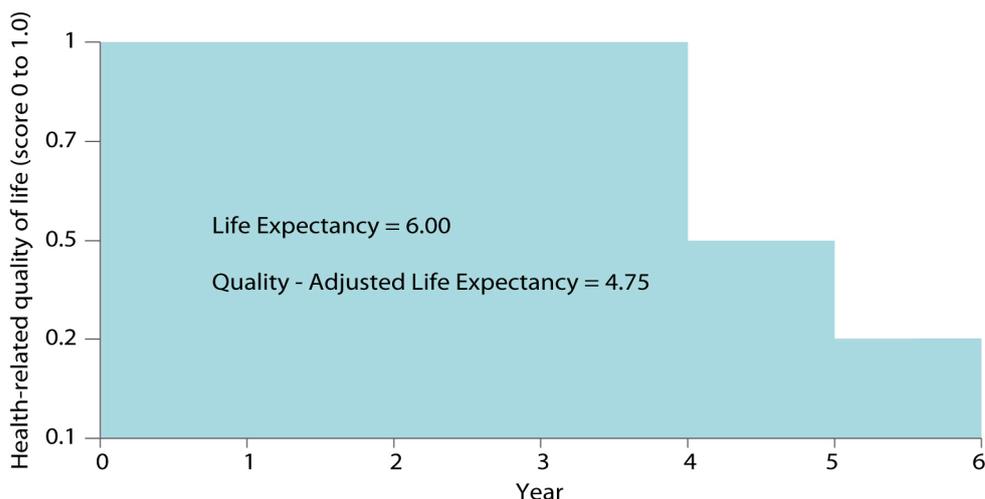
Key Recommendations: Health benefits should be measured using Quality-Adjusted Life Years (QALYs). QALYs take into account patients' health-related quality of life as well as duration of survival. Only the QALYs of the individual patient being treated should be included in the analysis.

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)²¹ and healthy year equivalents (HYEs)²².

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.

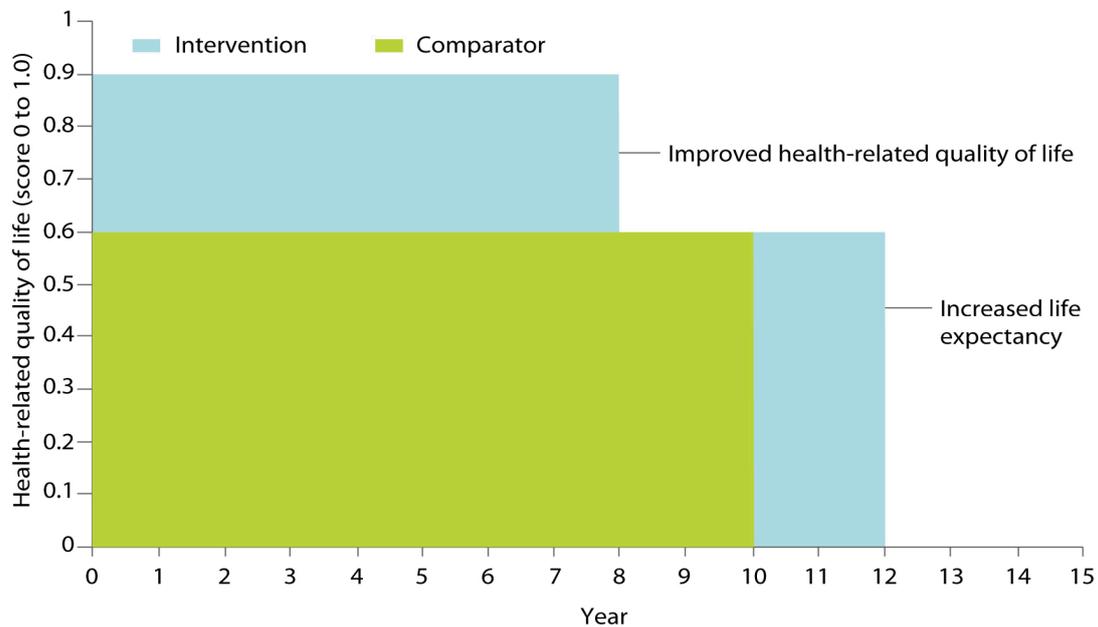
Under the QALY framework, one QALY is equivalent to living one year in perfect health, or two years at half of perfect health, and so on. This is illustrated in the following figure. Here, life expectancy (the number of years left before death) is 6.00. Quality-adjusted life expectancy (the number of 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.



²¹ 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.

²² HYE incorporates 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, John Rawls' Theory "Justice and Fairness", where in effect 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.

Note that QALYs focus on health as opposed to wellbeing more generally [68]. When estimating QALYs, only the impact on health-related quality of life is measured, as opposed to taking into account all factors that may affect a person's general quality of life. Other inputs to health decisions, such as equity and social justice, can be considered under PHARMAC's other decision criteria.

It is recommended that only the health-related quality of life (HR-QoL) of the patient being treated should be included in the analysis. If the treatment has an impact on the HR-QoL of others, such as family and caregivers, this can be discussed in the report.

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 and published literature should be used to check for consistency with the estimated EQ-5D values.

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, it seems that 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).

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 states²⁴ [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'²⁵ (hence, may be more representative of the population's views), and the other ('Tariff 2') that excluded these inconsistencies (hence, may more accurately reflect underlying preferences) [16].

²⁴ This included negative values for health states considered to be worse than death [75]. Survey results indicated that respondents can and do evaluate some health states as worse than death, and the study authors recommended the systematic inclusion of these states to describe a more complete range of preference values [76].

²⁵ Logical inconsistency was defined as "when a state that 'in logical terms' is unambiguously less severe than another is assigned a lower value" [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 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.

The EQ-5D is widely used internationally and utility weights have been derived from the New Zealand population. Therefore, it is 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.

6.3 Obtaining Utility Values

Key Recommendations: If subjective judgement is used to map health states, these health states should be validated either through published literature or expert clinical input. The report should provide a detailed description of the health state and impact on HR-QOL.

Utility values can be obtained directly or indirectly. Obtaining direct health utilities may require face to face interviews where people are asked to assign value to specific health states. Indirect health utilities use population-assigned weights to calculate utility scores for particular health states from health status instruments (e.g. the EQ-5D) [77].

Three common methods used when evaluating health states are the use of the standard gamble (SG), time trade-off (TTO) or visual analogue scale (VAS).

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.

It is essential that the symptoms patients experience in each of the health states are described in detail in the report. This will assist with the mapping process.

Further information on mapping can be found in 'Appendix 6: Utility valuation of health outcomes' at <http://www.pbs.gov.au/info/industry/listing/elements/pbac-guidelines/e-appendixes/f-appendix-6>.

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.

Existing utility values can be sourced from published cost-utility analyses (refer to section 4.2 for website links) or studies that estimate HR-QoL scores, such as the Global Burden of Disease (GBD) study²⁶ discussed in the next section.

6.3.3 Disability Weights – the Global Burden of Disease Study (GBDS)

The Global Burden of Disease Study (GBDS) [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 GBDS weights be used to check for consistency and face validity with the EQ-5D weights, but should not be used as the main source of utility values.

²⁶ Tengs TO, Wallace A, One thousand health-related quality-of-life estimates, Appendix A, Jun 2000, Med Care, 38(6):583-637

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. A wider range of costs should be 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
Pharmaceutical	Community and hospital pharmaceuticals
Hospital inpatient	Diagnostic Related Group (DRG) prices for inpatient diagnosis, treatment and/or procedures
Hospital outpatient	Healthcare professional costs DRG prices Laboratory and diagnostics
Direct patient healthcare	General practitioner visits Pharmaceutical co-payments Home or continuing care

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.

Cost data should be obtained from New Zealand. International prices and costs should not be used in analyses due to differences in resource use in New Zealand (even after exchange rate adjustments).

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. 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 Schedule²⁷, 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 the cost of a pharmaceutical intervention and comparator pharmaceutical(s), 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). This should be varied in the sensitivity analysis.

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 prices²⁸. The impact of this amendment should be discussed in the report.

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 providing this reflects clinical practice in New Zealand. In cases where the dose in the clinical trials does not reflect current clinical practice, 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.

²⁷ <http://www.pharmac.govt.nz/schedule.asp>

²⁸ 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.

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

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 kg²⁹, 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 due to inappropriate vial size; non-compliance; or if infusions cannot be stored once prepared.

7.2.3 Dispensing Fees and Pharmacy Mark-Up

The cost of dispensing community pharmaceuticals (the 'dispensing fee') and the pharmacy mark-up should be included in analyses. 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 the Cost Resource Manual, available on the PHARMAC website.

7.2.4 Administration of Pharmaceutical(s)

The cost of administering a pharmaceutical should be included in the analysis.

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 (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 and/or specialist time required to administer treatment;
- 'bed cost' associated use of outpatient facilities;
- 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); and
- cost of home visits for administration.

Further information on pharmaceutical administration costs in New Zealand is included in the Cost Resource Manual, available on the PHARMAC website.

²⁹ Ministry of Health, Portrait of Health Survey

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

Key Recommendations: Hospital inpatient costs can be calculated using DRG codes.

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.³⁰ 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.

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

³⁰ Further information and data at: <http://www.nzhis.govt.nz/documentation/wies/index.html>

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.

7.3.2 Capital Costs, Depreciation, and Hospital 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.

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:

- hospital outpatient or community-based services required for administration of the pharmaceutical (e.g. nurse and specialist time required for infusions);
- laboratory and diagnostic tests;
- emergency department visits;
- specialist visits and primary care services; and
- community-based services (e.g. nurse home visits, residential care, home help, hospice care).

The cost of outpatient hospital visits should be estimated using the specialist 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 few months 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); hospice care; and/or hospital care. Due to uncertainty, a range of costs should be included.

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, or 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 the Cost Resource Manual, available on the PHARMAC website.

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 the Cost Resource Manual, available on the PHARMAC website.

7.6 Direct Non-Healthcare Costs

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

7.6.1 Costs to Other Government Sectors

Costs to other non-healthcare government sectors 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 if significant.

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

Key Recommendations: Future healthcare costs should not be included in CUAs.

7.7.1 Future Healthcare Costs

Although future healthcare costs (i.e. costs associated with patients living longer and hence consuming health care resources) should technically be included in CUAs, this is very rarely done. A key concern with including these costs in CUAs is that it would result in life-saving (or life-extending) treatments potentially being less cost-effective, hence, biasing against those treatments that extend life. This is a particularly important issue when CUA results are used in the relative setting – i.e. where life-saving treatments need to be directly compared with treatments that improve quality of life. In addition, these costs are also very difficult to calculate and associated with a significant amount of uncertainty. In most cases there is limited data available on these costs, and obtaining data may be time-consuming. Further, future interventions may also be associated with health gains that would need to be taken into account in the analysis, significantly increasing the complexity of the analysis (and, hence, risk of error).

PHARMAC considers that interventions should be judged on their own merit in order to establish whether an intervention represents relatively good value for money. Therefore, it is recommended that future healthcare costs not be included in CUAs.

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, hence, suggesting 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 and Reporting of Cost Data

Key Recommendations: Only New Zealand costs should be used in CUAs. It is not recommended that cost data from overseas or clinical trials be used. Expert clinical opinion should be sought regarding likely treatment patterns and applicability of resource use.

When reporting cost data, costs and savings should be categorised as either real cost-savings, nominal cost-savings, or additional costs.

7.9.1 Sourcing 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 Ministry of Health, and DHBs.

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

7.9.2 Reporting Cost Data

When reporting cost data, it is recommended that costs and savings be separated into the following categories:

1. real cost savings (i.e. cases where the funding of a new pharmaceutical will result in actual cost savings);
2. nominal cost savings (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.).

8. Discounting

Key Recommendations: Costs and benefits included in CUAs should be discounted at a rate of 3.5%. Rates of 0% and 5% should be used in sensitivity analyses.

Discounting is used to 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 (the rationale is outlined in Appendix 4).

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.

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.

These are further discussed in Appendix 4.

8.2 Recommended Discount Rate

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). However, some 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.

PHARMAC does not incorporate risk into the discount rate when undertaking CUA. Discounting represents an individual's time preference and any risk (or future

uncertainty) is taken into account elsewhere in the model (e.g. in the extrapolation of benefits).

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. See Appendix 4 for the appropriate formula to adjust for inflation.

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

As it is preferable to use a 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 at 3.5%. This is based on the five-year average real risk-free long-term government bond rate.

Rates of 0% and 5% should be included (without exception) in sensitivity analyses³¹.

8.3 Discount Rate for Budget Impact Analysis

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), therefore, it is 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. Therefore, it is 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.

³¹ Rates of 0% and 5% enable comparison with analyses undertaken in other countries (5%), and the impact of the discount rate (0%).

9. Results of Cost-Utility Analysis

Key Recommendations: The results of cost-utility analysis should be reported as incremental utility cost ratios (IUCRs), i.e. incremental QALY gains per unit net costs. These reflect the opportunity cost of investment decisions when operating within a fixed budget, and are expressed as QALYs per \$1 million of the total budget invested. Incremental cost-utility ratios can be reported alongside IUCRs.

The results of cost-utility analyses can be expressed as incremental utility cost ratios (IUCRs), i.e. the incremental QALY gains per unit net cost; or as more traditional incremental costs per QALYs gained (ICURs). More consistent with PHARMAC's funding setting operating within a capped budget, IUCRs are the metrics now used at PHARMAC.

IUCRs at PHARMAC are expressed as QALYs per \$1 million of the total budget invested. This is the incremental QALY gains per incremental \$1 million net expenditure to the health sector (where 'incremental' is defined as the proposed treatment compared with the comparator treatment(s)).

The QALYs gained per \$1M spend emphasises health gain, by presenting the result as maximising health gains as opposed to minimising cost. This better represents the order and emphasis of PHARMAC's primary requirement under the NZPHD Act 2000 to secure the best health outcomes within the funds provided. It also places less inference on cost-effectiveness thresholds, but rather provides focuses on opportunity cost (the gains within a set budget) [67]. In addition, this approach better illustrates the trade-offs between pharmaceuticals due to the non-linear relationship between QALYs per million and cost per QALY.

IUCRs are directly interchangeable with, and in effect the inverse of, cost per QALY results, being very similar to net benefits/incremental net-health benefits (INHB) approaches [71,72,73,74] which have mathematical advantages over cost per QALYs [73,74].

Utility-cost ratios should be based on incremental results (i.e. the difference in QALYs gained and net costs to the health sector 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 effectiveness of the two treatments, divided by the difference in their costs.

The incremental QALY per \$1 million cost result is calculated as follows:

$$\begin{aligned} \text{Incremental QALY}/\$1\text{M} &= \text{discounted incremental QALYs} / \text{discounted incremental costs} \times 1,000,000 \\ &= \frac{(\text{net QALYs of intervention}) - (\text{net QALYs of comparator}), \text{discounted}}{(\text{net costs of intervention}) - (\text{net costs of comparator}), \text{discounted}} \times 1 \text{ million} \end{aligned}$$

9.1 Interpretation of Results

In general if:

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

where: Δ = change; E=effectiveness; C=costs

When presenting the results of the analysis, the overall incremental QALYs per \$1 million cost result should be reported as a point estimate as well as the range over which the QALYs per cost is likely to vary.

It is important that the key sources of uncertainty that have the greatest impact on the results of the analysis (i.e. the key driver(s) of the analysis) are clearly identified when reporting the QALYs per cost result. For further details on testing for uncertainty in the analysis, please refer to Section 10 on sensitivity analysis.

The traditional method that has been used when calculating and presenting the results of an analysis has been that of ICURs (the incremental cost per QALY). This long-established metric was reported by PHARMAC in the past and is still typically reported for most cost-utility analyses internationally. ICURs are in effect the inverse of IUCR results. To aid ease of reading, ICUR results should be reported alongside the IUCR QALY per \$1 million results.

QALY and cost 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-Utility Analysis Results

	Reporting Details
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
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

An outline of how the results should be presented is included in Section 11. 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 and multivariate analysis. When undertaking detailed analysis, probabilistic sensitivity analysis may be necessary. Any uncertainty in the analysis should be fully tested and described in the report.

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 – if a pharmaceutical is considered to be relatively cost-effective compared with other funding options, but is sensitive to several parameters, more extensive sensitivity analysis should be undertaken than for a pharmaceutical considered not to be relatively cost-effective;
- certainty in inputs – if there is significant uncertainty in inputs, for example if surrogate endpoints are used or long-term extrapolation of data is required, more extensive testing needs to be undertaken;
- quality of clinical trials – if the clinical inputs in the analysis were based on trials with a low grade of evidence (e.g. open-label, high risk of bias, allowed crossover of treatments), more extensive testing should be undertaken;
- risk – further testing is required for high expenditure pharmaceuticals due to the higher opportunity cost of funding;
- results of sensitivity analysis – if the initial results of a sensitivity analysis indicate some uncertainty in inputs, further testing should be undertaken; and
- level of analysis – rapid CUAs are often based on a number of assumptions that require extensive testing.

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 more than one parameter at once.	Generates more pragmatic results than univariate sensitivity analysis.	If there are a large number of uncertain variables it may be 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.
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 and multivariate sensitivity analyses. When undertaking detailed analyses, probabilistic sensitivity analysis should be considered. However, probabilistic sensitivity analysis should only be reported in addition to, rather than instead of, univariate and multivariate sensitivity analysis.

10.1.4 [Interpret Results](#)

PHARMAC recommends that sensitivity analysis be presented and interpreted using table format, graphical depiction, and/or elasticities.

Graphical presentations of CUA results are useful in gaining a visual interpretation of the sensitivity of parameters in the model. PHARMAC recommends tornado graphs for presenting the results of the sensitivity analysis. A tornado graph gives a clear presentation of the variability of a parameter. This method allows easy comparison between parameters variability through a straight comparison of the corresponding bar graphs.

Elasticities provide 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.

Regardless of the method used to present the results, the report should fully describe any uncertainty in the analysis, with a focus on the key parameters that influence the results of the analysis.

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

It is recommended that structural uncertainty be formally examined in sensitivity analysis. When testing the model, we consider that extreme sensitivity analysis should be used to ensure that the model generates logical results.

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.

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 current 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 Justification for excluding any citations.

Section	Details	Description
	Description of key clinical studies	Design Study population Follow-up period Intervention and comparator 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	Target population	Target population included in the analysis
	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.
	Transformation and extrapolation	Include information on transitional probabilities and how these were derived, including details of any extrapolation of data, synthesising data, etc. The inclusion of graphs and tables can be useful
	List of parameter values	Including confidence intervals
	List of assumptions	Assumptions regarding the structure of the model and data
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 (including a full description of the 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

Section	Details	Description
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 QALYs/\$1M (point estimate and range) Corresponding cost/QALY results (point estimate and range), placed in (brackets)
	Interpretation and discussion of results	Discussion on likely relative cost-effectiveness of pharmaceutical
Sensitivity analysis	Results of sensitivity analysis	Report using graphs, tables and/or elasticities. Include a full interpretation of the results.
	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 PHARMAC's decision criteria	For example, health need and Maori health
Validation	Description of validation method and result	For example, pharmacoeconomic review, and/or clinical review
	Comparison with published analyses, including analyses undertaken by Health Technology Assessment organisations.	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	PHARMAC's 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.	Alternative sources of utility values.
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% and 5%

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 (BIA)	Estimate of planned resource use and impact on budget over a period of time
Community pharmaceutical	A pharmaceutical that is funded from the Pharmaceutical Budget and used in the community (i.e. outside of the hospital).
Comparator	Treatment 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).
Confidence interval	Numerical measure of the range within which the true treatment effect is likely to lie
Cost per QALY gained	Measure of relative cost-effectiveness of a proposal, expressed as the monetary cost per quality-adjusted life year gained. Traditionally this measure has been used to report the results of previous PHARMAC cost-utility analyses.
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.

Term	Definition
Cost-utility analysis (CUA)	Cost-utility analysis (CUA) is similar to CEA, but health outcomes are measured using a common measure – that of quality-adjusted life-years (QALYs) gained. Results can be expressed as either: Cost per QALY, being the change in the costs and benefits (benefits being measured in quality-adjusted life years) resulting from adding to or substituting one treatment for another. Traditionally this measure has been used to report previous PHARMAC cost-utility analyses; or QALYs/\$1M, being the change in benefits (QALYs) and costs resulting from adding to or substituting one treatment for another. This is the incremental utility-cost ratio (IUCR). QALYs/\$1M are generated in current PHARMAC CUAs.
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.
District Health Board (DHB)	The Crown entities responsible for ensuring the provision of publicly funded health and disability support services for the population of a specific geographic area in New Zealand. There are currently 20 DHBs.
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.
Hospital pharmaceutical	Pharmaceutical that is predominantly administered within the hospital and is funded by DHBs.

Term	Definition
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.
Generic pharmaceutical	A pharmaceutical that contains the same active ingredients as the original branded (and usually patented) formulation. Generic pharmaceuticals are bioequivalent to the branded pharmaceutical with respect to pharmacokinetic and pharmacodynamic properties.
Graphic Appraisal Tool for Epidemiology (GATE)	Tool developed for the critical appraisal of clinical literature.
Incidence	The count of new cases of disease in a defined population during specified period of time.
Incidence rate	The count of new cases of disease in a defined population within a specified period of time, divided by the number of persons (i.e. population) at risk (or person-time) of developing the disease at the start of that time period.
Incremental cost	The difference between the cost of an intervention and the cost of the comparator.
Incremental utility cost ratio (IUCR)	The incremental QALY gains, when compared with the comparator, per incremental net expenditure to the health sector (when also compared with the comparator).
Indication	A valid, or generally accepted, use of a medicine.
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.

Term	Definition
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.
Patent	The official document (also known as letters patent) setting out the Government's grant of an exclusive right to an inventor to manufacture, use, or sell an invention for a certain number of years.
Perspective	Viewpoint of analysis (e.g. funder, society, government, individual).
Pharmaceutical	Medicine, therapeutic medical device, or related product.
Pharmaceutical Budget	The budget set by the Minister of Health for the funding of community pharmaceuticals – those medicines dispensed by a community pharmacist. It also includes funding for cancer medicines used in hospitals. The budget does not include funding for pharmaceuticals used in hospital; PHARMAC's operations; or payments for distribution (such as the fees a pharmacist receives).
Pharmaceutical Management Agency (PHARMAC)	The New Zealand Crown Entity directly accountable to the Minister of Health for, amongst other things, the management of the Pharmaceutical Schedule.
Pharmaceutical Schedule	List of pharmaceuticals available in the community and subsidised with funding from the Pharmaceutical Budget, and also the list of some pharmaceuticals purchased by DHBs for use in their hospitals (including those where PHARMAC has negotiated a national price).
Pharmacology and	An expert committee of senior health practitioners which provides

Term	Definition
Therapeutic Advisory Committee (PTAC)	objective advice to PHARMAC on pharmaceuticals and their benefits.
Prevalence	The number of existing cases of disease in a defined population at a set point in time.
Prevalence rate	The number of existing cases of disease in a defined population at a set point in time, divided by the number of persons in the population at that time.
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)	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. 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. The difference in QALYs and overall costs gained between two treatments informs the relative cost-effectiveness of an intervention.
QALYs per \$1 million	Result of current PHARMAC cost-utility analysis. Quality-adjusted life years (QALYs) per monetary unit cost, being QALYs gained per \$1 million of budget invested. In the PHARMAC context, this is the incremental QALY gains per \$1 million net expenditure to the health sector when compared with the comparator.
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.
Special Authority criteria	A Subsidy or additional Subsidy may only be claimed for certain pharmaceuticals if an application, relating to the specific patient, meeting the Special Authority criteria specified in the Schedule has been approved, and the valid Special Authority number is present on the prescription.

Term	Definition
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.
Technology Assessment Report (TAR)	Documentation of the economic analysis (including cost-utility analysis).
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.
TreeAge	Decision analysis software used for modelling cost-effectiveness.
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.

References

1. Revicki DA, Frank L. Pharmacoeconomic evaluation in the real world. Effectiveness versus efficacy studies. *Pharmacoeconomics*. 1999 May;15(5):423-34.
2. Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC, Gold MR. Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. Panel on Cost Effectiveness in Health and Medicine. *Pharmacoeconomics*. 1997 Feb;11(2):159-68.
3. Soto J. Health economic evaluations using decision analytic modeling. Principles and practices--utilization of a checklist to their development and appraisal. *Int J Technol Assess Health Care*. 2002 Winter;18(1):94-111.
4. Saint S, Veenstra DL, Sullivan SD. The use of meta-analysis in cost-effectiveness analysis. Issues and recommendations. *Pharmacoeconomics*. 1999 Jan;15(1):1-8.
5. Nuijten MJ. The selection of data sources for use in modelling studies. *Pharmacoeconomics*. 1998 Mar;13(3):305-16.
6. National Institute for Clinical Excellence (NICE), Guide to the methods of technology appraisal, April 2004.
7. Montori VM, Jaeschke R, Schunemann HJ, Bhandari M, Brozek JL, Devereaux PJ, Guyatt GH. Users' guide to detecting misleading claims in clinical research reports. *BMJ*. 2004 Nov 6;329(7474):1093-6.
8. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, Woolacoot N, Glanville J. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess*. 2004 Sep;8(36):iii-iv, ix-xi, 1-158.
9. Brennan A, Akehurst R. Modelling in health economic evaluation. What is its place? What is its value? *Pharmacoeconomics*. 2000 May;17(5):445-59.
10. Sculpher M, Fenwick E, Claxton K. Assessing quality in decision analytic cost-effectiveness models. A suggested framework and example of application. *Pharmacoeconomics*. 2000 May;17(5):461-77.
11. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics*. 1998 Apr;13(4):397-409.
12. Coyle D. Statistical analysis in pharmacoeconomic studies. A review of current issues and standards. *Pharmacoeconomics*. 1996 Jun;9(6):506-16.
13. Hughes DA, Bagust A, Haycox A, Walley T. Accounting for noncompliance in pharmacoeconomic evaluations. *Pharmacoeconomics*. 2001;19(12):1185-97.
14. Buxton MJ, Drummond MF, Van Hout BA, Prince RL, Sheldon TA, Szucs T, Vray M. Modelling in economic evaluation: an unavoidable fact of life. *Health Econ*. 1997 May-Jun;6(3):217-27.
15. Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. *Pharmacoeconomics*. 2000 Jan;17(1):13-35.
16. Devlin NJ, Hansen P, Kind P, Williams AH. Logical inconsistencies in survey respondents' health state valuations – a methodological challenge for estimating social tariffs. *Health Economics*. 2003; 12: 529-44.

17. Torrance GW. Measurement of health state utilities for economic appraisal. *J Health Econ.* 1986 Mar;5(1):1-30.
18. Mathers C, Vos T, Stevenson C. The burden of disease and injury in Australia. Australian Institute of Health and Welfare. 1999.
19. Luce BR, Elixhauser A. Estimating costs in the economic evaluation of medical technologies. *Int J Technol Assess Health Care.* 1990;6(1):57-75.
20. Koopmanschap MA, Rutten FF. Indirect costs in economic studies: confronting the confusion. *Pharmacoeconomics.* 1993 Dec;4(6):446-54.
21. West RR, McNabb R, Thompson AG, Sheldon TA, Grimley Evans J. Estimating implied rates of discount in healthcare decision-making. *Health Technol Assess.* 2003;7(38):1-60.
22. Cohen BJ. Discounting in cost-utility analysis of healthcare interventions: reassessing current practice. *Pharmacoeconomics.* 2003;21(2):75-87.
23. Bos JM, Postma MJ, Annemans, L. Discounting health effects in pharmacoeconomic evaluations – current controversies. *Pharmacoeconomics* 2005; 23(7): 639-49.
24. 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.
25. Nuijten MJ. Measuring sensitivity in pharmacoeconomic studies. Refining point sensitivity and range sensitivity by incorporating probability distributions. *Pharmacoeconomics.* 1999 Jul;16(1):33-41.
26. Desgagne A, Castilloux AM, Angers JF, LeLorier J. The use of the bootstrap statistical method for the pharmacoeconomic cost analysis of skewed data. *Pharmacoeconomics.* 1998 May;13(5):487-97.
27. Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Econ.* 1994 Mar-Apr;3(2):95-104.
28. Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, Brazier J, O'Hagan T. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. *Health Econ.* 2005 Feb 28;14(4):339-347.
29. Agro KE, Bradley CA, Mittmann N, Iskedjian M, Ilersich AL, Einarson TR. Sensitivity analysis in health economic and pharmacoeconomic studies. An appraisal of the literature. *Pharmacoeconomics.* 1997 Jan;11(1):75-88.
30. Nuijten MJ, Hardens M. Measuring sensitivity in pharmacoeconomic studies. An integration of point-sensitivity and range-sensitivity. *Pharmacoeconomics.* 1997 Nov;12(5):555-64.
31. Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics.* 2000 May;17(5):479-500.
32. Keeler EB, Cretin S. Discounting of life-saving and other non-monetary effects. *Manage Sci* 1983; 29:300-6.
33. Constitution of the World Health Organization. In: World Health Organization. *Handbook of basic documents.* 5th ed. Geneva: Palais des Nations. 1952:3-20.
34. New Zealand Ministry of Health. Primary Health Care Strategy. Government Funding of General Practice Services, updated August 2005, accessed 11 January 2006. http://www.moh.govt.nz/moh.nsf/wpg_index/-Primary+Health+Care+Funding

35. Nord E. A review of synthetic health indicators. Background paper prepared for the OECD Directorate for Education, Employment, Labour, and Social Affairs, June 1997.
36. Murray CJL. Rethinking DALYs. In: Murray CJL, Lopez AD. The global burden of disease. A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Harvard School of Public Health, on behalf of the World Health Organisation and the World Bank, 1996.
37. Stouthard MEA, Essink-Bot M, Bonsel GJ, Barendregt PGN, et al. Disability weights for diseases in the Netherlands. Rotterdam: Department of Public Health, Erasmus University, 1997.
38. Prieto L, Sacristan JA. Problems and solutions in calculating quality-adjusted life years (QALYs). *Health Qual Life Outcomes*. 2003 Dec 19;1(1):80.
39. Torrance GW, Blaker D, Detsky A, Kennedy W, Schubert F, Menon D, Tugwell P, Konchak R, Hubbard E, Firestone T. Canadian guidelines for economic evaluation of pharmaceuticals. Canadian Collaborative Workshop for Pharmacoeconomics. *Pharmacoeconomics*. 1996 Jun;9(6):535-59.
40. National Institute for Clinical Excellence (NICE), Guide to the methods of technology appraisal, April 2004.
41. Torrance GW. Measurement of health state utilities for economic appraisal. *J Health Econ*. 1986 Mar;5(1):1-30.
42. Kawachi I, Bethwaite P, Bethwaite J. The use of quality-adjusted life years (QALYs) in the economic appraisal of health care. *N Z Med J*. 1990 Feb 14;103(883):46-8.
43. Connolly MA, Johnson JA. Measuring quality of life in paediatric patients. *Pharmacoeconomics*. 1999 Dec;16(6):605-25.
44. Sonnenberg FA, Roberts MS, Tsevat J, Wong JB, Barry M, Kent DL. Toward a peer review process for medical decision analysis models. *Med Care*. 1994 Jul;32(7 Suppl):JS52-64.
45. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, Luce BR; ISPOR Task Force on Good Research Practices--Modeling Studies. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value Health*. 2003 Jan-Feb;6(1):9-17.
46. Perkins MR, Devlin NJ, Hansen P. The validity and reliability of EQ-5D health state valuations in a survey of Maori. *Qual Life Res*. 2004 Feb;13(1):271-4.
47. Tobias M. The burden of disease and injury in New Zealand. Public Health Intelligence occasional bulletin no. 1, Ministry of Health, Wellington, 2001. [http://www.moh.govt.nz/moh.nsf/0/a313645fbc60bf02cc2569f400791b9b/\\$FILE/BurdenofDisease.pdf](http://www.moh.govt.nz/moh.nsf/0/a313645fbc60bf02cc2569f400791b9b/$FILE/BurdenofDisease.pdf)
48. Schulz KF, Grimes DA. Multiplicity in randomised trials II: subgroup and interim analyses. *Lancet*. 2005;365:1657-61.
49. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991; 266: 93-98.
50. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*. 2003 Jan 25;326(7382):219.

51. Sterne JA, Davey Smith G. Sifting the evidence - what's wrong with significance tests? *BMJ*. 2001 Jan 27;322(7280):226-31.
52. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002;359:248-52.
53. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993 Oct-Dec;13(4):322-38.
54. Cook DI, GebSKI VJ, Keech AC. Subgroup analysis in clinical trials. *Med J Aust*. 2004 Mar 15;180(6):289-91.
55. Devlin N, Hansen P. Ethical precepts of cost-utility analysis. *Otago Bioethics Report*. 1999; 8(2): 16-20.
56. Freemantle N. Interpreting the results of secondary end points and subgroup analyses in clinical trials: should we lock the crazy aunt in the attic? *BMJ*. 2001 Apr 21;322(7292):989-91.
57. Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.1), December 2006. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacguidelines-index>
58. Jackson R, Ameratunga S, Broad J, Connor J, Lethaby A, Robb G, Wells S, Glasziou P, Heneghan C. The GATE frame: critical appraisal with pictures. *Evid Based Med*. 2006 Apr;11(2):35-8.
59. Cook DI, GebSKI VJ, Keech AC. Subgroup analysis in clinical trials. *Med J Aust*. 2004 Mar 15;180(6):289-91.
60. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003 Sep 6;327(7414):557-60.
61. Pocock SJ, Hughes MD. Estimation issues in clinical trials and overviews. *Stat Med* 1990; 9: 657-671.
62. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? *JAMA* 2003; 289:2554-2559.
63. Lauer MS, Topol EJ. Clinical trials--multiple treatments, multiple end points, and multiple lessons. *JAMA*. 2003 May 21;289(19):2575-7.
64. Altman DG, Bland JM. Absence of evidence is not evidence of absence. *BMJ*. 1995 Aug 19;311(7003):485.
65. Wells GA, Sultan SA, Chen L, Khan M, Coyle D. Indirect evidence: indirect treatment comparisons in meta-analysis. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2009.
66. Gray R, Bentham P, Hills R, Sellwood E, Stowe R, on behalf of the AD2000 Trial Steering Committee. Improvements in functional ability with galantamine in Alzheimer's have not yet been established. *bmj.com*, 17 January 2001. <http://www.bmj.com/rapid-response/2011/10/28/improvements-functional-ability-galantamine-alzheimer%E2%80%99s-have-not-yet-been->
67. Metcalfe S, Grocott R. Comments on "Simoens, S. Health economic assessment: a methodological primer. *Int. J. Environ. Res. Public Health* 2009, 6, 2950-2966" -New Zealand in fact has no cost-effectiveness threshold. *Int J Environ Res Public Health*. 2010 Apr;7(4):1831-4. <http://www.mdpi.com/1660-4601/7/4/1831/>

68. Drummond M, Brixner D, Gold M, Kind P, McGuire A, Nord E; Consensus Development Group. Toward a consensus on the QALY. *Value Health* 2009;12 Suppl 1:S31-5. <http://www.ispor.org/meetings/invitational/QALY/Paper7.pdf>
69. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care*. 2000 Jun;38(6):583-637. <http://www.jstor.org/stable/10.2307/3767166>
70. Center for the Evaluation of Value and Risk in Health. The Cost-Effectiveness Analysis Registry [Internet]. (Boston), Institute for Clinical Research and Health Policy Studies, Tufts Medical Center. www.cearegistry.org
71. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making*. 1998 Apr-Jun;18(2 Suppl):S68-80.
72. Lynd L. Quantitative Methods for Therapeutic Risk-Benefit Analysis. Issues Panel: Health outcomes approaches to risk-benefit analysis: how ready are they? 11th International Meetings of the International Society for Pharmacoeconomics and Outcomes Research. May 2006. Philadelphia, PA. <http://www.ispor.org/news/articles/dec06/riskbenefitsanalysis.asp>
73. Craig BA, Black MA. Incremental cost-effectiveness ratio and incremental net-health benefit: two sides of the same coin. *Expert Rev Pharmacoecon Outcomes Res*. 2001 Oct;1(1):37-46. <http://www.expert-reviews.com/doi/pdf/10.1586/14737167.1.1.37>
74. Zethraeus N, Johannesson M, Jönsson B, Löthgren M, Tambour M. Advantages of using the net-benefit approach for analysing uncertainty in economic evaluation studies. *Pharmacoeconomics*. 2003;21(1):39-48. http://adisonline.com/pharmacoeconomics/Fulltext/2003/21010/Advantages_of_Using_the_Net_Benefit_Approach_for.3.aspx
75. Lamers L. M., McDonnell J., Stalmeier P.F.M., Krabbe P. F. M., Busschbach J. J. V., The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies, *Health Econ*. 15:1121–1132 (2006). <http://onlinelibrary.wiley.com/doi/10.1002/hec.1124/pdf>
76. Patrick DL, Starks HE, Cain KC, Uhlmann RF, Pearlman RA. Measuring preferences for health states worse than death. *Med Decis Making* 1994; 14: 9–18.
77. Khanna D, Tsevat J, Health-related Quality of Life An Introduction, *Am J Managed Care*, 2007;13:S218-S223. <http://www.ajmc.com/publications/supplement/2007/2007-12-vol13-n9Suppl/Dec07-2719pS218-S223/2>

Appendix 1 – Amendments to Version 2.1 of the PFFA

The table below outlines the amendments that have been made to version 2 of the PFFA following publication in June 2007.

Section	Amendment	Reason for Amendment
Economic analysis at PHARMAC	Amendments to the definitions of the levels of analysis at PHARMAC (including amendments to the FTE required).	The types of analysis undertaken at PHARMAC have changed over time as we continue to seek to improve the quality of analysis whilst still undertaking analyses within tight timeframes.
Scope of analysis	Costs/savings to other non-healthcare government sectors should be considered qualitatively if significant (previously recommended that these be considered only in detailed CUAs).	A funding decision may have an impact on non-healthcare government sectors, therefore this should be considered qualitatively in the report if significant.
Clinical evidence	New section on presentation of clinical evidence.	This is consistent with the Application Guidelines.
	Recommend the use of the GATE <u>framework</u> for all critical appraisal of clinical evidence (rather than the use of full GATE for detailed CUAs and GATE-LITE for indicative and preliminary CUAs).	It is important that clinical trials are critically appraised, however it is not mandatory to specifically use the GATE or GATE LITE framework, given other critical appraisal instruments and practices are available. A more general recommendation to use a framework like GATE is considered more appropriate.
	Further details on key factors to consider when critically appraising a clinical trial. This includes information on assessing the applicability of a study to the New Zealand health sector (external validity)	Consideration of internal and external validity of trials is important when undertaking critical appraisal.
Economic modelling	Further details provided on transformation of evidence in economic modelling (e.g. use of surrogate measure, ITT analysis, and incorporation of relative treatment effects with baseline events).	This is important information for economic analysis, therefore further details are required.
	Further details provided on extrapolation of evidence, including extrapolating data to longer term and translating surrogate (intermediate) endpoints to obtain final outcomes measures.	As above
Health benefits	Recommend that only the health-related quality of life (HR-QoL) of the patient being treated should be included in the analysis, and that the impact of treatment on family and caregivers be discussed narratively in the report.	Version 2.0 of the PFFA did not specify whether CUAs should only include the QALYs of the patient treated or whether the impact on others should be taken into account.
	Removal of recommendation to use the NZ tariff 1 EQ-5D utility weights in the sensitivity analysis.	The EQ-5D Tariff 2 is more relevant as it excluded logical inconsistencies. It is important that a range of utility values are used in the sensitivity analysis, however

Section	Amendment	Reason for Amendment
		this does not need to include utility values generated from EQ-5D tariff 1.
Costs	Inclusion of overhead costs for human resources.	The hourly cost of health sector workers (e.g. hospital nurses and specialists) has previously been estimated based on average annual salary. It is likely that this is an underestimate of the actual cost of health sector workers, therefore these costs have been adjusted to allow for overheads. This is also consistent with other cost estimates included in CUAs, such as the cost of a GP or specialist consultation. Overhead costs have been calculated at 50% of average salary. Further details are available in the Cost Resource Manual.
	Further information included on the costs associated with administering a pharmaceutical; hospital outpatient costs; and future healthcare costs.	Clarification of costs to include (and exclude) when undertaking CUA.
Discounting	Removal of recommendation to use a discount rate of 10% in sensitivity analysis (only discount rates of 0% and 5% are now recommended)	A rate of 10% was used in sensitivity analyses in order to compare results with previous PHARMAC analyses (which were undertaken using a 10% discount rate). However, this is historical and no longer relevant to current CUAs.
	Background information shifted to Appendix.	This section was previously very detailed, relating to the then new change from the risk-adjusted discount rate for CUAs of 8% to the riskless rate of 3.5%.
Reporting of cost-utility analysis results	Results of CUA are to be reported using incremental utility cost ratios (IUCRs), i.e. incremental QALY gains per unit net costs (QALYs per \$1 million). The equivalent cost per QALY presentation is to be reported in brackets after the QALYs per \$1M.	IUCRs better emphasise the benefit (or incremental gain) associated with funding a treatment.
Sensitivity analysis	Further information provided on options for reporting and interpreting the results of sensitivity analysis.	Version 2.0 recommended the use of elasticities, however it is considered that other methods are also useful when reporting and interpreting results, such as graphical depictions.
Other	Updated information on PHARMAC's Application process included in Appendix 2.	This is consistent with information included in PHARMAC's Application Guidelines.
	Updated information on PHARMAC guidelines for reviewing CUA.	The guidelines PHARMAC uses for reviewing CUA were revised in 2009.

Appendix 2 – PHARMAC’s Application Process

PHARMAC has an established process for deciding which pharmaceuticals, and which of their possible indications, to fund. The decision-making process described below is the process that PHARMAC generally follows with an Application for a proposed change to the Pharmaceutical Schedule. PHARMAC may occasionally adopt a different process, or vary the process.

Receipt of Applications

Applications for the funding of new pharmaceuticals or for expanding access to pharmaceuticals may be initiated by anyone or any company. Applications are usually made by pharmaceutical suppliers; however, clinicians, interest groups, PHARMAC committees and consumers (patients) may also make Applications.

When an Application is received, PHARMAC reviews the Application to ensure that it contains the information PHARMAC requires in order to assess the proposal. If an Application is incomplete in any way, or if clarification is required, PHARMAC may contact the applicant and may defer consideration of the Application until the applicant has resolved any outstanding issues.

Application details are published on PHARMAC’s website, including the name of the pharmaceutical and the proposed indication for funding:

<http://www.pharmac.govt.nz/fundingapps>

If PHARMAC considers that clinical advice on the Application is required, the first step in the assessment process will be a review of the Application by the Pharmacology and Therapeutics Advisory Committee (PTAC) or, in some cases, one of the specialist PTAC Subcommittees.

Review of Clinical Evidence

PTAC is PHARMAC’s primary clinical advisory committee. Its role is to provide objective advice to PHARMAC on pharmaceuticals and their benefits. PTAC’s members are appointed by the Director-General of Health in consultation with the PHARMAC Board. PTAC comprises senior health practitioners with expertise in critical appraisal and broad experience and knowledge of pharmaceuticals and their therapeutic uses. There are also a number of PTAC Subcommittees, made up of experts in specialist clinical fields such as cardiology and oncology. PHARMAC and/or PTAC often seek advice from a specialist PTAC Subcommittees.

When considering an Application, PTAC will review and critically appraise the clinical evidence. It uses the same decision criteria as PHARMAC when evaluating Applications. PTAC makes recommendations to PHARMAC regarding amendments to the Pharmaceutical Schedule and assigns priority ratings to these recommendations (typically, high, medium or low). PTAC may also recommend that an Application be declined or deferred, giving reasons for the deferral, such as supply of further information. When making recommendations to PHARMAC, PTAC indicates which decision criteria it has given particular weight to. These recommendations are taken into account when PHARMAC sets its funding priorities. Generally, if a proposal in an Application is given a high PTAC priority and the proposed amendment to the Pharmaceutical Schedule is relatively cost-effective, it may be progressed sooner than a proposal that has been given a low PTAC priority or one that is not as cost-effective. A positive recommendation by PTAC and/or its Subcommittees, however, is no guarantee of funding as the role of PTAC and PTAC

Subcommittees is to advise PHARMAC objectively on matters referred to them. PHARMAC is not bound to follow the recommendations made.

If PTAC considers that further specialist advice is needed prior to making a recommendation to PHARMAC, the Application may be referred to a PTAC Subcommittee. Applications may also be referred to PTAC Subcommittees for advice on developing or refining access criteria. If PTAC considers that further information is required from the applicant, this will be referred back to the applicant.

Further details about PTAC and PTAC Subcommittees can be found in the PTAC Terms of Reference, which are available on the PHARMAC website <http://www.pharmac.govt.nz/PTAC> or by contacting PHARMAC on +64 (0)4 460-4990.

Economic Assessment

PHARMAC generally will undertake or review two forms of analysis on a proposal:

- (i) a cost-utility analysis (CUA); and
- (ii) a budget-impact analysis (BIA).

PHARMAC estimates the budgetary impact of the proposed change to the Pharmaceutical Schedule, usually over a period of five years (discounted at 8%)³². In some cases a longer time horizon is required.

If the pharmaceutical is more effective and more costly than currently funded alternatives, a CUA will be undertaken. PHARMAC has undertaken CUAs to inform pharmaceutical funding decisions since 1996. This is a key analytical tool in PHARMAC's management of drug subsidies.

PHARMAC uses CUAs to compare the incremental QALYs gained per unit cost of a pharmaceutical with other pharmaceuticals that could be funded instead. In other words, it is the *relative* (rather than absolute) cost-effectiveness of a pharmaceutical that is important. In this relative assessment context, it is critical that each analysis is undertaken based on the same methodology so that comparisons are valid and the results meaningful for decision-making. To assist with consistency, PHARMAC undertakes most of its analyses 'in-house'.

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 3.

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.

³² Note that the discount rate used by BIA differs from the rate used for CUA (the (nominal) discount rate for BIA is 8%, and the (real) discount rate for CUA is 3.5% for both costs and benefits.

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 effectiveness (incremental QALYs gained per \$1 million net cost to the health sector), and budget impact.

Prioritisation

Once full information on an Application is available (including PTAC priority and cost-effectiveness where necessary), it is compiled and considered by PHARMAC according to its nine Decision Criteria.

All Applications are prioritised against other funding options (either listing of new pharmaceuticals or widening access to pharmaceuticals that are already listed), whether received as a formal Application for funding or as a PHARMAC-initiated proposal. The overall aim is to identify potential amendments to the Pharmaceutical Schedule that would provide the best health outcomes. PHARMAC conducts regular prioritisation reviews of all outstanding Applications.

Negotiations

Therapeutic Group Managers are responsible for negotiating listing and supply agreements with pharmaceutical suppliers, where these are relevant to proposed changes to the Pharmaceutical Schedule. This commercial activity may include: price negotiations; Special Authority or other targeting criteria; expenditure caps; rebates on the pharmaceutical price; and/or multi-product agreements. Negotiation outcomes may lead to re-prioritisation of an Application.

Consultation and Decision

Section 49(a) of the NZPHD Act requires that PHARMAC must, when it considers it appropriate to do so, consult on matters that relate to the management of pharmaceutical expenditure with any sections of the public, groups or individuals that may be affected by decisions on those matters.

Prior to PHARMAC making a decision on a proposed change to the Pharmaceutical Schedule, it will, when we consider it appropriate, consult with people that may be affected by the proposed change (which may, according to the circumstances, include suppliers, PTAC and PTAC Subcommittees, health professionals or patients groups, Maori, Pacific peoples and other groups). Consultation responses are considered by PHARMAC with an open mind and, if appropriate, the proposal may be amended.

Decisions regarding any amendments to the Pharmaceutical Schedule are made by the PHARMAC Board, or PHARMAC's Chief Executive acting under delegated authority.

Appendix 3 – PHARMAC Guidelines for Reviewing CUAs

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

Model Input / Assumption	Questions
Type of analysis	What type of analysis was undertaken (e.g. CUA, CEA, CMA, CBA). Was this appropriate?
Target population	Was the analysis based on the correct target population (i.e. the target population most likely to receive treatment)?
Time horizon & cycle length	Was the time horizon and cycle length appropriate and justified in terms of the underlying disease and the effect of interventions?
Comparator	Have the appropriate comparator(s) been used in the analysis? Is this the treatment that most prescribers would replace in NZ clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace)?
Treatment regimen (including dose)	Does the report describe all relevant treatment paths? Is the correct pharmaceutical dose used?
Efficacy	Is the model based on the best quality data available? Were the sources of data used in the model clearly stated? Is there any evidence to suggest selective use of data?
Health states and model structure	Is justification of the choice of health states within the model provided? Have any important health states been omitted from the model? Is the model transparent? Does the model appear to be unnecessarily complicated or simplified too much?
Key Assumptions and inputs	Does the analysis outline the assumptions relating to the structure of the model? Are the assumptions reasonable and justified? Have all relevant statistically significant clinical events been included in the base-case analysis? 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? Have data from different sources been combined? If so, is the data compatible and combined using appropriate methodology? Is there a clear and reasonable justification of how data have been incorporated into the model (i.e. the methodology used in the calculation of probability values)? Have the probability values been calculated accurately given cycle length? Has a half-cycle correction been included? If not, what justification is given?
Quality of life	How was quality of life measured? Was this method justified? If subjective values were used, were these validated and tested in the sensitivity analysis? Were the estimated utility values reasonable?

Model Input / Assumption	Questions
	<p>Were utility values adjusted for cycle length?</p> <p>Were utility values discounted?</p>
Pharmaceutical cost	<p>Were pharmaceutical costs calculated correctly?</p> <p>Were there any rebates that have not been included?</p> <p>Is a generic pharmaceutical likely to become available in the near future?</p> <p>What dose was used in the cost calculations and where was this information sourced (note that the dose should be based on the dose used in the key clinical trials unless there is evidence of efficacy for different doses in clinical practice)?</p> <p>Are there likely to be dose adjustments over time?</p> <p>If relevant, was the correct bodyweight used in the calculation of pharmaceutical cost?</p> <p>Were dispensing fees included?</p>
Non-pharmaceutical cost	<p>How is the pharmaceutical administered? Have all costs associated with administration been taken into account?</p> <p>Have hospital costs been calculated correctly using NZ DRG costweights? Were these volume-adjusted?</p> <p>Are you aware of any costs that appear to be inaccurate?</p> <p>Have any important and relevant costs been excluded?</p> <p>Were costs discounted?</p>
Discount rate	<p>Was the correct discount rate used?</p>
Results	<p>Was the cost per QALY reported as a range as well as a point estimate?</p> <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>
Sensitivity analysis	<p>Were all key inputs and assumptions varied in the sensitivity analysis?</p> <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>
Report	<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 4 – Discounting

Discounting costs and benefits at the same rate

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.

Approaches to Determining the Discount Rate

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.

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.

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).

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, hence, reflecting 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.

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].

'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.

Formula to adjust nominal discount rate 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.