



DRAFT

Prescription for Pharmacoeconomic Analysis

Methods for cost-utility analysis

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Investing in Health

PHARMAC
Pharmaceutical Management Agency

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

Devlin and Hansen, 1999

Forward

I have pleasure in presenting the Prescription for Pharmacoeconomic Analysis - known by many as “the PFPA”. I have had a strong interest in this document for a number of years and it has been exciting to see the document develop and improve over this time.

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

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

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

Cost-utility analyses are undertaken at PHARMAC by a small but competent team of analysts. These analysts have a range of backgrounds, including economics, pharmacology and public health medicine. Considerable time has been spent by the team reviewing all aspects of PHARMAC's CUA methodology. This document is the result of that work. But there is more to be done. In particular, we want to hear your views. Through this consultation, we hope to hear from consumers, clinicians, pharmaceutical suppliers, health economists and any other interested parties.

I look forward to reading your submission and specifically your view on the methods we propose to use when doing cost-utility analysis.



Matthew Brougham
Acting Chief Executive

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Executive Summary

- Recommendation 1: Most PHARMAC analyses regarding new pharmaceuticals are in the form of a cost-utility analysis (CUA) as it is practical and enables comparisons across different pharmaceuticals.
- Recommendation 2: Undertake analyses from the perspective of the funder, with respect to PHARMAC's decision criteria. Always clearly state the decision problem.
- Recommendation 3: The target population is the New Zealand population most likely to receive treatment.
- Recommendation 4: The comparator(s) used in analyses should be current clinical practice.
- Recommendation 5: Well-conducted randomised-controlled trials (RCTs) and meta-analyses are the preferred data sources for use in cost-utility analysis. In the absence of valid RCTs, evidence from the highest available level of study design should be considered.
- Recommendation 6: All trials should be critically appraised and grades of evidence assigned.
- Recommendation 7: In most cases only statistically significant events should be included in base-case analyses, with consideration given to whether the results are likely to be clinically significant.
- Recommendation 8: Models should avoid unnecessary complexity and should be transparent.
- Recommendation 9: A lifetime horizon should be used in most CUAs.
- Recommendation 10: Data inputs should be based on effectiveness data by extrapolating efficacy data from clinical trials.
- Recommendation 11: Non-compliance should be included in the model in cases where there is evidence indicating that non-compliance rates may be significant and hence the effectiveness (and cost) of treatment may be impacted.
- Recommendation 12: Convert rates to transition probabilities for use in CUA.
- Recommendation 13: Measure health-related quality of life using Quality-Adjusted Life Years (QALYs).
- Recommendation 14: The EQ-5D New Zealand Tariff 2 should be referred to first when calculating utility values, with the Global Burden of Disease (GBD) disability weights used to check for consistency.
- Recommendation 15: If subjective judgment is used to map health states, these health states should be validated either through published literature or expert clinical input.

- Recommendation 16: The range of costs included in cost-utility analyses depends on the level of analysis undertaken, with a wider range of costs included in more detailed analyses.
- Recommendation 17: Pharmaceutical costs should take into account any rebate from the Supplier, and should be based on the dose used in the key clinical trials (unless there is evidence of efficacy for different doses in clinical practice). Dispensing fees and pharmacy mark-up should be included if these are likely to differ between treatment arms. The analysis should also include the lower cost of a future generic pharmaceutical, and prices should be deflated by two percent per year in order to account for inflation in non-pharmaceutical costs over time.
- Recommendation 18: Hospital inpatient costs can be calculated using Diagnostic Related Group (DRG) codes. Adjustments should be made for complexity, volume of patients and mechanical ventilation if necessary.
- Recommendation 19: Hospital outpatient costs should be included in CUAs. Terminal costs (i.e. costs occurred at the end of a person's life) should be included if these costs are likely to be significantly different between treatment arms.
- Recommendation 20: Direct patient healthcare costs should be included 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 continuing care.
- Recommendation 21: Costs to other government departments and indirect patient costs should not be included in PHARMAC CUAs.
- Recommendation 22: Discount all costs and benefits in CUAs at a 3.5% discount rate. Include rates of 0%, 5%, and 10% in sensitivity analyses.
- Recommendation 23: Cost-utility ratios should be based on incremental results.
- Recommendation 24: Sensitivity analysis should include univariate (simple) analysis, multivariate analysis, threshold analysis and/or extremes (scenario) analysis. The level of sensitivity analysis undertaken should be determined by the level of analysis, with probabilistic sensitivity analysis undertaken for more detailed analyses.

1. Background

1.1 What is PHARMAC?

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

PHARMAC's primary objective is:

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

Further information on PHARMAC can be found at: www.pharmac.govt.nz.

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. Rather, it describes the process involved and methods used when conducting cost-utility analysis. Documenting of this methodology aims to ensure that cost-utility analyses performed by (and for) PHARMAC measure costs, benefits, time preference and uncertainty in a similar fashion; hence enabling comparison between the cost-effectiveness of different interventions and ensuring that the results of analyses are meaningful for decision making.

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

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

1.3 Version 2 of the PFPA

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

PHARMAC staff consulted widely on the draft manual, and comments were received from lead national and international health economists, clinicians, the pharmaceutical industry, and the Health Funding Authority. Following amendments to the draft version, the manual, labelled the 'Prescription for Pharmacoeconomic Analysis' (PFPA), was finalised and published on the PHARMAC website in September 1999.

Since this time there have been changes within the New Zealand health system. There has also been further international debate on issues such as discounting of costs and benefits and the measurement of utility values. In 2004, PHARMAC staff considered that it was time to review the PFPA. The process involved in updating the PFPA is 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 key objective of PHARMAC is to secure the best possible health outcomes within the funding provided. As PHARMAC must work within a fixed budget, it is impossible to fund every new pharmaceutical that may potentially benefit someone. The demand for pharmaceuticals will always exceed our ability to pay for these pharmaceuticals. In short, choices are inevitable.

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

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

2.3 Does PHARMAC Consider Other Criteria when making Funding Decisions?

All pharmaceuticals awaiting funding are prioritised against other expenditure options (either listing of other new pharmaceuticals or expanding access to existing pharmaceuticals). This is based on PHARMAC's decision criteria.

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

http://www.pharmac.govt.nz/operational_policies_and_procedures/

PHARMAC's decision criteria include:

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

2.4 Types of Economic Analysis

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

Several forms of economic analysis are available including:

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

Cost-utility analyses, commonly referred to as CUAs, are generally done ‘in-house’ by the Technology Assessment Group (TAG). This is mainly due to the short timeframes within which analyses are required. It also ensures continuity of methods and quality control. In addition, analyses often need to be updated at short notice following the receipt of further clinical advice or proposed price reductions - the process thus has to be flexible.

PHARMAC analyses are based on the methods outlined in this document.

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

The levels of analysis are outlined in the Table 2

Table 2: Levels of PHARMAC Analyses

Type	Description
Detailed	Includes a detailed and systematic identification and synthesis of effectiveness, quality of life, and cost data. Requires on average 3-6 months of full-time analyst input. Reviewed internally (clinical assumptions reviewed by Pharmacology and Therapeutic Committee (PTAC)) and externally.
Indicative	An interim assessment using some opportunistic data, but more detailed than a preliminary analysis. These typically require 4-6 weeks of full-time analyst input. Typically reviewed internally (PTAC for clinical assumptions).
Preliminary	A rapid assessment largely using opportunistic data. Likely to take 1-2 weeks’ of full-time analyst input.
Rapid	A very rapid assessment using opportunistic data, usually involving 1-2 days’ of full-time analyst input. Includes supplier analyses that have not yet been evaluated by PHARMAC staff.

Very few proposals receive a full assessment as these take at least three to six months to complete and hence can be too slow in the policy context. The process is

usually iterative, meaning that rapid assessments are conducted first; then preliminary assessments; then if this is insufficient to justify the recommendation, an indicative or detailed analysis is undertaken.

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

Table 3: Determinates of Level of Analysis Undertaken by PHARMAC Staff

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

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

All 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 undertaking cost-utility analysis at PHARMAC is outlined in Appendix 2.

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.

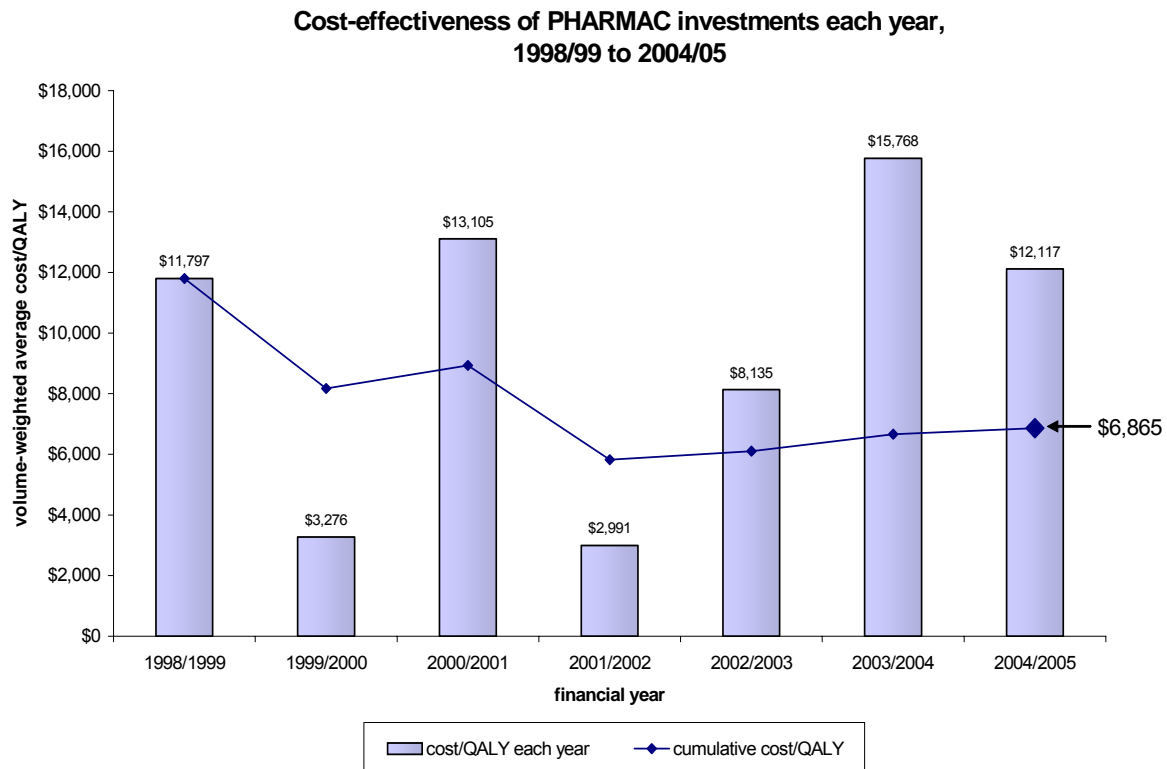
At PHARMAC, there is no threshold below which a pharmaceutical is considered “cost effective”. One reason for this is that spending on community pharmaceuticals is required to be kept within a fixed budget. Given the binding nature of this constraint and all things being equal, what is and is not considered “cost effective” will therefore vary with the amount of funding available.

Another reason for not having a threshold value is that cost effectiveness is only one decision criterion used by PHARMAC. One proposal may be more cost effective than

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

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).

The following data show that what is and is not considered cost effective changes over time². Between the 1998 and 2005 financial years, new investments made by PHARMAC have cost around \$6,900 per QALY (cumulative volume-weighted average³). However, the cost-effectiveness of new investments has varied widely each year – reflecting both the mix of investment opportunities and the funding available at the time. These features are illustrated in the graph below:

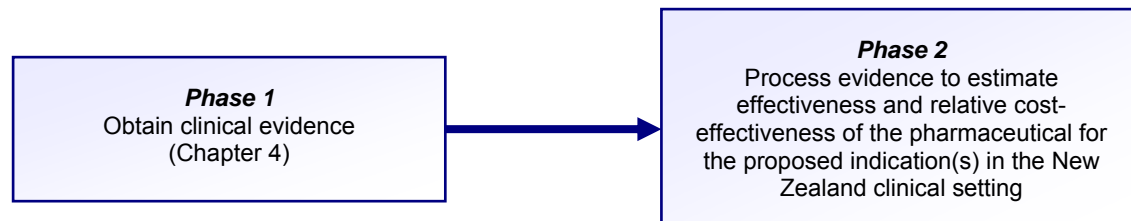


² Data derived from PHARMAC's Annual Reports to Parliament.

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

3. Scope of Analysis

Cost-utility analysis at PHARMAC has two distinct phases:



3.1 Decision Problem and Perspective

Key Recommendation: Undertake analyses from the perspective of the funder, with regards to the PHARMAC decision criteria. 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 includes 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.

3.1.2 Decision Problem

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

3.2 Target Population

Key Recommendations: The target population is the New Zealand population most likely to receive treatment. It may be necessary to use subgroup analyses if treatment can be targeted to those most likely to benefit. Such data should however be used cautiously, especially in cases where the subgroup has been defined retrospectively.

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.⁴

⁴ 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

In order for the results of subgroup analyses to be reliable, the subgroups should be defined *a priori* on the basis of known biological mechanisms or in response to findings in previous studies⁵. The choice of subgroup and expected direction of difference should ideally be 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.

Statistical tests of interaction [50] should be used to assess whether a treatment effect differs among subgroups (i.e. evidence of heterogeneity)⁶. However, even when there is heterogeneity between subgroups, results of subgroup analyses should still always 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 biologically plausible and statistically strong [48].

Subgroup analysis should 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 population⁷ or primary endpoint [48,56].

3.2.2 Comparator(s)

Key Recommendation: The comparator(s) used in analyses should be current clinical practice.

The comparator(s) included in PHARMAC analyses should be the treatment(s) used in current clinical practice (irrespective of whether this is the most effective treatment). This recommendation is in line with the perspective of the analysis (i.e. the funder of the treatment) and relates to the decision problem that initiated the analysis (i.e. do the additional benefits of the new drug compensate for the higher cost compared with what is currently available).

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) at PHARMAC may perform this role for analyses conducted by PHARMAC staff.

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

the complexity of the targeting decisions to be made. Some situations will require many subgroups, others just the overall group.

⁵ For a complete checklist for assessing and interpreting subgroup analysis, please refer to the following subgroup analysis article published in the Medical Journal of Australia:
http://www.mja.com.au/public/issues/180_06_150304/coo10086_fm.pdf

⁶ Statistical tests of interaction are preferred to individual tests within each subgroup – individual tests often overestimate the extent of true differences.

⁷ 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].

4. Clinical Evidence

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

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

4.1 Data Sources

Key Recommendations: All appropriate levels of evidence should be identified; however well-conducted randomised controlled trials (RCTs) and meta-analyses are the preferred data sources for use in CUA. 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 include published randomised controlled trials (RCTs), meta-analyses, and observational studies. Other possible sources include unpublished trial data, expert opinion, case reports, and data from medical records [1,2,3,4].

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

Table 4: Data Sources

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

Data Source	Advantages	Disadvantages	Recommended Use
Meta-analysis ⁸	<p>A single trial may be insufficiently powered to detect treatment effects.</p> <p>Useful when results conflict between trials, when inappropriate comparators are used, or when a trial consists of only one treatment arm.</p>	<p>Publication and inclusion biases (i.e. choice of trials included).</p> <p>May be difficult to assess validity.</p> <p>Incompatible trials may be included.</p>	<p>Meta-analysis may be useful when there is more than one key trial or when results conflict between trials.</p> <p>With more detailed analyses it may be necessary for the analyst to undertake a meta-analysis if there are no published meta-analyses available.</p>
Observational studies ⁹	<p>High real-world relevance.</p> <p>Allow observation of a new treatment on compliance and treatment switching patterns.</p>	<p>Lack of control over confounding factors.</p> <p>Underlying biases.</p> <p>Lack of control groups.</p>	<p>Use to compare with the results of a clinical trial.</p> <p>More than one independent source should be examined in order to gain confidence in the validity of the conclusions.</p>
Expert opinion	<p>Clarification of unreliable, conflicting or insufficient clinical information in the literature.</p>	<p>Subject to selection bias.</p>	<p>It is not recommended that expert opinion be used as the primary source for assessment of effectiveness. PHARMAC mainly uses expert opinion to review an economic model, in particular any clinical assumptions.</p>
Case reports and medical records	<p>High real-world relevance.</p>	<p>High risk of bias.</p> <p>Small patient numbers.</p>	<p>Generally not recommended that these be included in CUAs.</p>

⁸ Meta-analysis systematically combines the results of trials in order to draw overall conclusions regarding the efficacy and/or safety of the treatment.

⁹ Observational studies register outcomes of groups of patients treated in ordinary clinical practice.

4.2 Obtaining Data

4.2.1 Data Sources

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

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

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

General journals include:

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

Information on drug safety can be found at:

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

4.2.2 Search Strategy

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

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

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

4.3 Assessing Data Quality

Key Recommendations: All trials should be critically appraised and grades of evidence assigned. PHARMAC recommends that when high-quality studies are available, studies with a level of evidence below 1+ (see Table 3) should be rejected.

4.3.1 Critical Appraisal of Trials

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

Table 5: Factors to Consider in Critical Appraisal of Trials

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

The quality of studies tends to vary between therapeutic groups. For example, for cardiovascular drugs, a large number of RCTs are often undertaken involving large numbers of patients. However, for mental health drugs, in some cases it is more difficult to conduct good quality RCTs due to poorer compliance rates and difficulties with recruitment. PHARMAC therefore recommends that the quality of the clinical evidence should be assessed relative to the ability to conduct good-quality RCTs within the therapeutic group in order to reduce biases against pharmaceuticals where it may be difficult to conduct high-quality RCTs.

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

4.3.2 Grading the Evidence

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

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

A commonly used checklist is that developed by the MERGE (Method for Evaluating Research and Guideline Evidence) Group in Australia, and later modified by the Scottish Intercollegiate Guidelines Network (SIGN). The PHARMAC modification¹⁰ of the checklist is outlined below:

Table 6: PHARMAC Modification of SIGN Checklist

Grade 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 and 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. 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.

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).

¹⁰ PHARMAC modifications include pseudo-randomised controlled trials and differentiates between observational studies and case reports.

4.4 Interpreting Data

Key Recommendation: Confidence intervals, p values and sample sizes should be examined together, with consideration given to whether the results are likely to be clinically significant. In most cases only statistically significant events should be included in the base-case analysis.

4.4.1 Statistical Significance (confidence intervals and p values)

PHARMAC recommends that, in general, only statistically significant clinical events (i.e. p value less than 0.05)¹¹ should be included in the base-case analysis of CUAs.¹² However, rather than having a ‘cut-off’ value for statistical significance, the confidence interval should be examined together with the p value and sample size, and consideration should be given to whether the events are likely to be clinically significant (i.e. patient-focused outcomes with clinically meaningful effects on longevity or quality of life).

To help determine whether events are clinically significant, outcomes should be examined to determine whether their association with treatment is 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).

Accounting for clinical factors means that in some cases a result considered to be ‘statistically insignificant’ (i.e. p value greater than 0.05) should still be used 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.

The inclusion or exclusion of statistically insignificant events should be justified, and where applicable, included in the sensitivity analysis rather than the base-case analysis.

¹¹ The p value is the probability that an observed effect is simply due to chance; it therefore provides a measure of the strength of an association. Confidence intervals (CIs) are a numerical measure of the range within which the true treatment effect might lie with a certain probability – usually 95%.

¹² For clarity and simplicity, this section uses p values to notionally define statistical significance. It is noted that confidence intervals (CIs) may better summarise the strength and precision of the effect estimate and they also provide information on whether the findings of a particular study are consistent with those of previous studies and whether a lack of a statistically significant association could be due to lack of precision (lack of study power); however p values are both widely understood and used. It is therefore recommended that both p values and CIs be examined together when determining statistical significance.

5. Economic Modelling

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

Cost-effectiveness models combine information about disease progression, the clinical effectiveness of a pharmaceutical (usually obtained from RCTs), and the costs and savings associated with the funding of a pharmaceutical.

5.1 Models

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

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

5.1.1 Scope of Model

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

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

- **Simple Decision Trees**

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

- **Markov Models**

Markov models assume that an infinite cohort of patients is always in one of a finite number of health states. The whole cohort usually begins in an initial health state (or Markov state), and moves between states, at defined recurring intervals (Markov cycles), as determined by the transition probabilities. This results in a new distribution of the cohort among the various states. The model is usually run for enough cycles so that the entire cohort is in the 'dead' state. A branch of a Markov Model is shown on the following page.

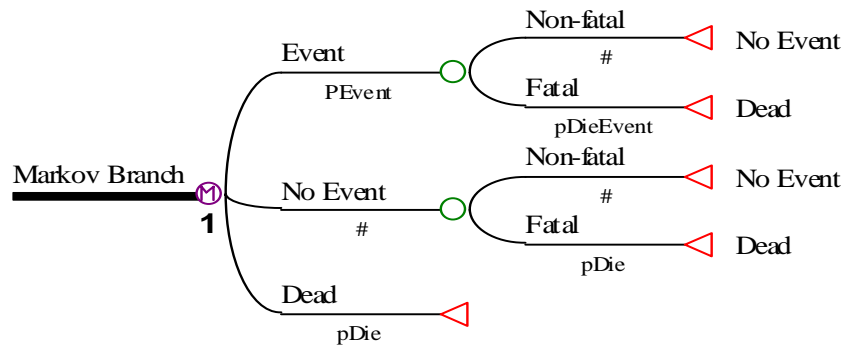
Each state is assigned a utility (i.e. quality of life score), and the contribution of this utility to the overall prognosis depends on the length of time spent in the health state. Summing QALYs across all cycles gives the QALY estimate for each treatment arm.

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

Markov models can be evaluated using first-order Monte Carlo simulation. This involves tracking large numbers of patients (e.g. 10,000) through a Markov model individually. Random number generation is used at each transition point to determine the point to which a hypothetical patient will move next (based on probability distributions). By repeating this process numerous times, an overall distribution of costs and health outcomes are generated for each patient - these

individual patient results are then averaged over a large number of patients to give the overall mean value, standard deviation and variance for costs and health outcomes for each treatment arm¹³.

The main advantage of first-order Monte Carlo simulation is that it is able to generate an estimate of the likely variance associated with parameters estimated by the model.



5.1.2 Transparency

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

5.1.3 Health States

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

5.2 Time Horizon and Cycle Length

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

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

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

5.2.1 Cycle Length

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

¹³ Monte Carlo simulation is not likely to give the same two results on any two occasions due to the random nature of the simulation. It is therefore important that the number of simulations over which the results are averaged is very large.

5.2.2 Half-Cycle Adjustment

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

Note however that when using TreeAge software for lifetimes models (when costs and benefits are discounted), the automated TreeAge half-cycle adjustment function should not be used¹⁴. Rather, to apply the half-cycle adjustment, half a reward should be applied to the current state, and then a half-reward to each transition node corresponding to the 'jump state' (i.e. death or survival). This adjusts for the fact that individuals transit throughout the cycle, not at the end of the cycle.

5.3 Data Inputs

Key Recommendations: Data inputs should be based on clinical effectiveness data by extrapolating intention-to-treat efficacy data from clinical trials.

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. Data should be pooled using recognised techniques (e.g. meta-analysis) and should incorporate all relevant literature.

5.3.1 Effectiveness Data

Clinical trials should be analysed using data from the intention-to-treat (ITT) population in order to take into account outcomes of all patients irrespective of whether they received treatment.

Outcomes included in the model may include the probability of success or failure, relapse, adverse events, discontinuation, loss to follow-up, or death. These outcomes should be well-defined, mutually exclusive, generally long-term or final outcomes, and be based on effectiveness data rather than efficacy data from clinical trials¹⁵. This requires consideration of:

- specific hospital, clinician and healthcare system characteristics (e.g. differences in treatment regimens or administration protocols);
- levels of patient compliance; and
- type of patients.

Compliance with treatment is the key determinant of differences between efficacy and effectiveness, and is considered in the following section on modelling.

¹⁴ This is because half of the benefits (in terms of survival) are taken from the first period but in the last period of the model all patients are in the 'dead' state, hence patients cannot be "given back" the half-cycle adjustment taken from the initial cycle. This can occur only in a non-absorbing model where a percentage of the cohort are still alive in the final cycle. To apply this method of half-cycle adjustment to lifetime models may result in significant underestimation of benefits.

¹⁵ Efficacy refers to the performance of the drug under ideal circumstances (i.e. clinical trials). Effectiveness refers to the performance of the drug in the real world (i.e. New Zealand clinical practice), with a wide variety of providers administering the drug as they see fit to a broad heterogeneous group of patients who are less well-informed and likely to be less compliant than those involved in clinical trials.

5.3.2 Incorporation of Effectiveness Data with Epidemiological Data

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

For example, the use of disease-specific mortality with all-cause mortality. All-cause mortality should be derived from NZ life tables,¹⁶ 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.

5.3.3 Availability of Data

If there are no data available on important clinical events, these events should still be modelled in the analysis if the events are likely to affect patient prognosis (and hence the overall efficacy of treatment)¹⁷.

For example, trial data for a drug may show reductions in a life-threatening event, but the duration of follow-up may be insufficient to indicate whether survival is improved. However, the potential effect of the pharmaceutical on survival should not be ignored. Rather, various assumptions regarding the impact of the pharmaceutical on survival should be included in the model with the most likely scenario used in the base-case.

Note that the availability of data may however limit the scope of the analysis - the model may need to be simplified to fit in with what data are available. All such simplifications should be acknowledged explicitly, and where possible should be subjected to sensitivity analysis. This will indicate the degree of uncertainty due to the (necessary) extensive assumption.

5.4 Modelling

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

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

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

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

¹⁶ <http://www.stats.govt.nz/datasets/population/life-tables.htm>

¹⁷ Note that if data are available, the events included in the model should be limited to those which are statistically significant. In cases where there is no data available on events that affect patient prognosis (for example, long-term results of a trial may not yet have been reported), these should not mean that these potentially important clinical events be excluded.

5.4.1 Extrapolation to Longer Terms or Final Outcomes

Many trials have endpoints that may be too early. It may therefore be necessary to use intermediate outcomes to obtain final endpoints by extrapolating data beyond the period observed in the clinical trials (for example, when estimating life-expectancy). This requires explicit assumptions regarding the continuation of treatment effect once treatment has ceased [3,9].

5.4.2 Extrapolation of Results to Different Populations

It may also be necessary to extrapolate the results of trials to different populations. 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 costs. 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 are included in Table 7.

Table 7: Types of Non-Compliance

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

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

Similarly, any additional costs associated with non-compliance (e.g. hospitalisation, co-morbidities), should be incorporated in the analysis.

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

5.4.3 Synthesising Head-to-Head Comparisons

Many trials may not use the most relevant treatment comparator for the New Zealand clinical setting, or a CUA may require comparisons against more than one alternative treatment. In such cases, it may be necessary to synthesise a head-to-head comparison¹⁸ [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.

¹⁸ This technique was applied when undertaking a CUA for a cardiovascular treatment for aspirin-intolerant patients that required the treatment to be compared to placebo. As there had been no clinical trial comparing the treatment with placebo, data were combined from two trials. One trial showed the benefits of aspirin over placebo, and another trial demonstrated the benefits of the new treatment over aspirin. By combining these we were able to derive a model of how the new treatment might relate to placebo for aspirin-intolerant patients.

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 (provided they are statistically significant). PHARMAC staff are currently reviewing the usefulness of probability distributions, and a recommendation will be made at a later date regarding whether they should be routinely used.

5.5.2 Converting Rates to Probabilities to Transition Probabilities

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

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

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

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

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

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

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

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

6. Health-Related Quality of Life

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

6.1 Measures of Health-Related Quality of Life

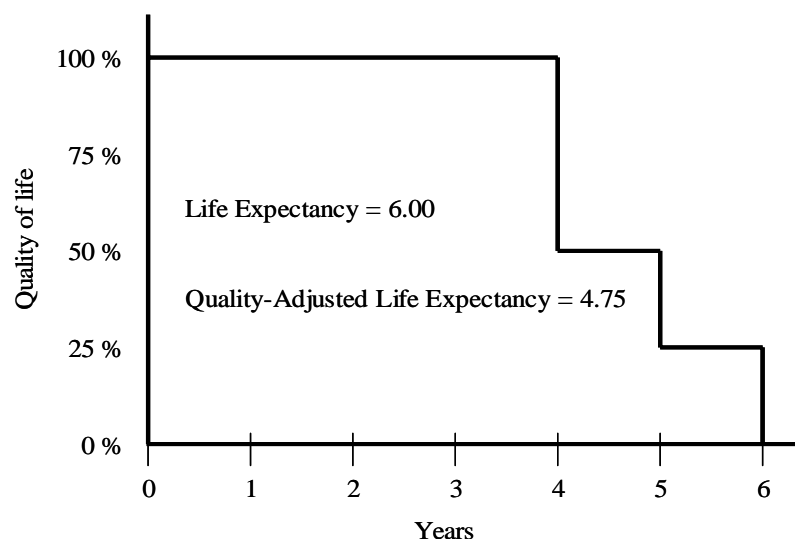
Key Recommendations: Health-related quality of life (HR-QOL) should be measured using Quality-Adjusted Life Years (QALYs) as they are simple to calculate, are universally used, and have face validity.

Health measures that incorporate both the quality and the length of life into a common currency include quality-adjusted life years (QALYs), disability-adjusted life years (DALYs) and healthy years equivalent (HYEs).

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.



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 in a utilitarian framework. However, CUA is capable of being applied to achieve any desired distribution of QALYs through attaching weights to the estimated

QALY gains [55]. One such alternative distributional theory is, for instance, Rawls' Theory of Justice, where those with relatively poor health are favoured over groups with better health.

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

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

6.1.2 Disability-Adjusted Life Years (DALYs)

DALYs are expressed in terms of years of life lost due to premature death and years lived with a disability of specific severity and duration¹⁹. DALYs apply unequal weights to years of life based on the age of the recipient and how long the effect lingers. For example, a life year gained for a 25-year-old is assigned a higher value than for a 75-year-old. Similarly, a bout of acute illness that is over quickly counts less in the DALY calculation than one that leaves lingering weakness.

6.1.3 Healthy-Year Equivalents (HYEs)

HYES were developed in response to concern that QALYs assume a uniform or average preference structure²⁰. HYES incorporate individual preference structures, over a complete path of health states (rather than discrete health states).

6.2 Health-Related Quality of Life Instruments

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

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

There has been much debate in the literature regarding the most appropriate tool for measuring preferences in health gains, and no single measure has yet been accepted as the gold standard. In fact, given the multidimensional nature of HR-QOL, it is unlikely that a single measure will ever become 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].

¹⁹ Advantages of DALYs are that they take into account the age of individuals and length of illness. Disadvantages include the relatively global level at which disease-based weights have been derived, the fact that they are based on an arbitrary life expectancy, and they do not explicitly incorporate suffering so may be insensitive to the effects of treatment on suffering such as pain.

²⁰ Advantages of HYES include the potential to provide better estimates of most-desired treatments (note however that there is evidence that indicates that patients' attitudes towards pain and suffering do not differ substantially based on demographic or clinical factors). Disadvantages of HYES include its dependence on personal interviews, and the difficulty associated with implementing such projects in practice.

They note that each instrument has different properties, and each member of the Panel valued these properties differently.

6.2.1 EQ-5D

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

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

As discussed in a key article by Devlin and Hansen et al., almost a third 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'²¹ (and hence may be more representative of the populations views), and the other ('Tariff 2') that excluded these inconsistencies (and hence may more accurately reflect underlying preferences) [16].

The validity and reliability of the EQ-5D health state valuations have also been examined in the Maori population. Perkins et al. [46] surveyed 66 Maori people to investigate the 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 (particular for the health state 'dead') and logical inconsistencies suggested that it lacked construct validity in this population.

As it is likely that health state preferences of New Zealanders differ from those of people from other countries, it is preferable to initially use the weights derived from the New Zealand population.

PHARMAC recommends that the New Zealand EQ-5D Tariff 2 be referred to first and should be used to describe the health states. The EQ-5D is widely used internationally and utility weights have been derived from the New Zealand population. It is recommended that Tariff 1 be used in the sensitivity analysis.

6.2.2 HUI

The HUI Mark III has eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain), and five to six levels per attribute, describing 972,000 unique health states. The HUI is based on the VAS and standard gamble (SG) measurements from a random sample of the general population in Ontario, Canada. Perfect health along a given dimension is allocated a unitary value – these values are then multiplied, with a transformation applied to allow for states with lower utilities than death.

²¹ 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 transformation is defined as:

$$QOL = 1.42U - 0.42$$

where U=unadjusted value obtained by multiplying the individual values associated with each attribute.

An advantage of the HUI is that it includes more health dimensions and levels compared with the EQ-5D, thus allowing for finer distinctions between health states. However, utility weights have not been derived from the New Zealand population.

6.2.3 Other Instruments

Other instruments include the Quality of Well Being index (QWB); Quality of Life and Health Questionnaire (QLHQ); Rosser-Kind Index; Australian Quality of Life instrument (AQOL); Sickness Impact Profile (SIP); and Index of Health Related Quality of Life (IHRQOL).

6.3 Obtaining Utility Values

Key Recommendations: If subjective judgment is used to map health states, these health states should be validated either through published literature or expert clinical input.

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.

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

Advantages of mapping are that it is quick, inexpensive, and in many cases sufficient providing the conclusions are relatively insensitive to the utility values used.

6.3.2 Literature

In some cases it may be possible to use existing utility values available in the literature, providing similar health states and patients are used, and that the measurement instrument is credible [17].

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

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

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

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

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

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

It is recommended that the GBD weights be used to check for consistency with the EQ-5D weights.

6.3.4 Direct Measurement

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

7. Estimating Costs

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

7.1 Costs Included in PHARMAC Analyses

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

Costs included in PHARMAC CUAs are outlined in Table 8.

Table 8: Costs Included in PHARMAC Cost-Utility Analysis

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

The reporting of costs should state how units were measured, resources were valued, and how final cost figures were derived.

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

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

7.2 Pharmaceutical Costs

Key Recommendations: Pharmaceutical costs should take into account any rebate from the pharmaceutical supplier, 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. Pharmaceutical costs should take into account the lower price of a future generic pharmaceutical, and should also be deflated by two percent per year in order to account for increases in non-pharmaceutical costs over time. Dispensing fees and pharmacy mark-up should be included if this is likely to differ between treatment arms. The cost of co-administered pharmaceuticals and any significant costs with administering the pharmaceutical should also be taken into account.

7.2.1 Price of Pharmaceutical(s)

For pharmaceuticals listed on the Pharmaceutical Schedule²², the price of the pharmaceutical should include any rebate that has been negotiated with the Supplier. The analysis should state whether the price is confidential.

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

When calculating pharmaceutical costs, consideration should also be given to the length of the pharmaceutical patent and when a generic pharmaceutical is likely to become available. The lower cost of a generic pharmaceutical should be included in the analysis. These estimates should be conservative (both in timing and amount) to allow for the risk of generic entry being significantly delayed.

Pharmaceutical prices should also be deflated by two percent per year in order to account for inflation in non-pharmaceutical costs over time²³.

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.

7.2.2 Dose of Pharmaceutical(s)

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

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

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 75.9 kg (source: Ministry of Health, 2005), however it may be necessary to adjust this according to the age and/or gender of the population treated.

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

²² <http://www.pharmac.govt.nz/schedule.asp>

²³ It is considered simpler to deflate pharmaceutical prices rather than inflate all other costs. Note that 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 increase.

7.2.3 Dispensing Fees and Pharmacy Mark-up

Dispensing fees should be included in the following circumstances:

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

The dispensing fee and pharmacy mark-up should be calculated without deduction of a patient co-payment.

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

Details on the current dispensing fee and pharmacy mark-up are provided in Appendix 3.

7.2.4 Administration of Pharmaceutical(s)

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

Further information on pharmaceutical administration costs in New Zealand is included in Appendix 3.

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 costs can be calculated using DRG codes. Adjustments should be made for complexity, volume of patients and mechanical ventilation if necessary.

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.²⁴ To a certain extent DRG prices are able to capture the resources used by

²⁴ Further information and data at: <http://www.nzhis.govt.nz/documentation/wies/index.html>

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.

Adjustments that may need to be made to DRG prices are included in Table 9.

Table 9: DRG Adjustments

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

7.3.2 Reporting of Hospital Costs

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

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

7.4 Other Health Sector Costs

Key Recommendations: Hospital outpatient costs should be included in CUAs. Terminal costs should be included in CUAs if these costs are likely to be significantly different between treatment arms.

7.4.1 Hospital Outpatient Costs

Hospital outpatient costs may include:

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

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

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

7.4.2 Terminal Costs

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

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

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 government partially subsidises. 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;
- travel costs;
- non-government subsidised costs such as private hospital, physiotherapy, unsubsidised pharmaceuticals.

7.5.1 GP Visits

The cost of a General Practitioner (GP) visit should be based on the average cost to the patient plus any government subsidy (if applicable). Details provided in Appendix 3.

7.5.2 Pharmaceutical Co-Payments

The amount of pharmaceutical co-payment a patient pays depends on whether the pharmaceutical is fully or partially subsidised, and whether the patient is enrolled in a Primary Health Organisation (PHO). Most pharmaceuticals on the Pharmaceutical Schedule are fully subsidised, in which case the charge to the patient is either the full cost of the pharmaceutical or the Government prescription charge.

For CUAs, it is recommended that the total pharmaceutical cost be included, irrespective of whether it is paid by the patient or government.

7.5.3 Cost of Home or Continuing Care

The cost of home care or continuing care (rest home or private geriatric/psychogeriatric care) should be included in CUAs, independent of who is paying for these services (i.e. the family, DHB, Accident Compensation Commission (ACC), or Ministry of Social Development). The inclusion of these costs also provides a proxy for the disutility associated with the requirement for additional care. Cost details are provided in Appendix 3.

7.6 Direct Non-Healthcare Costs

Key Recommendations: Direct non-healthcare costs should not be included in CUAs.

7.6.1 Costs to Other Government Sectors

Costs to other government sectors that occur as a result of pharmaceutical funding decision 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 sectors. Also, decisions made in other sectors may be based on very different assumptions and levels of analysis, so it becomes very difficult to incorporate these data in a consistent manner.

7.6.2 Direct and Indirect Taxes and Transfer Payments

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

7.7 Indirect Healthcare Costs

7.7.1 Future Healthcare Costs

Even though in theory future healthcare costs (i.e. costs associated with patients living longer and hence consuming health care resources) should be included in CUAs²⁵, these are very difficult to calculate as in most cases there is limited data available, and obtaining data may be time-consuming. These costs should however be considered in more detailed analyses.

7.7.2 Capital Costs, Depreciation, and Overhead Costs

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

²⁵ To exclude these costs would favour interventions that increase length of life at the expense of those that improve quality of life.

7.8 Indirect Patient Costs

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

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

Indirect patient costs include:

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

The arguments (and counter-arguments) for including indirect costs are outlined in Table 10.

Table 10: 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);
- the actual production loss for society from sickness is likely to be significantly lower than indicated by *a priori* estimates (for example, work can be covered by the unemployed);
- PHARMAC's objective is to maximise health gains from health sector funds. If societal costs were included in analyses, this could result in PHARMAC considering issues it has no control over (for example, an analysis including indirect costs could favour those with high incomes and hence suggest that it would be cost-effective to further subsidise primary education);
- it would be time-consuming and thus inefficient to include these costs in CUAs, as it would result in significant opportunity costs in terms of staff time. Given fixed analytical capacity at PHARMAC, by increasing the complexity of analyses there would be a trade-off in terms of numbers and timeliness of assessments. This in turn may cause delays to the listing of beneficial pharmaceuticals.

7.9 Sourcing of Cost Data

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

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

8. Discounting

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

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

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

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

8.1 Which Discount Rate?

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

There are six key approaches to determining a discount rate:

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

8.1.1 Discount Rate Used in Other Countries

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

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

8.1.2 Social Rate of Time Preference

The social rate of time preference is the rate at which society is willing to exchange present for future consumption, hence reflects societal preferences.

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

8.1.3 Social Opportunity Cost Rate

The social opportunity cost rate of discount is the real rate of return forgone in the private sector (i.e. the cost in financial market terms if government projects were undertaken in the private sector). The basic notion behind this is that public investments can displace or crowd out private investments or consumption. This can be estimated using a number of different models which aim to work out what the market would expect to receive for a particular project.

PHARMAC does not recommend that the discount rate be determined in this manner as it is likely that the discount rate in the public sector is lower than that in the private sector (if it was not there would be no need for government provision of health care and private health insurance markets would be more dominant).

8.1.4 Weighted Average Social Discount Rates

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

8.1.5 Shadow Price of Capital

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

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

8.1.6 'Bottom Up' Approach

In the 'bottom up' approach it is assumed that government spending should finance projects with the highest rate of return first and then in order of return rankings.

Therefore the opportunity cost is the rate of return of the last project funded (i.e. rate of return of the marginal project). Problems with this approach relate to the problems with IRR calculations, and level at which government spending is scrutinised.

8.2 Recommended Discount Rate

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

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

The following issues also need to be considered:

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

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

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

8.2.2 Should the Discount Rate be Adjusted for Inflation?

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

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

This can be approximated as the nominal rate minus inflation.

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

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

8.2.4 Recommendations

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

Rates of 0%, 5%, 10% should be included (without exception) in sensitivity analyses²⁶.

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

8.3 Exemptions

The above discount rate does not apply when undertaking budget impact analysis (BIA), which serves a very different purpose. The purpose of CUAs is to be able to rank treatments, hence a longer-term view is appropriate. The purpose of BIA is to determine if PHARMAC can afford to fund a treatment given the current budget (i.e. an investment decision). In this case it is more appropriate to use a different discount rate, as determined by the PHARMAC Board.

²⁶ Rates of 0%, 5%, and 10% enable comparison with analyses undertaken in other countries (5%), past PHARMAC analyses (10%), and the impact of the discount rate (0%).

9. Cost-Effectiveness Results

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

The incremental cost per QALY is calculated as follows:

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

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

9.1 Interpretation of Results

In general if:

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

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

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

10. Sensitivity Analysis

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

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

10.1 Parameter Uncertainty

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

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

10.1.1 Identify the Parameters

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

10.1.2 Specify the Plausible Range over which the Parameters may Vary

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

In the case of a distribution with a minimum and maximum value, the upper and lower limits should be based on those values. In the case of a continuous distribution (e.g. normal distribution), the upper and lower limits should be extended outside of the CI to those values that can be assumed not to contribute to overall sensitivity²⁷. [25].

An alternative approach for determining the range when the distribution is not known is to use the mean as an input variable and a range corresponding to the first and third quartile.

10.1.3 Calculate Results

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

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

²⁷ This allows the analyst to test the appropriateness of the chosen CI. When the extension only marginally increases the sensitivity, it can be assumed that the CI of the continuous distributions incorporates all relevant values.

Table 11: 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 correlated parameters by varying more than one parameter at once.	Generates more realistic 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.
Extremes (scenario or 'worst/best case analysis')	Assesses the impact of moving one or more variables to its potential extremes.	This approach is especially useful when there is little information available on the efficacy of a pharmaceutical (for example, treatments for rare diseases).	May overestimate the uncertainty associated with the results.
Probabilistic	Based on Monte Carlo simulations. Examines the impact on the results of the analysis when variables are varied simultaneously according to predefined distributions.	Permits varying all parameters in the model simultaneously and enables calculation of the expected value and variance of decision variables.	Can only handle uncertainty in data inputs and assumes that parameters are independent. 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.

10.1.4 Interpret Results

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

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

or:

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

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

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

For example, a pharmaceutical may have a cost per QALY of \$190,000. A sensitivity analysis may be undertaken to test how the results of the CUA change if the price of the pharmaceutical is reduced by 50%. If the cost/QALY subsequently decreased to \$98,000, the elasticity is calculated by taking the percentage change in cost/QALY after the price decrease (i.e. 0.48) and dividing by the percentage change in price (i.e. 0.5). The resulting elasticity is 0.97, indicating that the results are relatively sensitive to this reduction in price.

10.2 Model Structure Uncertainty

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

Modelling-related uncertainty includes [8,31]:

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

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

11. Presentation of Data and Results

It is important that CUAs are transparent so that quality and validity can be assessed. Table 12 outlines what information should be included when reporting detailed CUAs. Lower levels of analysis undertaken by PHARMAC staff may be less descriptive²⁸.

Table 12: Information to Include in Report for Detailed Cost-Utility Analyses

Section	Details	Description
Introduction	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
Epidemiology and treatment	Description of disease	Stage of disease Disease progression Prognosis
	Description of target population	Age Gender Risk factors Prevalence Incidence in New Zealand
	Description of treatment options available	Indications Contra-indications Aim of treatment Efficacy Adverse events.
Study drug	Description of pharmaceutical	Formulation Strength Dose Pharmacological action Adverse events Contra-indications
	Description of indication(s)	Registered and funded indication(s) Indication for which funding is sought (including any restrictions)
	Treatment details	Dose Length of treatment Concurrent medication (for indications or side-effects)
Clinical evidence	Description of literature search strategy	Database searched Time period search undertaken Search strategy used Keywords Refinements Justification for excluding any citations.
	Description of key clinical studies	Design Study population Follow-up period Withdrawals

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

Section	Details	Description
		Clinical endpoints
	Critical review of clinical studies	Grades of evidence Possible sources of bias Methods of randomisation
	Discussion of relevance of trial results to New Zealand clinical practice	Efficacy compared with effectiveness
Model	Comparator(s)	Rational for choice of main comparator
	Description of model	Model type Transition states Markov states Copy of decision tree or branch of decision tree
	Time horizon and cycle length	Justification for time horizon
	Discount rate	Description of discount rate used for costs and benefits
Outcome measures	Description of relevant outcomes and how they were measured	Adverse events, mortality, etc.
	List of parameter values	Including confidence intervals
	List of assumptions	Assumptions regarding the structure of the model and data (including any extrapolation)
Health-related quality of life	Description of how HR-QOL was measured	For example, methods for mapping to generic health state instruments, use of expert opinion, etc.
	Utility values used	
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 cost-savings, or additional costs
	Description of data sources	Including any strengths or weaknesses of data sources
Results	Results derived from the model	Total cost of pharmaceutical under analysis Total and net health sector costs of regime and comparator QALYs of regime and comparator Discounted net cost/QALY
	Interpretation and discussion of results	
Sensitivity analysis	Results of sensitivity analysis	Use of elasticity
	Discussion of sensitivity to modelling assumptions and data inputs	Direction of bias and magnitude of effect
Discussion	Discussion of results and other issues that should be considered under 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	Explanation of any differences in results
Conclusions	Description of setting to which the	List of factors that could limit

Section	Details	Description
	results of analysis can be applied	applicability
	Description of any research in progress	Description of how new data may alter results of analysis.

11.1 Rapid Checklist

Table 13 contains a rapid checklist of information to include in PHARMAC base-case analyses and sensitivity analyses.

Table 13: Checklist of Information to Include in Base-Case Analyses and Sensitivity Analyses

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

Glossary

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

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

Number needed to harm (NNH)	The number of patients who are treated that would lead to one additional person being harmed compared with patients who receive the control treatment. NNH=1/ARI
Number needed to treat (NNT)	The number of patients who need to be treated in order to prevent or create one additional event occurring over a predefined period of time. NNT=1/ARR
Opportunity cost	Value of the alternative options that could be undertaken with the same resources.
Perspective	Viewpoint of analysis (e.g. funder, society, government, individual).
Probabilistic sensitivity analysis	Method of sensitivity analysis where probability distributions are specified for uncertain parameters and a Monte Carlo simulation is performed to obtain a probability distribution of expected outcomes and costs.
Quality-adjusted life years (QALY)	Quality-adjusted life-years (QALYs) are a way of being able to compare quality of life gains with quantity of life gains in a simple and direct manner. Quality of life weightings (or utilities) are measured on a scale of 0 to 1, where 0 is equivalent to death and 1 to perfect health. These weights are then multiplied by life expectancy in order to calculate the number of QALYs.
Relative risk	Ratio of incidence of disease in exposed group divided by incidence of disease in non-exposed group.
Relative Risk Increase (RRI)	Proportional increase in rates of events between the experimental group and control group.
Relative Risk Reduction (RRR)	Difference in events between two treatment groups, expressed as a proportion of the event rate in the untreated group.
Sensitivity analysis	Process through which the robustness of an economic model is assessed by examining the changes in the result of the analysis when key variables are varied over a specified range.
Standard gamble	Technique of preference assessment in which individuals are asked to choose between the certainty of an intermediate health state and the uncertainty of a treatment with two possible outcomes, usually full health (utility of 1) and death (utility of 0). The probabilities are then systematically altered until the individual is indifferent between the choice of the certainty of continued life in the health state of interest and the gamble.
Time trade-off	Technique of preference assessment in which an individual is asked to choose between living for a defined period of time in a poor health state and living for a shorter period of time in full health, in order to determine what amount of time they would be willing to give up to be in a better health state. The time in full health is varied until the individual is indifferent between the two alternatives.

Utility	Values of the strength of preferences for, or desirability of, a specific level of health status or a specific health outcome.
Utilitarianism	Theory of social justice that considers that social welfare is improved through policies that produce the greatest good for the greatest number of people.
Value for money	Refers to whether the benefits of a pharmaceutical are significant enough to compensate for the higher cost.
Visual analogue scale	Technique of preference assessment 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 May 7-13;365(9471):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. <http://bmj.bmjournals.com/cgi/content/full/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 DJ, 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. <http://bmj.bmjournals.com/cgi/content/full/322/7292/989>

Appendix 1 - Process in Updating PFPA

This document has been developed through the following process:

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

Literature Review

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

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

Discussion Documents

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

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

Internal Discussion

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

Expert Advice

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

Appendix 2 – PHARMAC Assessment Process

Receipt of Proposals

Proposals for the funding of new pharmaceuticals or for expanding access to pharmaceuticals may be initiated by anyone or any company (suppliers, patients, doctors, minister, public sector staff). PHARMAC receives about thirty applications for funding each year.

Review of Clinical Evidence

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

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

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

Economic Assessment and Budgetary Impact

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

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

Peer Review

It is important that models are reviewed by colleagues who are able to examine the inner workings of the model.

Internal guidelines for peer reviewing economic analyses were finalised in March 2005 (#88270). The purpose of these guidelines was to:

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

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

Clinical Review

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.

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

Prioritisation

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

Negotiations with Pharmaceutical Suppliers

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

Interest Group Involvement

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

Decision

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

Appendix 3 – Costs

These costs were as at June 2006. Please note that these costs may change. PHARMAC staff will periodically update this Appendix.

Dispensing Fee

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

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

Pharmacy Mark-Up

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

Administration Costs

Pharmaceutical administration costs may include:

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

Cost of General Practitioner

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

Cost of Home and Rest Home Care

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