

# Consultation Responses on Version 2 of the PFFA

PHARMAC consulted on the draft version 2 of the Prescription for Pharmacoeconomic Analysis (PFFA) in August-October 2006. Consultation responses were received from twenty-five individuals and organisations – 13 health economists, three government departments, two district health boards, six pharmaceutical suppliers, one pharmacist, four academics/clinicians, and one patient interest group.

This document summarises the key issues raised in consultation with respect to each section of the PFFA, and also the response of PHARMAC staff to these issues.

## General Comments

This section includes the general comments that PHARMAC considers relevant to the revised PFFA.

In general there is wide support for the revised PFFA from national and international economists, pharmaceutical suppliers and government organisations.

### Economists

*“The systematic appraisal of pharmaceuticals by PHARMAC, documented in the PFFA, certainly brings NZ into the same league as the world leaders on health technology assessment (i.e. the UK, Canada and Australia)”.*

*“Overall I am impressed with the Prescription, both in terms of its content and style. It is very comprehensive and written clearly. Its authors are to be commended for what they have achieved”.*

*“The PFFA is relatively prescriptive, clearly presented, and leaves little room for ambiguity. This prescriptive approach is sensible and avoids the need to describe the set of possible alternatives and how each should be dealt with”.*

*“First, might I say how impressed I am by the work and thinking that has clearly gone into the new draft PFFA. I disagree on some issues, but overall I think the new version is very good”.*

*“I found this to be an impressive document.....From my experience in using CBA it requires a lot of judgement and skill to get it right. Like any tool it has comparative advantage and fails when pushed beyond what it does easily, which is to calculate the NPV of reasonably smooth and reasonably certain streams of costs and benefits from the perspective of a decision maker who knows the opportunity cost of her money. The more lumpy and uncertain are the costs and revenue streams and the more the analyst has to rely on estimated ‘shadow prices’ and account for things that are not easily quantified in money terms the more the quality of the decision depends on the skill and judgement of the analyst in interpreting results. A point is reached where the value of the technique is compromised to the point where it is no longer superior to the next best alternative. The PFFA pushes the technique pretty hard, which is why the emphasis on complementary decision criteria and processes in the report is well justified. However I would not want this comment to be interpreted as a reason for diminishing the value of the technique but rather as reason to invest in it and do it with great skill and consistency. The effort that has gone into the report is very encouraging in this regard. I say this for reasons drawn from the underlying concepts of CBA and from New Zealand experience”.*

*“The layout is good, and the clinical evidence and approach to economic evaluation are well specified (pending finalisation of the details in undertaking CUAs)”.*

*“The document provides a reasonably thorough overview of the main elements of economic evaluation methods required for decision making”.*

*“Overall, I thought the document was well pitched, being of the right length and the right level of detail to give both the guidance and the background to the recommendations made. In general, I found a lot to support in the document. I did, however, disagree with a number of elements of the detail”.*

*“Overall the willingness by PHARMAC to regularly update and review their methodology for undertaking economic analyses is welcomed”.*

## **Pharmaceutical Suppliers**

*"We found the guidelines succinct and easy to use and the inclusion of the rationale for each recommendation is considered to be helpful and informative. It was also easy to identify the salient points relative to each section. The summarized list of recommendations is helpful to identify the key points for each section. It is clear that the guidelines draw on worldwide best practice and the inclusion of supporting references will support the development of quality analyses for presentation to PHARMAC".*

*"We endorse the majority of the draft changes as overall these will provide a more comprehensive and modernised guide to pharmacoeconomic analysis for suppliers providing cost-utility analyses as part of funding submissions. Due to these changes the New Zealand guidelines will more closely reflect those of similar countries such as Australia and the UK. In particular, the reduction in the specified base-case discount rate to 3.5% is seen as a positive change. However a prescribed decision-making framework can only be effective if the manner in which it is applied is consistent and transparent. We trust that the positive changes to the guidelines will be further reflected in the PHARMAC decision-making processes moving forward".*

*"It is noted that the Government has agreed to the development of a National Medicines Strategy and it is [our] view that New Zealand's system for determining the relative merits of pharmaceuticals and which offer value for money should form an important part of that policy development. As such our approach to this consultation exercise conducted by PHARMAC has been to simply critique the guidelines as they have been presented and reserve further commentary regarding the system until these policies are being considered and debated as part of the National Medicines Strategy development".*

## **Government Departments**

*"We applaud PHARMAC's efforts to develop a robust methodology for evaluation of pharmaceuticals, including CUA. We suggest that these comments would help to strengthen the methods and to ensure that new technologies are evaluated using both clinical and economic analysis, which would in turn help to balance the emotive arguments that are often made by special interest groups".*

*"The draft is well written, well justified and has been reviewed by well-qualified external reviewers. It is important to retain and develop a robust analytical framework in order to aim for best value for the health dollar. It is also desirable to retain a centrally managed process of introducing new pharmaceutical technologies in a small country like New Zealand, because it is more likely to achieve better purchasing arrangements, value for money and should help to avoid duplication and inconsistencies".*

*"Overall I think that this document has been very well written and presented".*

## **Clinicians**

*"I think the recommendations are an entirely reasonable approach to the evolving field of cost-utility analysis. I like the way they outline the pros and cons of different levels of analysis, data sources, use of indirect costs, discounting rules, and sensitivity analyses. The document not only explains the methods, it also addresses their rationale".*

## Background

Issue	Details	PHARMAC Response
Use of the PFPA within the wider health sector	Several responders considered that the PFPA should be used within the wider health sector and considered that PHARMAC should lead the way in the expansion of CUA/prioritisation in the health sector.	<p>PHARMAC notes that the PFPA is not written for use within the wider health sector, but is focused on the assessment of pharmaceuticals. It is not considered to be PHARMAC's role to draft a CUA manual for the wider health sector. It is noted that Treasury has written a cost-benefit analysis manual, and that the Public Health directorate of the Ministry of Health is also drafting a manual for economic analysis.</p> <p>The section on the purpose of the PFPA has been further strengthened in the document to emphasise that it is a PHARMAC document focussed on the assessment of pharmaceuticals.</p>

## Economic Analysis at PHARMAC

Issue	Details	Response
Type of analysis – CUA/CBA	There was general support for the use of CUA above other types of economic analysis; however several organisations/individuals considered that PHARMAC should further investigate the use of CBA on the basis that it can address questions of allocative efficiency.	<p>It should be noted that with CBA the willingness of patients to pay for pharmaceuticals when unwell is high but the willingness of the population to pay for health insurance is low. Disadvantages of CBA include the difficulty in comparing treatments that improve quality of life with those that save lives, and the difficulty associated with placing a dollar value on health benefits. There are also ethical objections to placing a monetary value on health, particularly with respect to valuing a human life.</p> <p>PHARMAC is not convinced of the benefits of CBA.</p>
Role of supplier CUAs	Several responders questioned how PHARMAC deals with analyses received from Pharmaceutical Suppliers.	<p>PHARMAC staff agreed that this should be addressed in the PFPA, and have included the following information:</p> <p>“PHARMAC encourages Pharmaceutical Suppliers to provide a CUA when submitting a significant funding proposal. The provision of a good quality analysis, following the methods outlined in the PFPA, may expedite the proposal review and information acquisition process, enabling the proposal to be prioritised.</p> <p>When PHARMAC receives a CUA from a Pharmaceutical Supplier it is reviewed, and</p>

		<p>often amended, by PHARMAC analysts. The guidelines PHARMAC uses to review analyses are attached in Appendix 4.</p> <p>In order for analysts to be able to review CUAs more efficiently, a CD with a copy of the TreeAge model and/or Microsoft Excel spreadsheet should be provided. If amendments have been made to the analysis, PTAC will usually be supplied a copy of the supplier CUA and PHARMAC's amended CUA, with the differences between the CUAs clearly explained".</p>
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## Scope of Analysis

Issue	Details	Response
Perspective of analysis	<p>Whilst there is general support for PHARMAC basing its analyses on the perspective of the 'funder', several responders stated that PHARMAC should also consider a wider perspective (i.e. whole of government and/or societal) when the effect on non-healthcare sectors and/or individuals is significant. This is argued on the basis that the 'funder' is actually the government (as opposed to PHARMAC or DHBs); hence any costs and/or savings that accrue to the government should be considered in the analysis.</p>	<p>PHARMAC staff recommend that for the interim, these costs could be reported in a <u>qualitative</u> manner in the Technology Assessment Report (TAR) of detailed analyses. These analyses will then be reviewed at a later date.</p>
Use of subgroup analyses	<p>There is general agreement that subgroup analyses should be used if treatment can be targeted to those patients.</p> <p>A responder disagreed with the recommendation that subgroup analysis should not be used when a trial does not report an overall treatment effect in the ITT population yet reports a statistically significant effect in subgroups, as the largest effect may be seen in those with the highest risk. The responder considered that further information should be included on the different types of subgroup analyses.</p>	<p>PHARMAC staff sought further expert advice on the use of subgroup analysis when overall treatment effect in ITT population is not significant, and have extended this section of the PFPA to include further information on types of subgroup analyses.</p>
Treatment comparator	<p>The PFPA recommended that the comparator(s) used in analyses should be current clinical practice. However a responder considered that 'current clinical practice' is a very loose definition, and noted that PBAC specify that the main comparator should be the 'analogue prescribed for the largest number of patients' and the 'therapy that most prescribers will replace in practice'.</p>	<p>PHARMAC staff agreed that this was an important issue and that the comparator for economic analyses needed to be further defined.</p> <p>The definition of the comparator in the PFPA has been amended to the 'treatment that most prescribers would replace in practice at time of pharmaceutical funding AND treatment</p>

	<p>Several responders considered that the comparator should be defined as the treatment that is “most likely to be replaced in clinical practice”. They considered that current practice may not be appropriate in areas where practice is changing rapidly. It was also noted that most clinical trials compare an intervention to the gold standard of treatment at the time, however the trial may be conducted over a number of years and treatment protocols may change during this time. In addition, they recommended that consideration should be given to both current clinical practice and likely future practice, and that submissions include all relevant comparators (particularly relevant if there is an extended period of time between initial application and funding).</p> <p>Another responder considered that the comparator should be the ‘international evidence-based best practice standard’.</p> <p>One responder requested clarification on how PHARMAC would like the situation addressed when clinical practice differs between treatment centres.</p> <p>In addition, several responders considered that wider clinical opinions from expert panels should be used to select the appropriate comparator for economic analyses, particularly where the disease area requires a very specific knowledge of the current NZ treatment protocols.</p>	<p>prescribed to the largest number of patients’.</p> <p>It is also considered important to consider likely future practice (i.e. treatment practice at time pharmaceutical is likely to be funded) and the sequence of treatment as this can affect the comparator used. Also pipeline drugs that may effect the relative cost-effectiveness of the pharmaceutical under assessment should be considered</p> <p>In some cases a range of treatments may be prescribed, which may differ depending on treatment centre. In such cases it is recommended that analyses should use a range of comparators, and it may be necessary to take a weighted-average (weighted by patient numbers prescribed comparator treatment) of the cost/QALY result.</p> <p>It was agreed that the comparator should not be defined as best clinical practice, as this was often very subjective. Also, when determining if a pharmaceutical should be funded in NZ, the most relevant comparator(s) are the pharmaceuticals that are likely to be replaced.</p> <p>PHARMAC staff agreed that clinical advice should be obtained on the appropriate comparator to use in an analysis, and that this is usually addressed by PTAC.</p>
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## Clinical Evidence

Issue	Details	Response
Data sources for relative treatment effect	<p>There was general support for PHARMAC’s recommendation that well-conducted RCTs and meta-analyses are the preferred data sources for use in CUA, and that evidence from the highest level of study design be considered in the absence of valid RCTs.</p> <p>One responder considered that the PFPA should refer to other sources that may be used in economic modelling, and that all sources of evidence should be included in the base-case analysis.</p> <p>Another responder considered that good quality epidemiological/observational studies should also be considered in cases where RCTs are unethical or</p>	<p>It is noted that observational studies provide good baseline risk data, and are particularly useful when modelling non-compliance. However, when obtaining data on relative risk, RCTs are the preferred data source.</p> <p>The PFPA has been amended to advise that good quality observational studies (cohort studies and case control studies) should be considered in cases where the clinical evidence is limited to RCTs associated with a high risk of bias.</p> <p>PHARMAC staff have discussed the use of equivalence trials. It was noted that in most cases it is preferable to</p>

	<p>unworkable.</p> <p>A further responder considered that equivalence trials should also be referred to.</p>	<p>have head-to-head trials providing the correct comparator and doses are used in the trial. PHARMAC staff agree that the highest-quality evidence should be used, and that this does not exclude the use of equivalence trials.</p>
Use of unpublished evidence	<p>The contracted reviewers agreed that published trials are preferred to unpublished trials, but that use of unpublished trials (or lower levels of evidence) may be necessary. However, a responder considered that it is inappropriate that published evidence be given more weight than unpublished evidence, as frequently the trial report (which contains substantially greater detail on the trial) is available prior to the paper being published.</p>	<p>PHARMAC staff consider that unpublished data should not be disregarded, however it should only be used to supplement published data.</p>
Grading the Evidence	<p>There was considerable misunderstanding in consultation regarding PHARMAC's recommendation that when high-quality RCTs, meta-analyses, and systematic review (1+ or 1++) are available, these should be the preferred data source. Some responders interpreted this comment as PHARMAC only recommending use of evidence grade 1+ or above. The PFFA explicitly states that in some cases lower levels of evidence will need to be used.</p> <p>One responder considered that 1++ studies should also require high external validity. It was also questioned whether observations studies represent poorer evidence compared with RCTs with a high risk of bias.</p> <p>Another responder considered that the grading of evidence is subjective and prone to bias. They recommended that PHARMAC also take into consideration published assessments when determining the level of evidence, and justification should be given to any differences in the assignment of the level of evidence.</p>	<p>The PFFA has been amended to state that "these are the preferred data source for <u>relative treatment effects</u>". This should clarify that the preferred data source is not referring to data for baseline treatment effect, costs of quality of life (where lower levels of evidence are often required).</p> <p>PHARMAC staff noted that some considered that 1++ studies should also require high external validity. However it was agreed that external validity should be considered at the end of the process (i.e. first consider RCTs and then check observational studies), as described in step 4 in the 'Quality of the Evidence' section of PHARMAC's 'Recommend methods for deriving clinical inputs'.</p> <p>PHARMAC staff sought expert advice on critical appraisal of clinical evidence. As a result, the PFFA has been amended to recommend the use of GATE (Graphic Appraisal Tool for Epidemiology) when critically appraising key clinical trials. The use of GATE is likely to increase consistency between evaluations, and also ensure that all key issues are considered when critiquing a clinical trial.</p> <p>PHARMAC staff have also discussed whether the quality of clinical evidence should be assessed relative to the ability to conduct good-quality RCTs. It was considered that in some cases (e.g. mental health drugs), it is more difficult to conduct high-quality RCTs (often due to compliance). However, in other cases there is no reason why high-quality double-blinded RCTs should not be conducted. It was therefore agreed that when writing up</p>

		the analysis, poor data should be explicitly highlighted, especially in cases when higher-quality data could have been provided.
Inclusion/exclusion of statistically insignificant events	<p>There were mixed views regarding whether statistically insignificant events should be included in the base-case analysis.</p> <p>Several responders supported PHARMAC's recommendation that in most cases only statistically significant events should be included in the base-case analysis, with consideration given to whether events are likely to be clinically significant.</p> <p>However, a number of others disagreed with the recommendation. One responder considered that if an event was clinically and/or economically significant, it should be included in the base-case analysis regardless of statistical significance, as some trials are not sufficiently powered to determine statistical significance. Another responder considered that the exclusion of non-significant events was dangerous and could lead to counter-intuitive results.</p> <p>Another responder considered that clinically meaningful events should generally be included irrespective of statistical significance, unless there is no difference in survival (and any differences in mean events favours the comparator), or if the event occurs at the same rate between treatment arms and is not expected to differ in clinical practice. The responder noted that in some cases composite endpoints are used in clinical trials in order to achieve statistical significance, however when undertaking an economic analysis the individual endpoints need to be used.</p>	<p>PHARMAC staff have sought expert advice on this issue. PHARMAC staff were advised that rather than focusing on statistical significance (defined as <math>p &lt; 0.05</math>), the magnitude of the difference (i.e. confidence interval) is what is important, especially when the p-value is close to 0.05. In addition, it is important to check whether statistical significance has been demonstrated in more than one study – if it has been demonstrated in more than one study, this should give the analyst confidence that the events are not due to chance.</p> <p>PHARMAC staff subsequently amended the PFFA.</p>

## Economic Modelling

Issue	Details	Response
Time Horizon	There is general agreement that a lifetime time horizon is necessary in most cases.	No amendments required.
Modelling	<p>There was little feedback on this section of the PFFA.</p> <p>One responder suggested that a further issue to consider when evaluating the difference between effectiveness and efficacy data (aside from non-compliance)</p>	PHARMAC staff have met with PBAC regarding their economic guidelines, and note that they provide extensive guidance on synthesising head-to-head trials. PHARMAC staff agreed that the PFFA should refer readers to the PBAC guidelines for further information.

	<p>is the impact of when patients in the placebo arm of a clinical trial are assigned active treatment. In addition, it was considered that the section on synthesising head-to-head comparisons could more explicit and should reference key articles on the methods PHARMAC considers are appropriate.</p>	
<p>Probability distributions</p>	<p>There was disagreement amongst the reviewers on the necessity of using probability distributions as opposed to point estimates in economic models.</p> <p>One reviewer considered that probability distributions should be used in order to quantify uncertainty and also because many decision models have a non-linear relationship between inputs and outputs, hence expected costs and benefits can only be generated by probabilistic analysis. However, another reviewer considers that probabilistic analysis reduces transparency, is understood by few, and does not change the decision.</p>	<p>PHARMAC staff note that when including probability distributions in TreeAge software, the base-case analysis is still based on the mean value. However, probability distributions are useful when undertaking sensitivity analysis as they enable multivariate sensitivity analysis to be undertaken based on the distribution of variables, hence quantifying any uncertainty in the overall model. However, PHARMAC staff note the points raised regarding the potential for probability distributions to reduce transparency, the fact that they are understood by few, and his view that these analyses have rarely changed the results. PHARMAC staff also consider that in a number of cases there was inadequate data to support the use of probability distributions.</p> <p>PHARMAC staff agree that the use of probability distributions should be further investigated before they are recommended for routine use. It was noted that, from a practical point of view, making analyses more complex may mean that less analyses would be able to be undertaken.</p> <p>PHARMAC staff will meet in the near future to review CUAs undertaken previously, including the impact of probability distributions on clarity..</p> <p>The following statement is included in the PFPA:  <i>“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”.</i></p>

## Quality of Life

Issue	Details	Response
Utilitarian nature of QALYs	One responder considered that QALYs should not be characterised or criticised as being utilitarian, rather he considers that they should be referred to as 'extra-welfarist'.	<p>PHARMAC staff note that the PFPA states that "a key criticism is that QALYs assume uniform preferences....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 QALY gains".</p> <p>PHARMAC staff considered that it was important to note that QALYs are criticised as being utilitarian, but to point out that QALYs do not have to be applied in this framework. PHARMAC staff considered that the explanation in the revised PFPA was sufficiently clear and that this did not need to be amended.</p>
QALY weightings for age and inclusion of impact of illness on QALYs of family members and caregivers	<p>Several responders considered that QALYs should be weighted lower for the elderly compared with the young (at least in the sensitivity analysis), although it was acknowledged that further work still needed to be done in this area.</p> <p>However others considered that the value of older people and their contribution to kaupapa and the knowledge they pass on to following generations were of great importance, hence the elderly QALYs should be weighted higher (as they are already disadvantaged due to having fewer life years remaining).</p> <p>One responder considered that it is appropriate to include the impact of family illness on family members or caregivers when calculating QALYs, or at least discuss this in the report.</p>	<p>PHARMAC staff note that the proposed reduction in the discount rate would advantage the young, and that the elderly were already 'disadvantaged' as they had fewer life years remaining.</p> <p>PHARMAC staff do not consider that QALYs should be weighted for age as this ensures that CUAs are kept as 'clean' and 'value-free' as possible. In addition, other values (such as placing a higher value on the young) can be taken into account in PHARMAC's other Decision Criteria.</p> <p>In addition, including the impact of illness on QALYs of family members would be difficult and subjective, and hence is not recommended.</p>
Health-related quality of life instruments	<p>There was a substantial amount of feedback on the instrument used for measuring health-related quality of life.</p> <p>Several suggestions were given for other HR-QOL instruments (aside from the EQ-5D) that PHARMAC could consider, including the SF-6D/SF-36 (an algorithm to convert the scores of the SF-36 and SF-12 into utility scores).</p>	<p>PHARMAC staff reviewed the suggested instruments for measuring HR-QOL. It was noted that the SF-6D includes a large number of health states and studies, and is widely used in research (including in New Zealand). However, PHARMAC staff were concerned that the worst surviving health state in the SF-6D is 0.35, and that the preferences are those of the UK population (weights are currently being developed for the Australian population). PHARMAC staff were particularly concerned about the small range in which the SF-6D weights varied (for poor health states the SF-6D was consistently higher compared with the EQ-5D, and for healthier states the SF-6D tends to be lower than the EQ-5D). This</p>

		<p>would disadvantage pharmaceuticals where the sole benefit was improvements in quality of life.</p> <p>Even though an advantage of the SF-6D was that it has 6 levels within each dimension, as PHARMAC has tended to use mid-values of the EQ-5D in the recent past, in effect this means that the EQ-5D has 5 levels within each dimension.</p>
<p>Recommended Health-Related Quality of Life Instruments</p>	<p>Responders to consultation had mixed views on what was the most appropriate instrument to use – overall the majority supported the use of an instrument where NZ preferences are available, but requested that PHARMAC further investigate the use of other instruments.</p> <p>Concerns regarding the EQ-5D included:</p> <ul style="list-style-type: none"> <li>• lack of sensitivity to detect changes in some conditions (especially towards the ceiling of full health);</li> <li>• deficient in aspects of mental health as it does not include cognition;</li> <li>• use of the Visual Analogue Scale (VAS) rating of health states – these do not reflect society preferences as it does not require individuals to make trade-offs between quality of life and survival (this trade-off is considered using Time Trade Off (TTO), Standard Gamble (SG) or Discrete Choice);</li> <li>• small sample size;</li> <li>• does not explicitly consider impact of disability.</li> </ul> <p>The main reasons given for supporting the use of the EQ-5D included:</p> <ul style="list-style-type: none"> <li>• NZ weights available;</li> <li>• simplicity;</li> <li>• widely used (used in approximately 48% of published CUAs).</li> </ul>	<p>PHARMAC staff have discussed in detail whether there were sufficient reasons to not continue to recommend the use of the EQ-5D.</p> <p>PHARMAC staff agreed that the EQ-5D has its limitations; in particular the use of the VAS is a concern as PHARMAC often needs to compare treatments that improve quality of life with those that improve length of life. It was however noted that length of life is taken into account separately in the modelling process. PHARMAC staff agreed that each of the techniques for generating utility values had their disadvantages. The Standard Gamble (SG) is often not well understood and the Time Trade Off (TTO) assumes that individual discount rates reflect that of society and the funding organisation.</p> <p>However, PHARMAC staff consider it is important the quality of life is measured using New Zealand preferences. It is therefore recommended that at this stage the EQ-5D should continue to be used for measuring HR-QOL for the base case analysis, until a better instrument is available. However, although the EQ-5D is the preferred instrument, other instruments can be used providing their use is well justified.</p> <p>PHARMAC staff are planning on further investigating the use of other instruments.</p>
<p>Use of the Global Burden of Disease (GBD) weights</p>	<p>Several responders disagreed with PHARMAC's use of the GBD weights. They noted that these weights are not based on preferences, and are mostly the opinion of up to 17 panel members in the Netherlands. They considered that the opinions of NZ clinical experts would hold much greater validity and applicability to NZ.</p>	<p>PHARMAC staff agree that the GBD weights should not be used as the main source for obtaining utility values. However, they are considered to be useful to check for consistency with the values obtained using the EQ-5D. In many cases the values are very similar.</p>

<p>Mapping health states</p>	<p>One responder considered that PHARMAC's process for mapping health states is unacceptable. The responder considered that patient-derived weights from clinical trials should be the preferred data source, and if that is not available, the next preferred source would be expert panels of relevant health professionals.</p> <p>Another responder considered that the literature is generally better than expert opinion due to peer view.</p> <p>One responder pointed out that small scale surveys of utility of particular health states are increasingly being used. He considered that if surveys are used, these should be based on the preferences of the general public (in dual role as taxpayer and potential patient) rather than experts or patients.</p>	<p>The problem with using patient-derived weights is that they are not representative of the general population. Patients have a higher tolerance for a health state, and their focus is on how much their quality of life improves (as opposed to the valuation of avoidance of disease). The use of patient-derived utility values would therefore be less likely to favour a pharmaceutical. Clinical trials do however provide useful information regarding how many patients are in each health state.</p> <p>PHARMAC staff are currently investigating options for improving the mapping of health states.</p>
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## Estimating Costs

Issue	Details	Response
<p>Manual of Resource items</p>	<p>A number of responders requested that PHARMAC publish a standard list of costs to be used by Pharmaceutical Suppliers in economic evaluations (similar to the Manual of Resource Items published by PBAC). This would ensure that suppliers preparing submissions can be confident that all other submissions are referring to the same set of costs, hence improving transparency.</p>	<p>PHARMAC staff consider that there would be benefits in publishing a manual of resource items (similar to that published by PBAC). Initially the costs would be limited to those costs that are most frequently used in CUAs, and also costs that are relatively stable. These costs would need to be published as a separate document (linked from the PFFA), as the costs will need to be updated periodically.</p>
<p>Deflation of pharmaceutical prices</p>	<p>The proposal to deflate pharmaceutical prices by 2% was not supported by Pharmaceutical Suppliers. It was pointed out that deflating by 2% is not the inverse of inflating by 2% - the difference depending on the relative proportion to which pharmaceuticals costs contribute to total costs. In addition, deflating pharmaceutical prices by 2% assumes all other costs will inflate, which is not always the case (e.g. contracted services such as laboratory testing).</p>	<p>The proposal to deflate pharmaceutical prices by 2% was only intended to be a proxy for inflation. PHARMAC staff agreed however that it may be more appropriate to include this in the sensitivity analysis (either by deflating pharmaceutical prices by 2% or inflating all other prices).</p>
<p>Inclusion of</p>	<p>The proposal to include generic</p>	<p>PHARMAC staff note that including</p>

<p>generic pharmaceutical prices</p>	<p>pharmaceutical prices in cost calculations was not supported by Pharmaceutical Suppliers. They did not consider this proposal to be feasible and would require many assumptions regarding whether a generic substitute would be available, the contractual arrangements and by how much the price would change (particularly for biologicals and products where no generic is anticipated).</p> <p>It was also considered that including future expected prices adds additional uncertainty and complexity to the analysis, and that the pharmaceutical appraised should be judged on its own merit, and sensitivity analysis used to model future effects of generics.</p>	<p>generic prices would favour pharmaceuticals where prices are expected to decrease within the next few years, compared with those pharmaceuticals where a generic is unlikely to be available (or unlikely to be available for some time). PHARMAC staff considered that including these prices this is more likely to reflect the true cost-effectiveness of pharmaceuticals. It was noted that this was one of the consequences of using a lower discount rate, as costs in the future become more important. It was therefore agreed that these prices should be included in CUAs, but that the estimates would need to be conservative.</p> <p>PHARMAC staff consequently amended the PFPA to recommend the following:</p> <ul style="list-style-type: none"> <li>• if patent expiry is within 10 years from expected date of funding, the expected time and price reduction should be included in the analysis,</li> <li>• if patent expiry is after 10 years, estimate time and price reduction using a proxy (e.g. 25 years until expiry and 70% price reduction with introduction of generic).</li> </ul>
<p>Use of DRGs to calculate hospital costs</p>	<p>There was general support for the use of DRGs in calculating hospital costs.</p> <p>However, one responder considered that it may be necessary to adjust these costs (provided the adjustment can be justified with available evidence), as DRGs may underestimate or overestimate the actual cost of treatment. They also considered that clinical trials should be used as a source of resource use data, and that this should be preferred to expert opinion.</p> <p>A further responder considered that in some instances it is more appropriate to approximate national costs with data collected from a single hospital or use data from similar markets such as Australia.</p>	<p>PHARMAC staff agree that in some cases it may be necessary to adjust DRG prices, however evidence should be provided on why adjustments have been made.</p> <p>It is recommended that international cost or resource use data (e.g. data from Australia or international trials) should not be used, due to differences in resource use between countries.</p>
<p>Direct patient healthcare costs</p>	<p>Most supported the proposal to include direct patient healthcare costs in CUAs, however several considered that PHARMAC's definition of direct patient was too restrictive (these are defined in the PFPA as GP visits, pharmaceutical co-payments, and home or continuing care).</p> <p>An opponent of including direct patients costs considered that</p>	<p>Direct patient costs included in CUAs are restricted to health sector costs (i.e. vote health), as this is consistent with PHARMAC's decision criteria. This means that costs paid by other government organisations are outside the scope of PHARMAC analyses.</p>

	analyses done strictly from the payer's perspective are more valid and require fewer assumptions. He considered that people can and should be free to spend their own health care over and above what they pay in taxes to ensure an adequate level of care for themselves and everyone else – without this counting towards decisions on public subsidies.	
Cost to other (non-healthcare) government organisations	Several responders considered that costs to other government organisations should be included in CUAs (or at least reported on), as Government is a unified entity and is the "funder". One responder considered that it would increase transparency to include these costs in analyses, but that unless it was institutionalised in the budget process PHARMAC would be spending money to the benefit of other entity budgets.	Addressed previously when considered perspective of analysis. PHARMAC staff consider that these costs should be included qualitatively for a trial period.
Indirect patient costs	<p>There were mixed views regarding whether PHARMAC should include indirect patient costs. One responder considered that including indirect patient costs makes the analysis more complex and suspect in its conclusions due to the number of assumptions required. In addition, it was noted that the inclusion of these costs would result in double-counting as most indirect costs are included in HRQOL and/or life expectancy estimates.</p> <p>However, others considered that indirect patient costs should be included in analyses, or at least considered in the decision criteria.</p>	<p>PHARMAC staff note that including indirect patient costs in analyses would result in double-counting. By incorporating the impact of these 'costs' in the QALYs, it has the advantage of not needing to weight the QALYs according to whether the patient is working.</p> <p>The reasons for excluding indirect patient costs are outlined in the PFPA.</p>

## Discounting

Issue	Details	Response
Recommended discount rate	<p>There was wide support for the proposed discount rate (3.5%) from economists, pharmaceutical suppliers, and the government sector.</p> <p>In addition, although not explicitly supportive of the 3.5% discount rate, several economists considered that the discount rate should be lower than the current rate of 8-10%.</p>	<p>PHARMAC staff note that the 8% discount rate is based on the capital charge to government departments (i.e. risk-adjusted long-term government bond rate).</p> <p>PHARMAC staff discussed the different approaches to determining the discount rate – the social rate of time preference, social opportunity cost, weighted average of social discount rate, shadow price of capital, and 'bottom up' approach.</p>

		<p>PHARMAC staff considered that the social opportunity cost rate (i.e. current market cost of capital) was not appropriate 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 insurance markets would be more dominant. One reason individuals have positive time preference is that death is inevitable, whereas this does not apply to societies.). It was also noted that applying the current market cost of capital to benefits is difficult to justify. These arguments also apply to the other approaches of determining the discount rate (weighted average of social discount rate, shadow price of capital, and 'bottom up' approach) as they all use variations of the cost of capital.</p> <p>PHARMAC staff therefore agree that the social rate of time preference was the most relevant approach for PHARMAC as it reflects social preferences not just financial sector considerations. It was noted that the long-term government bond rate is often used an approximate for the rate at which society is willing to exchange present for future consumption.</p> <p>PHARMAC staff discussed whether it was more appropriate to adjust the discount rate for risk and therefore whether to use the risk-free or risk-adjusted long-term government bond rate. It was noted that PHARMAC currently uses a risk-adjusted rate. The main argument for using a risk-adjusted rate is that it reflects the risk of the investment and the compensation for covering this risk (e.g. risk of an uncertain future). However this risk can be taken into account by including higher costs and/or lower benefits in the sensitivity analysis, and that it was inappropriate to use the discount rate to compensate for this risk.</p> <p>PHARMAC staff therefore agree that the discount rate should not be used to compensate for the risk associated an investment, and that it is more appropriate for risk to be taken into account in the sensitivity analysis by varying the model inputs.</p>
<p>Discounting costs and benefits at the same rate</p>	<p>There were two opponents to PHARMAC's recommendation that costs and benefits should be discounted at the same rate. They considered that on average the population does invest in their health which would imply a neutral to slightly negative discount rate for benefits.</p>	<p>PHARMAC staff note that discounting benefits at a lower rate would result in the cost-effectiveness of interventions improving on delay, and in a number of cases the results would be counter-intuitive (for example, benefits in the future would be considered better than immediate health benefits). Other reasons for discounting costs and benefits at the same rate are outlined in the PFPA.</p>

		PHARMAC staff consider that costs and benefits should continue to be discounted at the same rate.
Discount rate for budget impact analysis	Most of the contracted reviewers agreed that it is appropriate to use a different rate for BIA compared with CUA, due to their different purposes.	The main reason for using a higher discount rate for BIA is to address the question: what is the financial risk to PHARMAC, in terms of the pharmaceutical budget, of investing in the pharmaceutical? In the longer-term pharmaceutical prices decrease and PHARMAC's budget may change, hence the rationale for discounting future costs at a higher rate. This is particularly the case when forecasts indicate that PHARMAC has very tight budget constraints. When undertaking CUA the longer-term perspective is more important, particularly when discounting benefits.

## Cost-Effectiveness Results

Issue	Details	Response
Reporting of CUA results	Several responders considered that this section needed to include more information on how the cost per QALY results are calculated. It was also considered that all health outcomes of both treatments should be reported, not just QALYs.	<p>PHARMAC staff agree that it would be useful to report on more than just total and incremental costs and QALYs. In particular, costs information should be disaggregated into:</p> <ul style="list-style-type: none"> <li>• DHB costs;</li> <li>• DHB cost savings; and</li> <li>• costs to the pharmaceutical schedule.</li> </ul> <p>QALY information should be disaggregated into:</p> <ul style="list-style-type: none"> <li>• length of life (utility=1);</li> <li>• quality of life loss (for example, pharmaceutical associated with adverse events);</li> <li>• quality of life gain; and</li> <li>• normal life expectancy.</li> </ul> <p>This information will be included in the TAR template.</p>

## Sensitivity Analysis

Issue	Details	Response
Probabilistic sensitivity analysis	<p>Several responders consider that the PFPA should recommend the use of probabilistic sensitivity analysis (PSA) as it provides quantitative information on the joint uncertainty of all parameters modelled.</p> <p>One responder considered that the use of probabilistic sensitivity analysis was appropriate for detailed analyses, and considers that the PFPA should have a firmer statement and clarification as to when PSA is required. Another responder agreed with PHARMAC's recommendation that PSA may necessary when undertaking detailed analyses (i.e. permit but do not require PSA).</p>	<p>PHARMAC staff consider that there were insufficient reasons to amend the current recommendation in the PFPA (i.e. recommend PSA for use in detailed analyses only). PHARMAC staff agree that PSA can provide usual information regarding the sensitivity of the analysis, however the results are not always well understood and are difficult to communicate. In addition, it requires the analyst to choose distributions to represent uncertainty, and the most appropriate distribution is not always obvious.</p>
Interpreting results – use of elasticity	<p>There were some concerns regarding the use of elasticities when interpreting the results of sensitivity analysis.</p> <p>One responder considered that all parameters should be included in the sensitivity analysis. The responder also considered that there are problems associated with elasticities in that they do not make any reference to the strength of evidence available for a parameter and in turn draw attention away from decision uncertainty.</p> <p>Another responder noted that elasticities failed to reflect simultaneously the uncertainty in other parameters in the model.</p> <p>A further responder considered that the use of elasticities makes sense logically, but that PHARMAC may have difficulty communicating the results.</p>	<p>PHARMAC staff consider that elasticities provide useful and easily communicated information on sensitivity of parameters, but that in some cases it would be useful to also use Tornado diagrams. PHARMAC staff note that parameters should not be not varied over arbitrary values (such as +/-10%) if this produces results that are incongruous. Rather parameters, such as utility values, should be varied over the range of possible values (for example, utility values may be varied over possible range of EQ-5D values). PHARMAC staff discussed whether it would be useful if the PFPA specified the ranges over which parameters should be varied (for example, 95% confidence intervals for effect size, outlier DRGs, etc.). It was agreed however that at this stage the information should only be included in the template for PHARMAC's technology assessment reports, in order to allow for variances when required.</p>