

**Guidelines for Funding Applications
to PHARMAC**

Version 2
2009

Foreword

PHARMAC, the Pharmaceutical Management Agency, is primarily responsible for managing the funding of community pharmaceuticals for New Zealanders, on behalf of the District Health Boards. PHARMAC's objective is to secure the best possible health outcomes from within the funding provided.

In any given year, PHARMAC receives a large number of Applications requesting funding for new pharmaceuticals or widening of access to pharmaceuticals that are already funded. As PHARMAC must work within a fixed budget, difficult choices need to be made on which of the Applications should be progressed to a funding decision at any given time. This involves assessing a large amount of often complex information, to identify those Applications that would provide the best health outcomes.

In deciding which proposals to fund, PHARMAC assesses each proposal against its nine decision criteria, which include consideration of health need and assessment of cost-effectiveness. All proposals are prioritised against all other funding options according to these criteria.

In this context of what we call 'relative assessment' (comparing one option against another), it is even more important that applicants provide good quality, complete and balanced Applications that follow these Guidelines. Good quality Applications comprise of the following elements:

- critical appraisal of key clinical evidence;
- information relating to PHARMAC's nine decision criteria;
- complete market and epidemiological information;
- information on cost-effectiveness (based on PHARMAC's methodology for cost-utility analysis); and
- disclosure of information on all known ongoing trials and patent information.

Applications should be clear, cite all sources, explain all assumptions, and include all information of material importance. A thorough, yet succinct Application is likely to expedite our review, enabling the Application to be prioritised earlier.

We would like to highlight that Applications can be submitted by anyone. We strongly encourage all applicants to contact the relevant Therapeutic Group Manager at PHARMAC (+64 (0)4 460-4990) prior to submitting an Application. The Therapeutic Group Manager can answer any questions you may have and confirm what the appropriate procedure is and what information needs to be provided.

Inquiries

All inquiries regarding Funding Applications for a proposed amendment to the Pharmaceutical Schedule should be directed to the relevant Therapeutic Group Manager at PHARMAC (+64 (0)4 460-4990).

Applications and supporting information should be sent to:

Manager, Funding & Procurement
PHARMAC
Level 9
Cigna House
40 Mercer Street
PO Box 10-254
WELLINGTON 6143

Checklist for Funding Applications

The checklist below outlines the information required when submitting a Funding Application to PHARMAC for an amendment to the Pharmaceutical Schedule.

CHECKLIST FOR FUNDING APPLICATIONS TO PHARMAC	
CRITERIA	
Application is for an addition or amendment to the Pharmaceutical Schedule	Y/N
STRUCTURE OF APPLICATION	
Separate synopsis provided	Y/N
Spiral bound copies are clearly labelled and each section indexed	Y/N
Front cover states pharmaceutical name, brand name, date of Application, name of pharmaceutical supplier and name of applicant (including name, phone number and email address of contact person)	Y/N
Table of contents included	Y/N
Three hard copies provided and one electronic copy	Y/N
MAIN CONTENT	
Pharmacological information	Y/N
Proposed change to the Pharmaceutical Schedule	Y/N
Epidemiological information	Y/N
Price information	Y/N
Market information	Y/N
Patent information	Y/N
Impact on health sector	Y/N
Search strategy used for identifying clinical trials	Y/N
Summary of the key randomised controlled trials (methods and outcomes)	Y/N
Assessment of the quality of the evidence	Y/N
Incidence and descriptions of adverse drug reactions	Y/N
Summary of Application evaluated against PHARMAC's nine decision criteria	Y/N
OPTIONAL CONTENT	
Critical appraisal of trials using Graphic Appraisal Tool for Epidemiology (GATE)	Y/N
Applicability of the evidence	Y/N
Cost-utility analysis based on the methods outlined in the Prescription for Pharmacoeconomic Analysis (including all costs estimated in \$NZ)	Y/N
Information on health need and public health significance	Y/N
Information on health need by Maori and Pacific peoples	Y/N
REQUIRED ATTACHMENTS	
Medsafe approved datasheet	Y/N
New Zealand Medicines Assessment Advisory Committee (MAAC) response to the registration application	Y/N
Copies of all identified randomised controlled trials published in peer-reviewed journals, subdivided by grade of evidence and ordered by date of publication	Y/N
One complete hard copy of the clinical study report summaries from the pivotal trials	Y/N

CHECKLIST FOR FUNDING APPLICATIONS TO PHARMAC	
Copies of all errata and journal correspondence relating to published trials	Y/N
Register of all ongoing trials on the pharmaceutical	Y/N
A declaration that all known unpublished clinical trials have been disclosed	Y/N
SAMPLES	
One labelled sample of the pharmaceutical inside its packaging (unless Application is for widening of access)	Y/N
OPTIONAL ATTACHMENTS	
Editorial articles and published critiques	Y/N
Copies of relevant EMEA European Public Assessment Reports (EPARs) and FDA Medical reviews	Y/N
Review articles and expert opinion	Y/N
International guidance and recommendations	Y/N
Published cost-utility analyses	Y/N
If a cost-utility analysis is included, provide a CD with a copy of the TreeAge™ model or Excel™ spreadsheet	Y/N
REAPPLICATIONS	
The Reapplication addresses all of the issues/concerns raised when the original Application was assessed	Y/N
List of all new information provided, along with copies of the new information	Y/N
APPLICATIONS FOR THE FUNDING OF GENERIC PHARMACEUTICALS	
Registration and indication details	Y/N
Pharmaceutical information (including one labelled sample)	Y/N
Price information	Y/N
Market information	Y/N
Patent information	Y/N
Lead times	Y/N

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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 for the performance of its statutory functions as set out in section 48 of the New Zealand Public Health and Disability Act 2000 (NZPHD Act). One of PHARMAC's functions is to manage the Pharmaceutical Schedule, the list of community pharmaceuticals that are publicly funded. It also negotiates national contracts for some medicines used by District Health Board (DHB) hospitals, and related products.

PHARMAC's statutory objective is:

“to secure for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided.” S47(a) NZPHD Act

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

1.2 Purpose of the Funding Application Guidelines

The purpose of these *Guidelines* is to provide guidance on the preparation of Applications to PHARMAC for proposed amendments to the Pharmaceutical Schedule.

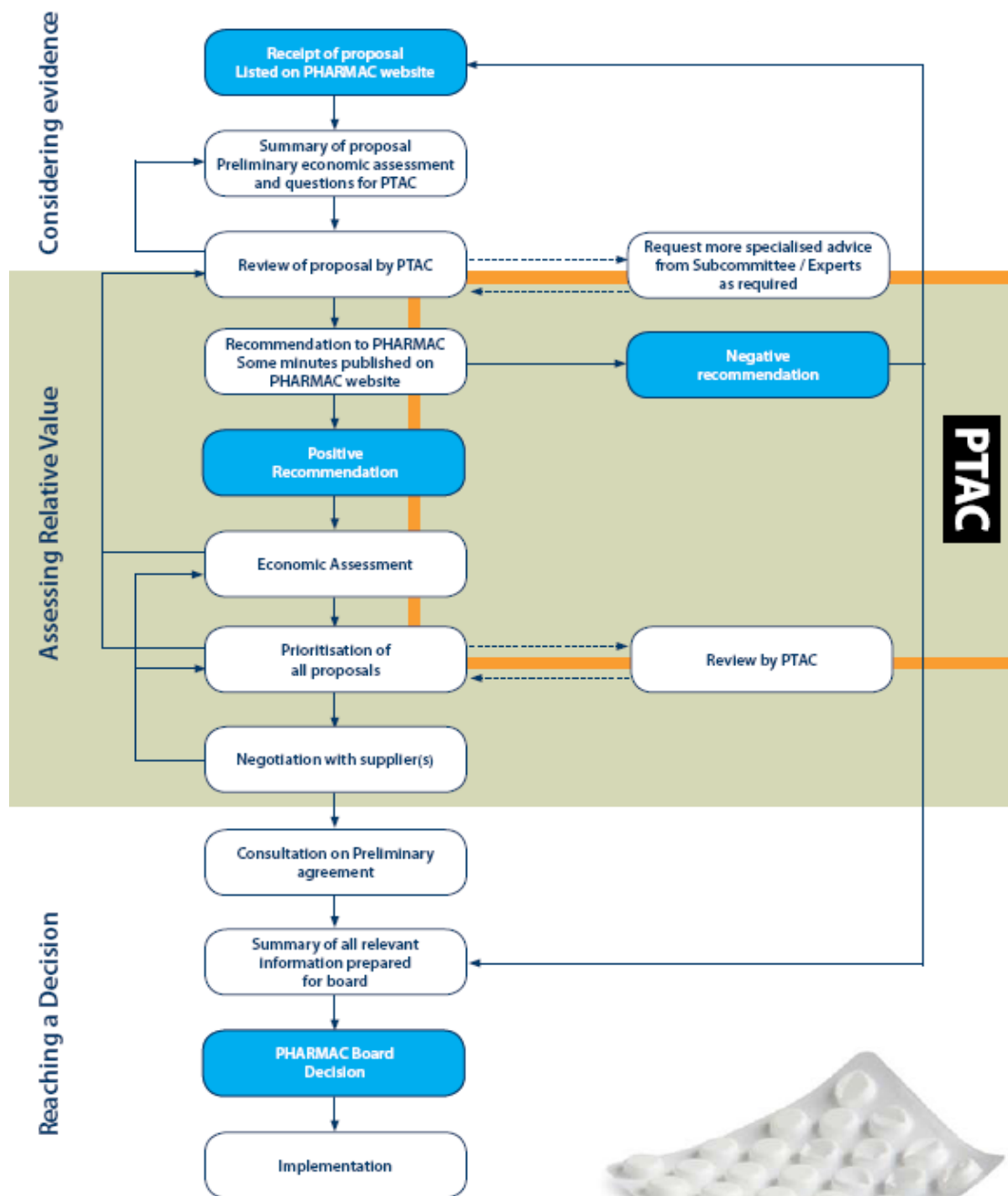
These *Guidelines* are subject to the policies and procedures set out in PHARMAC's Operating Policies and Procedures:

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

This document is intended for use by anyone wanting to make an Application to PHARMAC for a proposed amendment to the Pharmaceutical Schedule. See section 2.2 of this document for further information on the use of these *Guidelines*.

2. The Application Process

PHARMAC has an established process for deciding which pharmaceuticals (and indications of pharmaceuticals) to fund. The process set out in the diagram below is intended to be indicative of the process that PHARMAC may follow for an Application with a proposed change to the Pharmaceutical Schedule. PHARMAC may, at its discretion, adopt a different process, or variations of the process (for example decisions on whether or not it is appropriate to undertake consultation are made on a case-by-case basis). PHARMAC's decision-making process is outlined in the flowchart below.



2.1 Who can initiate an Application?

There are no restrictions on who can initiate an Application. Applications are usually initiated by pharmaceutical suppliers; however, clinicians, interest groups, PHARMAC committees and, to a lesser extent, consumers (patients) may also initiate Applications.

Before seeking to initiate an Application for a proposed amendment to the Pharmaceutical Schedule, please contact the relevant Therapeutic Group Manager at PHARMAC (+64 (0)4 460-4990) to discuss the nature of the proposed amendment and to confirm what the appropriate procedure is in its particular case and what information needs to be provided to PHARMAC.

2.2 When do these Guidelines apply?

Proposed amendments to the Pharmaceutical Schedule where these *Guidelines* apply include Funding Applications for:

- (i) listing of new chemical entities for use in the community;
- (ii) listing of new hospital oncology pharmaceuticals;
- (iii) changing access to an already listed pharmaceutical (e.g. for new indications);
- (iv) listing generic pharmaceuticals where an application to list the pharmaceutical has not previously been considered by PHARMAC;
- (v) listing new formulations or strengths of already listed pharmaceuticals; and
- (vi) listing combination products (products that consist of two or more pharmaceuticals).

Funding Applications relating to a generic pharmaceutical where the pharmaceutical has previously been considered by PHARMAC should follow Section 8 of these *Guidelines* only.

These *Guidelines* do not apply to the following:

- (i) listing of hospital pharmaceuticals funded by District Health Boards (DHBs);
or
- (ii) funding for individual patients (eg through Exceptional Circumstances schemes).

If you have concerns regarding the safety of a pharmaceutical funded by PHARMAC, or consider that a pharmaceutical should be delisted from the Pharmaceutical Schedule, please write to the Therapeutic Group Manager outlining your concerns. PHARMAC staff will inform you of what course of action will be taken. Please note that it is Medsafe (a business unit of the Ministry of Health) that is responsible for medicines regulation and safety matters (under the Medicines Act 1981 and Regulations 1984), and Medsafe should be approached in the first instance.

Funding Applications to PHARMAC should be for Medsafe-registered products and indications. If the pharmaceutical is not registered, or if the Application is for an unregistered indication, please discuss with the relevant Therapeutic Group Manager prior to submitting an Application to PHARMAC.

2.3 What is the process for submitting an Application?

Applications should adhere to the content, format and organisation guidelines stipulated in this document. Please refer to Section 3 of these *Guidelines* for details on the required format of Applications to PHARMAC.

2.3.1 Confidentiality

PHARMAC recognises that certain information submitted to and held by it may be regarded as confidential and commercially sensitive. Applicants should clearly identify any portions of their Application that are confidential by marking the document where relevant. PHARMAC respects the confidentiality and commercial sensitivity of this information; however, applicants should be aware that PHARMAC must balance this against the need to provide information during its consultation processes. In addition, PHARMAC is subject to the Official Information Act. PHARMAC will, at all times, act in good faith where it considers it necessary or appropriate to release information, including in any consultation with affected parties.

2.4 How does PHARMAC process and assess Applications?

When an Application is received, PHARMAC staff review the Application to ensure that it is complete. If an Application is incomplete in any way, or if clarification is required, PHARMAC may contact the applicant and may defer consideration of the Application until the applicant has resolved any outstanding issues.

Application details will be published on PHARMAC's website, including the name of the pharmaceutical and the proposed indication for funding (<http://www.pharmac.govt.nz/fundingapps>).

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

PHARMAC staff and the PTAC Chair may consider, at their discretion:

- (i) whether a particular Application(s) should be referred directly to PTAC for advice; or
- (ii) whether a particular Application(s) should be referred directly to the relevant Subcommittee (i.e. prior to its consideration by PTAC); or
- (iii) whether they wish to invite relevant medical groups and other interested parties to comment on the pharmaceutical that is the subject of the Application prior to consideration of the Application by PTAC or a Subcommittee. Where comments are sought, the main objective will be to enable interested parties to outline specific issues relating to the pharmaceutical (in relation to PHARMAC's Decision Criteria) early in the PHARMAC decision making process. These comments will then be considered by PTAC or a Subcommittee when it considers the Application.

The decision to submit an Application to the next scheduled PTAC meeting following receipt of the Application is at the discretion of PHARMAC staff in consultation with the PTAC Chair; however, PHARMAC staff will inform the applicant of the reasons should a decision be made not to submit the Application to the next scheduled meeting (or to PTAC at all). To avoid unnecessary delays we strongly advise applicants to discuss the proposed Application with the relevant Therapeutic Group Manager prior to sending an Application to PHARMAC.

If an Application is submitted for consideration at a particular PTAC or Subcommittee meeting, PHARMAC staff will usually draft a cover paper for the Application. These papers usually contain the following details:

- (i) summary of the proposal;
- (ii) summary of the pharmaceutical(s) under consideration (e.g. indications, pharmaceutical supplier, proposed subsidy, etc.);
- (iii) questions to PTAC;
- (iv) previous PTAC and/or Subcommittee minutes (if relevant);
- (v) brief description of the disease and current treatment in New Zealand;

- (vi) brief description of the pharmaceutical under consideration (including clinical evidence and any proposed restrictions or changes to access);
- (vii) international prices of the pharmaceutical;
- (viii) estimated cost of listing or changing access;
- (ix) cost-effectiveness (if available and relevant); and
- (x) PHARMAC's decision criteria and Government priorities for funding.

2.4.1 PTAC Review of Applications

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

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

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

Following the PTAC meeting, PHARMAC staff draft the minutes from the meeting relating to each Application, which are then scrutinised and edited by the Committee. Once these are approved by the Committee, a copy of the relevant portion from minute is sent to the applicant, whereupon the applicant has two weeks to review the minute and to make a request for the withholding of all or part of the minute from public release. In considering requests for withholding part or all of PTAC minutes, PHARMAC is guided by the rules for withholding information specified in the Official Information Act. In some instances where the Application has not been made by the pharmaceutical supplier, the minute may be sent to the relevant pharmaceutical supplier and the applicant for review and feedback, usually this occurs if it is

considered that there is a possibility that the supplier may object to the release of part or all of the minute. Following this review, the minutes may be published on the PHARMAC website.

Further details about PTAC and PTAC Subcommittees may be found in the PTAC Terms of Reference, which are available on the PHARMAC website <http://www.pharmac.govt.nz/2008/10/30/2008%20PTAC%20ToR.pdf> and on request from PHARMAC.

2.4.2 Economic Assessment

PHARMAC staff generally will undertake or review two forms of analysis on a proposal: a cost-utility analysis (CUA) and a budget-impact analysis (BIA).

The budgetary impact of the proposed change to the Pharmaceutical Schedule is estimated by PHARMAC staff, usually over a period of five years (discounted at 8%) but in some cases a longer time horizon is required.

The methods PHARMAC uses when undertaking CUA are outlined in PHARMAC's Prescription for Pharmacoeconomic Analysis (PFPA) – www.pharmac.govt.nz/2007/06/19/PFPAPFinal.pdf

PHARMAC encourages applicants to provide a CUA when submitting an Application. The provision of a good quality analysis, following the methods outlined in the PFPA, may expedite the Application review and information acquisition process, enabling the Application to be prioritised earlier.

When PHARMAC receives a CUA from an applicant it is reviewed, and amended if required, by PHARMAC analysts. In order for the 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 with a copy of the Pharmaceutical Supplier's CUA and PHARMAC's amended CUA, with the differences between them clearly explained.

If an economic analysis has not been provided in the Application to illustrate the cost effectiveness of the proposed amendment to the Pharmaceutical Schedule, PHARMAC staff will undertake a CUA. The stage at which this occurs depends on availability of health economist resources and the PTAC priority.

Very few Applications receive a detailed CUA assessment as these take around 2–6 months to complete and, hence, can be too slow and resource-intensive when operating in a purchasing environment. The process is usually iterative, meaning that rapid assessments are conducted first; then preliminary assessments; then if this is insufficient to inform a recommendation, an indicative or detailed analysis is undertaken. The level of analysis undertaken depends on the factors outlined in Table 1 below.

Table 1: Determinants of Level of Analysis Undertaken by PHARMAC

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

Most CUAs are written up as ‘Technology Assessment Reports’ following a template. CUAs are then peer reviewed by colleagues who examine the economic methodology. Analyses may also be reviewed by PTAC or the relevant specialist PTAC Subcommittee, or by other relevant external experts.

Note that at PHARMAC there is no threshold below which a proposed amendment to the Pharmaceutical Schedule is considered “cost effective”. The main reason for this is that cost effectiveness is only one decision criterion used by PHARMAC. One Application may be more cost effective than another but rate poorly on other decision criteria and, therefore, may not be progressed (hence, on ‘successfulness grounds’, it will not be considered cost effective). Another reason for not having a threshold value is that the spending on community pharmaceuticals is required to be kept within a fixed budget. Given the binding nature of this constraint and all other things being equal, what is and is not considered “cost-effective” will vary with the amount of funding available (not just in terms of the total budget each year, but the available budget at any point in time). An Application to fund a pharmaceutical can, therefore, only be considered “cost-effective” in comparison with other Applications under consideration at any one particular time.

2.4.3 Prioritisation

Once full information on an Application is available (including PTAC priority and cost-effectiveness where necessary), this information is compiled and considered by PHARMAC, according to PHARMAC's nine decision criteria (outlined below).

PHARMAC's decision criteria are:

- the health needs of all eligible people within New Zealand;
- the particular needs of Māori 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.

All Applications are prioritised against other expenditure options (either listing of new pharmaceuticals or expanding access to existing pharmaceuticals), with the overall aim of identifying potential amendments that would maximise health outcomes if funded. PHARMAC conducts regular prioritisation reviews of all outstanding Funding Applications.

2.4.4 Negotiations

A Therapeutic Group Manager is responsible for negotiating listing and supply agreements with pharmaceutical supplier(s), where relevant to a proposed change to the Pharmaceutical Schedule. This commercial activity may include discussion related to price reductions; targeting criteria; expenditure caps; rebates on the pharmaceutical price; and/or multi-product agreements. Negotiation outcomes may lead to re-prioritisation of an Application.

2.4.5 Decision

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

Prior to PHARMAC making a decision on a proposed change to the Pharmaceutical Schedule, public consultation on the proposal is generally undertaken. Consultation responses are considered and, if appropriate, the proposal may be amended.

The PHARMAC Board, or PHARMAC's Chief Executive acting under delegated authority from the Board, makes decisions regarding any amendments to the Pharmaceutical Schedule.

3. Structure of Applications

Applications to PHARMAC for the listing of new pharmaceuticals, new indications and/or new formulations should be separated into the following three sections:

- (i) synopsis;
- (ii) the main body of the Application; and
- (iii) supporting information.

Hard copies of the Applications should be provided in separate spiral bound volumes. It is particularly important that copies of the synopsis are provided separately from the rest of the Application.

Each binder should be clearly labelled and the Application should be indexed in such a way that information can be easily located. A table of contents should be provided in each binder. Although not required, it is useful if the Application has labelled tabs for each of the sections in the Application (i.e. pharmacology, epidemiology, etc.).

The front cover of the Application should include the following information:

- (i) pharmaceutical, brand name and indication;
- (ii) date of the Application;
- (iii) the name of the pharmaceutical supplier and (if different) the name of the applicant (including name, phone number and email address of contact person).

The Application must include all relevant information known to the applicant, including data that is contrary to, or does not necessarily support, the case presented in the Application. Any information required for the Application (as outlined below) that is not available or is otherwise not supplied, should be stated explicitly under the relevant heading(s). Explain all sources and assumptions. If PHARMAC is not provided with information it considers is required to assess the Application, this is likely to result in delays. Be clear and succinct, yet thorough.

Applications must also include one labelled sample of the pharmaceutical inside its New Zealand packaging, as appropriate (more samples may be required). A sample is not however required with Applications for widening of access for treatments already listed on the Pharmaceutical Schedule. Please refer to Section 5.10 for further details on the provision of samples.

3.1 Submitting an Application

Applicants must initially provide three hard copies and one electronic copy of the Application to PHARMAC. PHARMAC staff will undertake an initial screening of the Application (as outlined in section 2.4) within ten working days of receipt to ensure that it is complete (in accordance with the information required by these *Guidelines*). If the Application is incomplete or further clarification is required, PHARMAC may contact the applicant and may defer consideration of the Application until the applicant has resolved any outstanding issues.

If an Application is approved for consideration by PTAC, PHARMAC staff will notify the applicant. Following notification, the applicant must provide fifteen copies of the Application.

Applicants must also supply one additional electronic copy of the entire Application on Compact Disk (CD). If an economic analysis is included in the Application, please also provide a copy of the analysis on the CD, along with the Excel spreadsheet and/or TreeAge model as outlined in Section 2.4.2.

If you have any questions, please contact the relevant Therapeutic Group Manager at PHARMAC.

4. Information Required in the Synopsis to an Application

Sections 4 and 5 outline the information required for Applications to PHARMAC for new chemical entities (pharmaceuticals), new indications (expanded access) and new formulations. Applications for generic pharmaceuticals (where the chemical entity has previously been considered by PHARMAC) should refer to Section 8. Please refer to Section 7 of these *Guidelines* for details on the format and content required for reapplications.

4.1 Synopsis

The synopsis should include high-level summary of key aspects and issues presented in the Application. This should generally be about 10 pages or less and should include the following:

- (i) official or approved names of the pharmaceutical;
- (ii) form(s), strength(s), pack size(s);
- (iii) registered indication(s);
- (iv) proposed restriction(s) for listing;
- (v) recommended course of treatment;
- (vi) main comparator(s) and the main expected changes in the clinical management algorithm;
- (vii) numbers of patients treated (restricted and unrestricted listing),
- (viii) proposed price;
- (ix) net cost of the proposed drug each year over five years;
- (x) summary of all relevant New Zealand patents (both granted and pending);
- (xi) cost per patient per course (for acute therapy) or the cost per patient per year (for chronic therapy);
- (xii) any wider health sector resources affected by the listing of the proposed drug;
- (xiii) main results of the clinical evaluation in terms of comparative effectiveness and comparative toxicity, including key data sources;
- (xiv) if available, a summary of the cost-utility analysis, including the main sources of uncertainty in the structure and variables in the economic evaluation and the results of associated sensitivity analyses.

The synopsis will be used as a general information guide for PHARMAC staff and will be provided to PTAC members.

5. Information Required in the Application

5.1 Pharmacological Information

Please provide the following information:

- (i) official or approved names of the pharmaceutical;
- (ii) pharmaceutical form (eg ampoule, vial, sustained-release tablet);
- (iii) pharmaceutical strength;
- (iv) arranged pack sizes (in the case of a preparation such as an aerosol, state the number of doses available from the container);
- (v) principal pharmacological action of the pharmaceutical;
- (vi) indications registered for use in New Zealand – attach the Medsafe approved datasheet and the New Zealand Medicines Assessment Advisory Committee (MAAC) response to the registration application;
- (vii) other common (unregistered) indications;
- (viii) details of countries where registration has been approved or declined;
- (ix) details of countries where an application for funding has been approved or declined;
- (x) pipeline information for any other presentations of the pharmaceutical (e.g. oral tablet);
- (xi) recommended dosages for each of the indications provided in connection with (vi) above - in the case of a pharmaceutical that is not used for chronic therapy, provide information on the average length of a treatment course and anticipated frequency of repeat courses of treatment;
- (xii) any contra-indications and drug interactions- include information on any necessary dosage adjustments and cautions required when using the pharmaceutical in conjunction with other pharmaceuticals;
- (xiii) common adverse effects (including frequency);
- (xiv) serious adverse effects; and
- (xv) a summary statement of the main therapeutic claims for the pharmaceutical and its proposed use.

5.2 Proposed Changes to the Pharmaceutical Schedule

Please provide the following information:

- (i) the therapeutic group and/or subgroup into which the applicant considers the pharmaceutical should be listed on the Pharmaceutical Schedule;
- (ii) details of any proposed restrictions to access (e.g. Special Authority criteria or endorsement criteria);
- (iii) details of the comparator treatments available in New Zealand (funded and unfunded);
- (iv) present the current clinical treatment algorithm and outline the main expected changes in the treatment algorithm;

- (v) describe how the pharmaceutical compares clinically with pharmaceuticals already listed on the Pharmaceutical Schedule, including:
- what (if any) advantages the pharmaceutical offers over existing listed pharmaceuticals in terms of efficacy and/or side effects:
 - whether the pharmaceutical is equivalent to existing listed pharmaceuticals;
 - whether the pharmaceutical is more effective than existing listed pharmaceuticals;
 - whether the pharmaceutical has a similar efficacy to existing listed pharmaceuticals but has fewer side effects;
 - whether the pharmaceutical is associated with similar, greater or fewer side effects and/or toxicity than existing listed pharmaceuticals;
 - whether the pharmaceutical offers greater compliance (e.g., once daily dosing) than existing listed pharmaceuticals (include evidence supporting this claim);
- (vi) if available, include dose equivalencies with comparator pharmaceuticals (whether listed or not) and justify these. State whether dose equivalencies were derived from direct or indirect comparisons.
- (vii) whether the pharmaceutical has a longer shelf life than existing listed pharmaceuticals, or other points of difference; and
- (viii) other pharmaceuticals, medical devices, related products or things, if any, likely to be prescribed for use in conjunction with the pharmaceutical as part of a course of treatment (whether listed or not). Include pharmaceuticals that may be used to manage any side effects.

5.3 Epidemiological Information

For each requested indication(s), please provide estimates for the first five years of the proposal (shown on a year-by-year basis) of:

- (i) the number of people in New Zealand with the particular condition(s);
- (ii) where available, the number of Māori people in New Zealand with the particular condition(s);
- (iii) where available, the number of Pacific people in New Zealand with the particular condition(s);
- (iv) the number of additional people in New Zealand likely to be prescribed the pharmaceutical under the proposal; and
- (v) a breakdown of the number of people in New Zealand treated for the condition by:
 - those who can be successfully treated by the pharmaceutical only;
 - those who can be treated by both the pharmaceutical and other pharmaceuticals (whether listed or not) that treat the same condition;
 - those who can be treated by only other pharmaceuticals (whether listed or not); and

- those who can be treated, completely or partially, by other therapies.

In all cases where estimates and assumptions are made or used, please clearly and explicitly state the bases underlying those estimates and assumptions, including sources. Estimates and assumptions may be indicated in ranges.

Further information on deriving numbers of Maori and Pacific people with the particular condition(s) can be found in Section 6.6.

When estimating the likely number of patients projected to be eligible under access scenarios, please use an epidemiological approach. This should be based on the incidence and/or prevalence of the condition to be treated, current patterns of and time trends in utilisation for the indication, and patterns seen in other medicines markets internationally with the introduction of the new agent(s).

Applicants should cite the data sources used, and clearly and explicitly state the bases of the assumptions made for the estimated numbers, including the quality of the data and relevance to the New Zealand setting. Estimates and assumptions can be indicated in ranges or similar.

The table below provides a suggested format for presenting this information.

Assumption / parameter	Central estimate	Type of estimator used (mean, median, mode, etc.)	Variation (as a range, percentile, standard deviations, 95% confidence interval, etc.)	Source (e.g. publication, reference from the literature - state; expert estimate (who/credentials))	Rationale for using this/these particular source/s

As with evidence of effectiveness (Section 5.8), all prevalence estimates and assumptions should be obtained systematically. Please supply details of the search strategies used to identify these (the medium used; databases searched; time period when undertaken; search strategy and keywords/MeSH headings used). Also specify the pre-defined inclusion and exclusion criteria for selecting the relevant epidemiological data used for estimates and assumptions.

Prevalence and outcomes data may be located using relevant on-line Medline searches (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) using search terms that incorporate [the disease/indication], (epidemiology OR prevalence OR risk factors OR natural history OR prognosis OR outcomes OR survival), and specific outcomes relevant to the disease/indication. Local epidemiology/outcomes data can be located more specifically by including the terms (Austral* OR Zealand OR NZ OR Aotearoa) in the search.

As subsets of prevalence and outcomes data, useful sources of New Zealand mortality and morbidity data include cancer registry data, hospitalisation episode data, mental health episode data, and mortality data. These are available from NZ Health Information Service (<http://www.nzhis.govt.nz>). Details on the range of data available can be obtained from the Ministry of Health's Public Health Metadata Database (see <http://www.moh.govt.nz/PHMetadata.nsf/>).

5.4 Price Information

Please provide the following price information:

- (i) the supplier's selling price in \$NZ (ex-manufacturer, GST exclusive);
- (ii) the supplier's selling prices to wholesalers in other countries where the pharmaceutical is marketed (in local currencies (excluding local taxes) and New Zealand dollar equivalents – please specify the exchange rates used); and
- (iii) alternative pricing proposals (e.g., possible price/volume trade-offs).

5.5 Market Information

Please provide the following market information:

- (i) estimated average daily dose (ADD) information for New Zealand (and other markets where possible) and estimated average daily cost (ADC) of treatment for New Zealand;
- (ii) expected sales (dollars and volume) for the first five years of listing, to be shown on a year-by-year basis with anticipated market segments and projected market shares;
- (iii) what marketing will be used for the pharmaceutical and how this would relate to market penetration; and
- (iv) estimate the change in the extent of use of other pharmaceutical agents.

The ADD, ADC and expected sales information referred to in (i) and (ii) above should be supported by data from major OECD markets and other markets where the pharmaceutical is available (i.e. therapeutic indication(s) and use, ADD information, ADC of treatment, and sales). These data should cover the time period from product launch within each market to the date of the Application, on a year-by-year basis.

5.6 Patent Information

Please provide information on all relevant New Zealand patents (both granted and pending) including:

- (i) patent numbers and a summary of the main claims (including Swiss-style claims);
- (ii) patent application and expiry date(s).

This information is required to help inform PHARMAC's assessment of the budget impact associated with the Application. However it is not necessary for Applications from non-pharmaceutical suppliers to include this information, although PHARMAC may subsequently seek such information from the relevant pharmaceutical supplier.

5.7 Impact on Health Sector

Please provide information the impact listing of the pharmaceutical will have on the health resources in the sector (increase or decrease), including (but not limited to) the following:

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

If possible, please quantify this impact (refer to Section 7 of the PFPA for details on how to estimate these costs).

5.8 Evidence of Effectiveness and Safety

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

5.8.1 Search Strategy

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

- (i) medium used to conduct any search and by whom;
- (ii) databases searched;
- (iii) time period in which the search was undertaken; and
- (iv) search strategy and keywords/MeSH headings used.

Please specify the pre-defined inclusion and exclusion criteria for selecting relevant studies.

5.8.2 Clinical Evidence to Include in Application

When presenting clinical data to PHARMAC on relative treatment effects, please include the following:

- (i) all identified RCTs published as full articles in peer-reviewed journals in the English language that report (or give sufficient data to calculate) outcomes by intention-to-treat;
- (ii) one complete hard copy of the clinical study report summaries from the pivotal trials;

- (iii) a register of all ongoing trials on the pharmaceutical for the relevant indication(s), including trials not directly funded by the pharmaceutical supplier (this can be in the form of a print-out from ClinicalTrials.gov);
- (iv) copies of all published errata (or corrections), retractions and journal correspondence directly relating to the published trials included in the Application;
- (v) if including data from unpublished trials, specify why each trial has not been published and expected dates of publication (if applicable); and
- (vi) a declaration that all known unpublished clinical trials have been disclosed, including those undertaken by other companies that may distribute, market or licence the pharmaceutical in New Zealand.

In evaluating therapeutic effectiveness and safety, greater weight is placed on well-designed RCTs than other data sources. Of particular interest are head-to-head comparison RCTs between the proposed product and principal comparators.

As outlined above, unpublished articles or studies that have been submitted for publication in peer-reviewed journals should be provided. In cases where the study is published after the Application has been submitted, applicants may substitute the draft submitted version with the final published version. However, if a trial remains unpublished and it is not registered on a public trial register, then it is less likely that PHARMAC will consider the trial. PHARMAC is committed to international efforts to mitigate publication bias through the provision of central trial registries.

Details on supplementary information that may be provided in a separate section of the Application are included in Section 6 of these *Guidelines*.

Please do not include the following information in the Application as such information will not be reviewed:

- (i) information unrelated to the pharmaceutical and disease(s)/indications under consideration;
- (ii) phase I clinical trials relating to the pharmaceutical.

Please also note that abstracts and posters are not appropriate sources for descriptions of the study methodology or primary outcomes of studies. However, if adequately detailed, they may be used as references to update data subsequent to the primary analyses or any analyses of secondary outcomes not detailed in the published report.

5.8.3 Order of Attachments

Subdivide the copies of the articles, with their accompanying appraisals and gradings (where applicable, see 5.8.6 below), into the following three categories:

- (i) published Grade 1 evidence of effectiveness – randomised controlled trials (RCTs) of efficacy (individual RCTs and meta-analyses of RCTs);
- (ii) published Grade 2-3 evidence of effectiveness, prognosis or adverse effects – controlled but non-randomised experimental studies and non-analytic uncontrolled descriptive data for efficacy or prognosis/natural history or adverse effects (prospective cohort studies, case control

studies, before-and-after studies longitudinal studies, uncontrolled observational studies, case reports); and

- (iii) published Grade 4 evidence of effectiveness and all other published material – non-systematic reviews, expert opinion, economic modelling/analyses and intervention logic in absence of direct empirical data, other background epidemiology and natural history of the disease/indication, and other published material relevant to the proposal.

Within each group, please order articles by date of publication, starting with the most recent.

5.8.4 Presentation of Clinical Evidence

For each direct RCT, provide the following details of the trial:

- (i) objective of trial;
- (ii) the eligibility criteria for participants considered for recruitment into the trial;
- (iii) the baseline demographic and clinical characteristics of each randomised group;
- (iv) sample size;
- (v) methods for randomisation, blinding, handling of withdrawals and drop-outs, and allocation concealment;
- (vi) the duration of follow-up (median and range) and whether the trial has been completed or is ongoing;
- (vii) numbers of withdrawals and drop-outs (with reasons);
- (viii) details of the interventions administered to each randomised group, including form, dose, method of dose administration, dose timing and frequency, dose titration, dose titration criteria, treatment duration and previous treatments;
- (ix) primary outcome, how it was analysed (including units of measurement), and results, including measures of dispersion (e.g. standard deviations or standard errors for continuous outcomes; numerators and denominators for dichotomous outcomes);
- (x) patient-relevant secondary outcomes, how they were analysed and results;
- (xi) all harmful patient effects, including an itemisation of fatal and nonfatal serious adverse events; and
- (xii) information about pre-planned extension of the trial (if relevant).

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. Where intention-to-treat analysis has not been reported, ideally recalculate effectiveness rates by subtracting from reported numbers of patients responding all patients who withdraw/drop-out/are otherwise lost to follow-up. In addition, information should be provided on Numbers Needed to Treat (NNT) and Numbers Needed to Harm (NNH).

The clinical importance of the primary outcome and secondary outcomes should be discussed in the Application, and references provided supporting the validity of these outcomes.

The primary and secondary outcome data should be obtained from the complete published reports of the trials. If these are not available, clinical study reports should be used – these should be clearly highlighted and will be treated as commercial- or academic-in-confidence.

Where clinical trial data have been taken from more than one source, this should be made clear. Examples include:

- (i) a clinical trial report and a published paper;
- (ii) an open-label extension to a trial; or
- (iii) additional analyses (e.g. interim or post-hoc).

5.8.5 Critical Appraisal

Where possible, critically appraise and grade the articles using the methods described in PHARMAC’s Prescription for Pharmacoeconomic Analysis (PFPA). PHARMAC recommends the use of the full Graphic Appraisal Tool for Epidemiology (GATE) for the critical appraisal of clinical trials. Further details on this tool are provided in Section 6.

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

Table 2: Factors to Consider in Critical Appraisal of Trials

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

5.8.6 Grading of Clinical Trials

There are many different methods of assigning levels of evidence, and there has been considerable debate regarding which method is best. A commonly used checklist is that developed by the Scottish Intercollegiate Guidelines Network (SIGN), outlined below:

Table 3: SIGN Checklist

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

PHARMAC recommends that in cases where there are well-conducted RCTs, systematic reviews and meta-analyses available for relative treatment effects (i.e. grade of evidence 1+ or 1++), these should be the preferred data source.

5.8.7 Safety

Information on the incidence and descriptions of adverse drug reactions should include data collected from:

- (i) observational longitudinal clinical studies;
- (ii) RCTs;
- (iii) case reports on adverse drug reactions and expected/unexpected side effects; and
- (iv) post-marketing data.

5.9 Decision Criteria

When making decisions on proposals, PHARMAC uses the decision criteria set out below and gives such weight to each criterion as it considers appropriate. These decision criteria are set out in Section 2.2 of PHARMAC's OPPs which are available on the PHARMAC website. The criteria are also used by PTAC when it assesses Applications.

Please provide a summary of the Application, evaluated against as many as possible of PHARMAC's nine decision criteria, described below. The questions included for each criterion have been included to help applicants to address each criterion. PHARMAC has also identified some potentially relevant supporting information, which it would, where available, be helpful for applicants to provide in relation to each criterion.

The questions and supporting information identified below do not limit either the application of each criterion or the factors PHARMAC may consider under each criterion.

Table 4: PHARMAC Decision Criteria

Decision Criteria	Questions to address	Supporting information
Criterion 1 - the health needs of all eligible people within New Zealand	What health need(s) does this proposal meet?	<p>What is the morbidity (e.g. annual number of hospitalisations) and premature mortality of the condition in New Zealand (e.g. annual number of deaths; number of potential years of life lost)?</p> <p>What are the population disability-adjusted life years (DALY) lost for the disease(s)?</p> <p>What is the disease's percent of population total DALY loss across all diseases? Refer to Section 6 for further information.</p> <p>What is the estimated extent (%) to which the disease(s) might be modifiable by the proposal?</p>
Criterion 2 - the particular health needs of Māori and of Pacific peoples	What particular health need(s) of Māori and of Pacific peoples does this proposal meet?	<p>Describe the extent of disparity in disease prevalence, incidence, notifications of new cases, public hospital hospitalisations, deaths, etc. between Māori, Pacific people and non Māori/non Pacific people.</p> <p>Where data are available, describe the degree of impact on Māori and Pacific people relative to non Māori/non Pacific people, using age-adjusted relative risks for notification / hospitalisation / mortality rates for disease for Māori or Pacific people versus non Māori/non Pacific people (as the reference group). Refer to Section 6 for further information.</p>

Decision Criteria	Questions to address	Supporting information
Criterion 3 - the availability and suitability of existing medicines, therapeutic medical devices and related products and related things	What other interventions are currently available to meet these health needs – if there are none, what other health sector resources are used managing the need(s)?	
Criterion 4 - the clinical benefits and risks of pharmaceuticals	What health benefits and risks does the proposal provide, including in comparison with the other interventions outlined above?	<p>What are the absolute risk reductions (ARR) in events (specify) or improvement in health states (specify) caused by the proposal?</p> <p>What other benefits are conferred for patients (e.g. evidence of improved efficacy through increased compliance)?</p> <p>What are the discounted QALY gains per patient treated over one year?</p>
Criterion 5 - the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services	What is the incremental cost (or saving) and incremental benefit (or risk) compared with the other interventions?	What is the estimated cost per QALY associated with funding the proposal? Refer to Section 6 for further information.
Criterion 6 - the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule	What impact does this proposal have on the pharmaceutical budget and the overall health budget, both for the current financial year and the net present value (NPV) of the effects over future years?	
Criterion 7 - the direct cost to health service users	How are patients' out-of-pocket expenses changed by the proposal?	
Criterion 8 - 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		Information on Government priorities for health funding is available at: http://www.moh.govt.nz/nzhs.html
Criterion 9 - such other criteria as PHARMAC thinks fit.		

Note that PHARMAC is not bound to accept the applicant's evaluation of the Application against the decision criteria, and may attribute different weightings to the criteria.

5.10 Sample

Please provide one labelled sample of the pharmaceutical inside its New Zealand packaging, as appropriate (more samples may be required). If the pharmaceutical is cyto-toxic or a controlled pharmaceutical, please send a sample separately directly to the Medical Director with clearly labelled packaging.

Nothing in this requirement to send samples acts as an exemption for the applicant from relevant legislation relating to the importation or distribution of pharmaceuticals, including but not limited to the Medicines Act 1981 (and its Regulations), the Misuse of Drugs Act 1975 or relevant patents legislation.

Note that a sample is not required to be provided with Applications for widening of access for treatments already listed on the Pharmaceutical Schedule.

6. Optional Information in Applications

This section outlines the information that would be useful to provide in addition to the required information detailed in Section 5 of these *Guidelines*. Some of this information may not be relevant or necessary for every Application. However, while not compulsory, provision of this information may reduce delays in the assessment and prioritisation of the Application.

Please provide this information in a separate section from the main body of the Application.

6.1 Supplementary Clinical Information

The following supplementary clinical information may be provided in a separate section:

- (i) editorial comment;
- (ii) review articles and published critiques;
- (iii) publications produced by international regulatory authorities, including European Public Assessment Reports (EPARs) produced by the European Medicines Agency (EMA) and Medical reviews produced by the American Food and Drug Administration (FDA);
- (iv) international guidance and assessments by regulatory authorities or health technology assessment agencies (for example, reports produced by the National Institute of Health and Clinical Excellence, Canadian Agency for Drugs and Technologies in Health, Scottish Medicines Consortium, and the Pharmaceutical Benefits Advisory Committee);
- (v) published CUAs;
- (vi) reviews by expert bodies such as specialist colleges/professional bodies;
- (vii) consensus reports from expert panels;
- (viii) expert opinion.

“Expert opinion” is opinion provided by groups with any relevant expertise in the area of concern, for example, specialist professional societies or consumer support groups. Expert opinion cannot substitute for sound scientific evidence, but will help interpret data, particularly the relevance and potential impact of clinical trial results and economic aspects.

Where expert opinion is provided, applicants should justify the need for any such expert opinion, and describe the methods used to obtain and collate those opinions, which must be systematic and robust. Applications with expert opinion should include the following information:

- (i) criteria for selecting the experts;
- (ii) number of experts approached;
- (iii) number of experts who participated;
- (iv) whether a declaration of potential conflict(s) of interest was sought from all experts;

- (v) medical specialty groups whose opinions were sought;
- (vi) background information provided and its consistency with the totality of the evidence provided in the submission;
- (vii) method used to collect the opinions;
- (viii) medium used to collect the opinions;
- (ix) questions asked;
- (x) whether iteration was used in the collation of opinions and, if so, how it was used;
- (xi) number of responses received for each question;
- (xii) whether all experts agreed with each response, and, if not, then the approaches used to both finalise the estimates and present the variability of the opinions;
- (xiii) whether the experts received benefits (monetary or non-monetary) for the advice provided; and
- (xiv) relevant conflicts of interest.

Applicants should indicate how the opinions have been used in the Application, and state the extent to which opinions may have varied. Any clinicians providing expert advice must declare all potential conflicts of interest, including (but not limited to) financial interests in the development of the technology, likely financial gains arising from the proposed technology and research funding. Experts must not supply any data able to identify individual patients.

6.2 Critical Appraisal of Trials

PHARMAC recommends that the full Graphic Appraisal Tool for Epidemiology (GATE) be used when critically appraising clinical trials.

The GATE framework involves the following five steps:

- (i) asking focused questions based on PECOT (population, exposure, comparison, outcome, time);
- (ii) searching the literature for best available evidence;
- (iii) appraising the study by 'hanging' on the GATE frame;
- (iv) assessing study quality;
- (v) application of evidence in practice.

Details on the GATE framework, including critical appraisal spreadsheets, are available at: www.epiq.co.nz, and it is described further in Evidence Based Medicine at <http://ebm.bmj.com/cgi/content/full/11/2/35>.

6.3 Applicability of the Evidence

For each clinical study provided in the Application, assess how applicable the study is to the New Zealand health sector and pharmaceutical funding environment.

Consider the following:

- (i) Are there any known biological factors that may alter the effect of the pharmaceutical?
- (ii) What effects does the timing of administration of the pharmaceutical have?
- (iii) What effects do variations in the nature and severity of the disease have?
- (iv) Is the effectiveness of the pharmaceutical dependent on the way it is administered and/or by whom (eg by a nurse as opposed to by the patient)?
- (v) Is administration of the pharmaceutical part of a complex procedure with many components?
- (vi) Is any infrastructure required/available, such as monitoring with regular blood tests?
- (vii) Any other factors that may affect transferability of study results to the New Zealand clinical setting.

6.4 Economic Analysis

PHARMAC encourages applicants to provide a CUA when submitting a funding Application. The provision of a good quality analysis, following the methods outlined in the PFPA, may expedite the assessment and prioritisation of the Application.

If a CUA has been submitted to the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, PHARMAC will accept the same CUA to be included in the Application to PHARMAC, providing the following information is included:

- (i) whether there were any reviews undertaken by PBAC contracted reviewers of the CUA submitted to the PBAC, and a copy of those reviews;
- (ii) an electronic copy of the Excel spreadsheet and/or TreeAge model – this ensures that PHARMAC staff can amend the costs (and any other relevant inputs) to ensure that the model is applicable to the New Zealand clinical and funding environment.

When PHARMAC receives a CUA from an applicant it is reviewed, and often amended, by PHARMAC analysts. The guidelines PHARMAC uses to review analyses are included in Appendix 4 of the PFPA <http://www.pharmac.govt.nz/pdf/PFPAFinal.pdf>

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

6.4.1 Recommended Methods for Economic Analysis

Economic analyses should be undertaken in the form of a CUA where benefits are measured in terms of quality-adjusted life years (QALYs). In cases where the clinical outcomes of the drug and the comparator have been shown to be equivalent, a cost-minimisation analysis may be appropriate. Other forms of cost-effectiveness or cost-benefit analyses should not be provided to PHARMAC.

Economic models should avoid unnecessary complexity and should be transparent, well described and reproducible. 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.

The key recommendations to consider when undertaking CUAs for funding Applications (as outlined in the PFFA) are summarised in Table 5 below.

Table 5: CUA Inputs/Outputs

Input / Output	Recommendation
Perspective	PHARMAC's decision criteria.
Target population	Population most likely to receive treatment.
Comparator	Treatment that most prescribers would replace in New Zealand clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace).
Clinical outcomes	Statistically and clinically significant outcomes obtained, preferably, from high-quality RCTs, systematic reviews or meta-analyses (grade of evidence of 1+ or 1++). Include impact of non-compliance if significant.
HR-QOL	Base on NZ EQ-5D Tariff 2. Use of GBD weights to check for consistency.
Pharmaceutical Costs	Pharmaceutical costs should take into account any proposed rebate, and should be based on the dose used in the key clinical trials (unless there is evidence of efficacy for different doses in clinical practice). Dispensing fees and pharmacy mark-up should be included if these are likely to differ between treatment arms. The analysis should also include the lower cost of a future generic pharmaceutical.
Other Costs	Hospital, outpatient and direct patient costs should be included. Direct patients should be restricted to healthcare costs that the government partially subsidises, and should be based on the cost to government plus the additional cost to the patient. These costs include General Practitioner visits, pharmaceutical co-payments and continuing care. Costs to non-healthcare government departments and indirect patient costs should not be included in CUAs for PHARMAC.
Discount rate	Discount all costs and benefits in CUAs at a 3.5% discount rate. Include rates of 0%, 5%, and 10% in sensitivity analyses.

Input / Output	Recommendation
Results	The overall incremental cost per QALY result should be reported as a point estimate as well as the range over which the cost per QALY is likely to vary. In addition, information on discounted real and nominal costs, savings, life-expectancy and quality of life gains/losses resulting from treatment should be reported separately.
Sensitivity Analysis	Sensitivity analysis should include univariate (simple) analysis, multivariate analysis and extremes (scenario) analysis.

6.5 Health Need and Public Health Significance

PHARMAC encourages applicants to provide information on health needs and public health significance when submitting a funding Application (relating to PHARMAC's Decision Criterion 1). This includes:

1. Description of the burden of the disease or condition (impact of the disease or condition on the individual and the community), including:
 - (i) the incidence and prevalence of disease/condition in New Zealand;
 - (ii) the morbidity associated with the condition (e.g. annual number of hospitalisations);
 - (iii) the premature mortality associated with condition in New Zealand (e.g. annual number of deaths; number of potential years of life lost before age 80 (PYLL(80))¹);
 - (iv) the average disability-adjusted life years (DALYs) lost by an individual patient due to the disease(s)²;
 - (v) the population loss of disability-adjusted life years (DALY loss) for the disease(s);
 - (vi) the population DALY loss attributable to the disease as a percent of all diseases (where in 1996 there were 543,000 total DALY lost from all diseases³);

2. Description of the estimated uptake of the pharmaceutical (i.e. the number of people likely to be prescribed the pharmaceutical, divided by number of people with the particular disease or condition who should benefit from the pharmaceutical). This should use both the epidemiological data above and in section 5.3 and the estimates of likely usage from section 5.3.

¹ PYLL80 = sum across all individuals of (80 years minus age at death for an individual)

² Where an individual's normal life expectancy minus their loss of disability-adjusted life years (DALY loss) from their disease/condition equals their disability-adjusted life expectancy (DALE)

³ The Burden of Disease and Injury in New Zealand. Public Health Intelligence Occasional Bulletin No. 1. Wellington: Ministry of Health, 2001.

[http://www.moh.govt.nz/moh.nsf/82f4780aa066f8d7cc2570bb006b5d4d/a313645fbc60bf02cc2569f400791b9b/\\$FILE/BurdenofDisease.pdf](http://www.moh.govt.nz/moh.nsf/82f4780aa066f8d7cc2570bb006b5d4d/a313645fbc60bf02cc2569f400791b9b/$FILE/BurdenofDisease.pdf)

6.6 Health Need by Māori and Pacific peoples

The health needs of Māori and Pacific people are a specific PHARMAC decision criterion (Criterion 2). PHARMAC encourages applicants, where possible, to provide information on health needs and public health significance specific to Māori and Pacific peoples when submitting a funding Application (relating to PHARMAC's Decision Criterion 2). This information should include the following:

1. A description of the availability and quality of data indicating the extent of disparity between Māori, Pacific peoples and non Māori/non Pacific people. This may include data on disease prevalence, incidence, notifications of new cases, public hospital hospitalisations, and/or deaths.
2. Where data are available, quantification of the degree of impact of the disease on Māori and Pacific people relative to non Māori/non Pacific, using age-adjusted relative risks for notification, hospitalisation and mortality rates. In each instance this should describe:
 - (i) the number of cases occurring in Māori, along with the age-standardised rate per 1000 (further details below);
 - (ii) the number of cases occurring in Pacific people, along with the age-standardised rate per 1000;
 - (iii) the number of cases in non Māori/non Pacific, along with the age-standardised rate per 1000;
 - (iv) both risk differences for age-standardised rates and age-adjusted rate ratios with 95% confidence limits for Māori vs non Māori/non Pacific; and
 - (v) both risk differences for age-standardised rates and age-adjusted rate ratios with 95% confidence limits for Pacific peoples vs non Māori/non Pacific.
3. Where data are available, the key age-specific differences between Māori or Pacific people and non Māori/non Pacific. This includes data on particular age-sex groups for Māori/Pacific that have the greatest age-specific risk differences when compared with non Māori/non Pacific.
4. Comment on the extent to which notification rates, hospitalisation rates, and mortality rates correlate with need for pharmaceuticals.

Those applicants providing such information should use standard sources (e.g. NZHIS mortality, hospitalisation and mental health data), supplemented where required by discussion with relevant experts and/or Medline searches. Sources could include prevalence data, incidence/notifications data, hospitalisation data, mental health episode data, and mortality data for relevant indicator(s), combined with New Zealand age-ethnic-specific populations (available at <http://www.stats.govt.nz/>).

Where able and available, applicants should calculate age-standardised rates using the direct method against Segi's Standard World population. Calculate age-standardised rate ratios (relative risks) and 95% confidence limits using standard binomial techniques. (Age-standardised rate ratios summarise disparity for Māori or Pacific people over all ages when compared with non-Māori/non Pacific, mitigating bias due to differences between ethnic groups' age structures.)

Applicants providing such information should please be aware that the use of incidence (notification) rates to proxy need for pharmaceuticals is valid only if survival

times are similar between ethnic groups. This is often not the case with Māori and Pacific peoples, who have worse mortality and case fatality rates. In addition, hospitalisation rates do not necessarily correlate well with prevalence (here, the need for pharmaceuticals), although they might proxy the total burden of disease.

Applicants also need to be aware that at least historically there have been major problems with the accuracy and validity of the data routinely available within the New Zealand health sector, especially with ethnicity. In general there are few timely data available about the types of patients, disease/disability rates and pharmaceutical indications conditions treated in primary care, particularly when subdividing ethnicity by disease/indications. Mortality data are less timely than hospitalisations data and give less precise estimates of risk (given smaller numbers of deaths). Māori death rates have in past decades been substantially under-represented due to ethnicity miscoding. Causes of death described on death certificates can be inaccurate. Routinely collected hospitalisations data are less accurate than mortality data, with historically over one-quarter of discharge diagnoses being incorrectly coded. Hospitals had systematically under-counted Māori admissions, hence numerator-denominator mismatches historically. Hospital admissions only indirectly measure need, being also affected by supply factors (regional etc variations in admitting practices relating to bed/service availability and clinical protocols), in turn affecting ethnic rates. Double counting of readmissions and of inter-hospital transfers as “new” admissions further biases the data.

It should be also noted that describing Māori or Pacific peoples’ representation (i.e. what proportion of patients in the community are Māori or Pacific peoples) has only partial relevance to PHARMAC’s decision-making. Disease prevalence does not necessarily correlate with need for pharmaceuticals. In addition, deviations from expected-need for ethnic groups have little relevance if these ethnic groups are not accessing appropriate treatment. This is where accessing appropriate treatment comprises being able to visit a GP or similar primary care professional available and the disease being identified and treatment prescribed – all at probabilities equal to non Māori. There is evidence with many aspects of healthcare that Māori access is lower than for non-Māori.

7. Reapplications

Key reasons for Reapplications include:

- (i) new information has become available (e.g. clinical trials, cost-utility analyses); and
- (ii) the applicant wishes to respond to issues or questions raised by PTAC or specialist PTAC Subcommittees (as recorded in the minutes of the meeting).

7.1 Information Requirements

It is important that Reapplications address all of PTAC or the PTAC Subcommittee's concerns raised when the original Application was considered. A list of all new information (not included in the original Application or previous reapplications) should be provided along with copies of all new information and supporting documentation.

Applicants are not required to provide copies of their original Application, however PHARMAC staff may contact you if this information is required.

8. Applications for the Funding of Generic Pharmaceuticals

This section of the *Guidelines* should be used only for Applications to fund a generic pharmaceutical where the pharmaceutical, including the indication applied for, has previously been assessed by PHARMAC. This should be confirmed by contacting the relevant Therapeutic Group Manager at PHARMAC (+64 (0)4 460-4990).

Applicants should provide as much of the following information as possible.

8.1 Registration and Indication

Please provide a copy of the Medsafe gazette notice and approved New Zealand data sheet. If the pharmaceutical is not registered for use in New Zealand, please outline the date, or likely date, of submission of the dossier, and whether or not this would be subject to any of Medsafe's abbreviated registration processes. If known, please indicate the expected date of registration.

Please state whether there are any differences, or likely to be any differences, in the approved indications for the pharmaceutical compared with the brand(s) of the pharmaceutical previously considered by PHARMAC.

Please also state the indication for which funding is being sought.

8.2 Pharmaceutical Information

Please provide the following pharmaceutical information:

- (i) the official or approved names of the pharmaceutical;
- (ii) available forms, strengths, pack sizes and packaging for which funding is sought (In the case of a preparation such as an aerosol, state the number of doses available from the container);
- (iii) whether there are any other available forms, strengths and pack sizes;
- (iv) if available, provide one labelled sample of the pharmaceutical inside its New Zealand packaging – if the pharmaceutical is cyto-toxic or a controlled pharmaceutical, please send the sample separately directly to the Medical Director (note that more samples may be required subsequently)⁴;
- (v) detail any differences between the pharmaceutical and any other brand(s) of the pharmaceutical previously considered by PHARMAC, including (but not limited to):
 - differences in the efficacy, side effect and toxicity profiles;
 - differences in the pharmacokinetic profile;
 - differences in the shelf-life;
 - differences in appearance/taste (eg, colour, shape, size, coating, ability to be split);
 - difference in excipients;

⁴ Nothing in this requirement to send samples acts as an exemption for the applicant from relevant legislation relating to the importation or distribution of pharmaceuticals, including but not limited to the Medicines Act 1981 (and its Regulations), the Misuse of Drugs Act 1975 or relevant patents legislation.

- any other differences that the applicant is aware of that could be of relevance.

8.3 Price Information

Please provide the following price information:

- (i) the selling price (GST exclusive); and
- (ii) any alternative pricing proposals (e.g., possible price/volume trade-offs).

8.4 Market Information

Please provide the following market information:

- (i) which (if any) international markets the generic pharmaceutical is registered for use in;
- (ii) which (if any) international markets where registration of the generic pharmaceutical has been declined;
- (iii) the market share of the generic pharmaceutical in international markets;
- (iv) a description of uptake and acceptance of the generic in international markets.

8.5 Patent Information

Please provide information about any patent investigation carried out by the applicant in relation to the introduction of the pharmaceutical to the New Zealand market and any other relevant patent information about which the applicant is aware.

8.6 Lead times

Please provide information about the length of time following a funding decision which would be required to obtain sufficient stock to supply the market in New Zealand.

Appendix 1 – Glossary

Term	Definition
Absolute Risk Reduction (ARR) or Absolute Risk Increase (ARI)	The absolute difference in event rates between an intervention and its comparator.
Adherence	Continuation and consistency with recommended treatment regimen.
Applicant	Any person or organisation making an application to PHARMAC.
Application	A Funding Application or proposal made by a third party to PHARMAC for (a) the funding of a pharmaceutical; or (b) changes to the funding of a pharmaceutical that is already on the Pharmaceutical Schedule (e.g. a proposal to widen or restrict access).
Average cost	Total cost divided by total number of units.
Community pharmaceutical	Pharmaceutical used in the community (i.e. outside of the hospital).
Budget impact analysis (BIA)	Estimate of planned resource use and impact on budget over a period of time.
Combination product	Products that consist of two or more pharmaceuticals
Comparator	Treatment most prescribers would replace in New Zealand clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace).
Confidence interval	Numerical measure of the range within which the true treatment effect is likely to lie.
Cost/QALY gained	Result of cost-utility analysis. Monetary cost per quality-adjusted life year (QALY).
Cost-benefit analysis (CBA)	Cost-benefit analysis (CBA) measures costs and benefits in monetary terms, and expresses the results as one figure representing the difference between benefits and costs ($B-C > 0$), or as a ratio (B/C).
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis (CEA) compares the relative costs of interventions against some clearly definable outcome; such an outcome may be, for example, hospitalisation days avoided, strokes prevented or hip fractures averted. The final result is a value called the incremental cost-effectiveness ratio (ICER).
Cost-minimisation analysis (CMA)	Cost-minimisation analysis (CMA) assumes that there is no net health change between different treatment options (i.e. there is no significant difference in the effectiveness of the treatments). In this case the analysis is essentially a search for the least costly alternative.

Term	Definition
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 age standardisation	<p>Age standardisation (age adjustment) is a technique to better compare populations when their age profiles differ. It uses a weighting approach to match the age distribution of a common reference population, thereby obtaining a weighted average of age-specific rates to derive a summary event rate.</p> <p>Methods of age standardisation can be direct or indirect. Direct age standardisation gives a summary rate of events that would have been observed had the study population had the same age structure as the reference group (e.g. the number of cases of disease that would be expected if the disease rates in the study population were applied to the reference population). Further details are available in standard epidemiology texts.</p>
Direct cost	Fixed and variable costs (medical and non-medical) directly related to the treatment.
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.
Disability-adjusted life year (DALY)	Burden of disease measure that combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health.
District Health Board (DHB)	Organisation responsible for ensuring the provision of publicly funded health and disability support services for the population of a specific geographic area in New Zealand. There are currently 21 DHBs.
Health-related quality of life	Physical, social and emotional aspects of patient's well-being.
Hospital pharmaceutical	Pharmaceutical that is predominantly administered within the hospital
Effectiveness	Benefit of treatment in 'real world' setting.

Term	Definition
Efficacy	Benefit of treatment in defined population in controlled or ideal circumstances (e.g. randomised controlled trials).
Exceptional Circumstances (EC) process	Exceptional Circumstances offers individuals access to medicines that aren't otherwise funded through the Pharmaceutical Schedule, or through DHB Hospitals. Separate schemes, with distinct criteria, operate for community, hospital and cancer medicines.
Gazette notice	Announcement of Medsafe approval for the marketing of a pharmaceutical in New Zealand
Generic pharmaceutical	A pharmaceutical that contains the same active ingredients as the original branded formulation. Generic pharmaceuticals are bioequivalent to the branded pharmaceutical with respect to pharmacokinetic and pharmacodynamic properties.
Graphic Appraisal Tool for Epidemiology (GATE)	Tool developed for the critical appraisal of clinical literature.
Incidence	The count of new cases of disease in a defined population during specified period of time
Incidence rate	The count of new cases of disease in a defined population within a specified period of time, divided by the number of persons (i.e. population) at risk (or person-time) of developing the disease during that time period
Incremental cost	The difference between the cost of an intervention and the cost of the comparator.
Marginal cost	The additional cost of one extra unit of product or treating one additional patient.
Markov model	A statistical representation of discrete, recurrent events over time in which the probability of transition from one to another depends on the current state.
Medsafe	New Zealand Medicines and Medical Devices Safety Authority
Medsafe datasheet	Prescribing information provided by the pharmaceutical supplier (and approved by Medsafe) on a specific medicine registered by Medsafe.
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.

Term	Definition
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
Official Information Act (OIA) 1982	An Act (i) to increase the availability of information to the people of New Zealand in order to (a) to enable their more effective participation in the making and administration of laws and policies and (b) to promoted the accountability of Ministers of the Crown & officials; (ii) to provide for proper access by each person to official information relating to that person; and (iii) to protect official information to the extent consistent with the public interest and the preservation of personal privacy.
Opportunity cost	Value of the alternative options that could be undertaken with the same resources.
Patent	The official document (also known as letters patent) setting out the Government's grant of an exclusive right to an inventor to manufacture, use, or sell an invention for a certain number of years.
Perspective	Viewpoint of analysis (e.g. funder, society, government, individual).
Pharmaceutical	Medicine, therapeutic medical device, or related product or related thing
Pharmaceutical Benefits Advisory Committee (PBAC)	Independent statutory body in Australia that makes recommendations and gives advice to the Minister about which drugs and medicinal preparations should be made available as pharmaceutical benefits.
Pharmaceutical Management Agency (PHARMAC)	New Zealand Crown Entity directly accountable to the Minister of Health for the management of the Pharmaceutical Schedule.
Pharmaceutical Schedule	List of pharmaceuticals available in the community and subsidised by the Government with funding from the Pharmaceutical Budget, and also some pharmaceuticals purchased by DHBs for use in their hospitals and includes those where PHARMAC has negotiated a national price.
Pharmacology and Therapeutic Advisory Committee (PTAC)	An expert committee of senior health practitioners which provides objective advice to PHARMAC on the benefits of pharmaceuticals.
Prescription for Pharmacoeconomic Analysis (PFPA)	The document that provides an overview of PHARMAC's cost-utility analysis methodology.

Term	Definition
Prevalence	The number of existing cases of disease in a defined population at a notional point in time
Prevalence rate	The number of existing cases of disease in a defined population at a notional point in time, divided by the number of persons in the population at that time
PYLL(80)	Potential Years of Life Lost before the age of 80. PYLL measures the time (in years) lost by a population due to premature death. This involves choosing an arbitrary limit to life, so that the duration of life lost due to each death is that potential limit minus the age at death. In the case of PYLL(80), the arbitrary age limit chosen is 80 years. Note that the subtraction is truncated, so that any deaths occurring after people attain that arbitrary age limit have a potential loss of life of zero years.
Quality-adjusted life years (QALY)	<p>A QALY ('quality adjusted life year') is a standard economic measure, which combines the effects of changes in the length and quality of life that result from treatment. Quality-adjusted life-years help compare gains in the quality of life with gains in the quantity (length) of life, in a simple and direct manner.</p> <p>Quality of life weightings (or utilities) are typically measured on a scale of 0 to 1, where 0 is equivalent to death and 1 to perfect health. These weights can then be summed over life expectancy in order to calculate the total number of QALYs.</p> <p>The difference in QALYs and overall costs gained between two treatments informs the relative cost-effectiveness of an intervention.</p>
Relative risk	Ratio of incidence of disease in exposed group divided by incidence of disease in non-exposed (control) group.
Relative Risk Increase (RRI)	Proportional increase in rates of events between the experimental group and control group.
Relative Risk Reduction (RRR)	The relative (not absolute) difference in events between two treatment groups, expressed as a proportion of the event rate in the untreated group. Similar to RRI, a RRR is therefore a proportional <u>decrease</u> in rates of events between the control and experimental group.
Sensitivity analysis	Process through which the robustness of an economic model is assessed by examining the changes in the result of the analysis when key variables are varied over a specified range.
Special Authority criteria	The Pharmaceutical is only eligible for Subsidy or additional Subsidy for a particular person if an application meeting the criteria specified in the Schedule has been approved, and the valid Special Authority number is present on the prescription.
Subsidy	Maximum amount paid by Government to a person entitled to receive payment from the Crown for the pharmaceutical (this may differ from the final cost paid by Government, depending on the nature of PHARMAC's contractual arrangements).

Term	Definition
Technology Assessment Report (TAR)	Documentation of the economic analysis (including cost-utility analysis).
Therapeutic Group Manager (TGM)	PHARMAC staff member responsible for managing PHARMAC's processes for pharmaceutical funding, within an assigned therapeutic group.
TreeAge	Decision analysis software used for modelling cost-effectiveness
Utility	Values of the strength of preferences for, or desirability of, a specific level of health status or a specific health outcome.
Value for money	Refers to whether the benefits of a pharmaceutical are significant enough to compensate for the higher cost.