Guidelines for preparing a submission to the PBAC

Version 5.0

Draft for public consultation

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# Abbreviations and acronyms

ARTG Australian Register of Therapeutic Goods

ATC Anatomical Therapeutic Chemical

CEA cost-effectiveness analysis

CUA cost-utility analysis

DES discrete event simulation

DHS Department of Human Services

DPMQ dispensed price for maximum quantity

DUSC Drug Utilisation Sub-Committee

HTA health technology assessment

ICER incremental cost-effectiveness ratio

MAUI multi-attribute utility instrument

MBS Medicare Benefits Schedule

MCID minimal clinically important difference

NIP National Immunisation Program

PBAC Pharmaceutical Benefits Advisory Committee

PBS Pharmaceutical Benefits Scheme

QALY quality-adjusted life year

QUM quality use of medicines

RPBS Repatriation Pharmaceutical Benefits Scheme

TGA Therapeutic Goods Administration

# About the guidelines

These *Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee* (PBAC Guidelines), version 5.0, provide practical information for the pharmaceutical industry for making a submission to the Pharmaceutical Benefits Advisory Committee (PBAC).

The PBAC Guidelines provide applicants with the information they need to prepare a submission to the PBAC for the public funding of a new medicine or medicinal product. The guidelines provide detailed instructions on what information is required by the PBAC to support a proposed new medicine for listing on the Schedule of Pharmaceutical Benefits, as part of the Pharmaceutical Benefits Scheme (PBS). Guidance is provided on the most appropriate form of clinical evidence and economic evaluation for specific submissions.

The guidelines reflect best practice as far as possible and seek to maximise the confidence of the PBAC in accepting the many inferences necessarily made in submissions for public funding. They are designed to facilitate the evaluation and translation of the best available comparative clinical evidence to the requested PBS listing, followed by the most appropriate economic evaluation. They also ensure that the predicted use of the medicine in clinical practice is aligned with a standardised Excel workbook to allow these analyses to be presented consistently across submissions. The approaches presented in the guidelines aim to minimise decision-maker uncertainty and promote comparability across submissions, wherever possible. However, while the guidelines present the currently preferred approach to the preparation of submissions to the PBAC, these are not prescriptive. Alternative approaches are permitted when adequately justified and supported by data.

Additional information is available on the PBS website [URL to be supplied] about:

* the role of the PBAC
* different types of submissions
* the rationale and basis that the PBAC uses for an economic evaluation
* the timeline for PBAC procedures

the PBAC process.

The information in these guidelines is also available as an online resource at the PBAC Guidelines website [URL to be provided]. A submission template, Excel workbook, and other forms and checklists to assist with preparation of a submission are provided on the ‘Downloads’ section of the website.

## Who uses the guidelines?

The PBAC considers submissions from industry sponsors of medicines and medicinal products, medical bodies, health professionals, and private individuals and their representatives. However, for new products or new indications, it is normally the sponsor or manufacturer who holds the data required for such a submission. Sponsors usually engage public health and health economics experts to review the academic literature and help the company prepare a submission to the PBAC. These guidelines are primarily to assist these people in their task.

Although the guidelines have been written for the pharmaceutical industry, they are also intended to help the PBAC assess submissions and provide information to other interested stakeholders, including clinical and patient groups, and the general community.

## Structure of a submission to the PBAC

A submission to the PBAC for listing a proposed new medicine on the PBS consists of five sections:

* **Section 1 – Context.** Describes the proposed medicine, its intended use on the PBS and rationale for funding, and the therapy likely to be most replaced by prescribers in practice (the ‘main comparator’).
* **Section 2 – Clinical evaluation.** Provides the best available evidence comparing the clinical performance of the proposed medicine with that of the main comparator (preferably from direct randomised trials, but if these are not available, from other suitable trials or studies). Concludes with a therapeutic conclusion stating whether the proposed medicine is superior, noninferior or inferior to the main comparator, taking account of any differences between the trial population and circumstances of use and those proposed for the listing (applicability).
* **Section 3 – Economic evaluation.** Presents an economic evaluation of the consequences of substituting the proposed medicine for the main comparator in the context of the listing requested.
* **Section 4 – Predicted use of the medicine in practice.** Includes the predicted extent of use of the medicine in the health system and financial analyses for the PBS/Repatriation Pharmaceutical Benefits Scheme (RPBS) and the Australian Government health budget.

**Section 5 – Other information (optional).** Includes information about quality use of medicines, antimicrobial resistance and other relevant information to support a submission.

All submissions should have an **executive summary** that clearly sets out the key aspects and issues presented in the main body of the submission. Additional information can be included as attachments or technical documents.

The most common – and preferred – approach to major submissions is an assessment of direct randomised trials to support a superior therapeutic conclusion (Section 2), modelling of these trial results to inform a cost-effectiveness analysis (Section 3), and an epidemiological analysis of the likely uptake and budget impact associated with the use of the medicine in clinical practice (Section 4).

Alternative submission approaches include an assessment of nonrandomised studies or an indirect comparison of randomised trials (to inform Section 2 when no direct randomised trials are available), a cost-minimisation approach to the economic evaluation (for Section 3 when there is a therapeutic conclusion of noninferiority), and a market-share analysis of medicine uptake and budgetary implications (to inform Section 4 when a cost-minimisation approach is taken, or to complement an epidemiological analysis).

## Structure of the PBAC Guidelines

The guidelines are presented in two parts.

**Part A** provides all of the information requests, and further information on content and presentation for the majority of submissions. The information is arranged in exactly the same sections and order as you will use for your submission (Sections 1–5).

Section 3 (Economic evaluation) has two alternative pathways:

* Section 3A – guidance for preparing Section 3 based on a cost-utility (preferred) or other cost-effectiveness analysis

Section 3B – guidance for preparing Section 3 based on a cost-minimisation approach.

**Part B** provides additional information requests for major submissions concerning the following types of products:

* fixed dose combination products
* nutritional products
* vaccine products

codependent technologies.

**Appendixes** provide additional background about the guidelines, and further information on various aspects of the submission.

### Section designations and cross-references within these guidelines

The following principles describe the scheme used for naming sections and subsections within the guidelines, and cross-referencing between parts and sections of the document:

* In Part A, the sections are labelled according to the main section to which they refer (ie 1–5). Each main section is made up of a series of subsections (eg Subsection 1.1, Subsection 2.1), which correspond to the subsections that should appear in a submission.
* In Part B, the product types are labelled P1, P2 etc, with subsections as Subsection P1.1, Subsection P1.2 etc.
* Appendixes are labelled Appendix 1, Appendix 2 etc, with subsections as A1.1, A1.2 etc (but only as required for cross-referencing).
* Cross-references to other sections and subsections within the same part are given as ‘see Section 3’ or ‘Subsection 3.6’ etc. However, cross-references across parts are given as ‘see Part B, Section P1’ etc.
* Tables are numbered consecutively within each subsection – for example, Table 2.1.1, Table 2.1.2 etc in Subsection 2.1. Tables are labelled consecutively within each appendix – for example, Table A2.1 (in Appendix 2).

Flowcharts are labelled by section as Flowchart 1.1, Flowchart 2.1 etc. Other figures are labelled consecutively within each main section of the guidelines, as for tables.

### Writing and style conventions used in the guidelines

The PBAC Guidelines include a series of requests for specific types of information. The aim is to provide an ordered series of reference points (information requests) against which the specific information presented in a submission can be assessed to ensure that the submission is complete.

The ‘default’ writing style for requests for information uses the imperative voice, as follows:

‘Describe the proposed course of treatment.’ ‘Justify the exclusion of the study.’

Readers should interpret these imperative statements as indicating what, in general, **should** be done.

Within each section, the main requests for information expected to be addressed by each major submission are highlighted as a checklist of ‘**information requests**’ in boxes. Further explanation for each request and any subsidiary requests are provided in the text following these boxes. The text headings therefore provide a template for your submission. Following these requests and heading template helps to improve the comparability of submissions considered by the PBAC, and hence the consistency of decision making.

In rare instances, the request box includes the separate heading ‘**information requirements**’. Information requirements include the word ‘**must**’ (eg the requirement to provide all relevant direct randomised trials when these are available). Failure to comply with these requirements is sufficient to render the submission unacceptable, and for the submission to be returned to the sponsor.

In some other instances, there is no basis to indicate a preference for one type of information over another. In these instances, options about what **could** be presented are usually given. The PBAC is generally indifferent about which option is presented, although the context of a particular submission might suggest the basis for expressing a preference. The submission should therefore explain the basis for selecting the information presented.

**Submissions should attempt to address all of the information requests in the PBAC Guidelines. Where an information request cannot be addressed, a clear explanation should be provided.** The PBAC will find a submission difficult to assess when information requests are not addressed and no justification has been provided for the omission.

## Key factors influencing decision making by the PBAC

PBAC decision making is primarily influenced by five quantitative factors:

* **Comparative cost‑effectiveness.** Presented as incremental cost-effectiveness ratios (including incremental cost-utility ratios) or a cost-minimisation approach. Includes a consideration of comparative costs, including the full spectrum of cost offsets (discussed in Section 3).
* **Comparative health** **gain**. Assessed in terms of both magnitude of effect and clinical importance of effect. Presented as both effectiveness and safety (discussed in Section 2), and the denominator of the incremental cost-effectiveness ratio or incremental cost-utility ratio (discussed in Section 3A).
* **Patient affordability in the absence of PBS** **subsidy**. Presented as cost per patient per course for acute or self-limited therapy, or cost per patient per year for chronic or continuing therapy (discussed in Section 3A).
* **Predicted use in practice and financial implications for the** **PBS**. Presented as the projected annual net cost to the PBS/RPBS (discussed in Subsection 4.4).

**Predicted use in practice and financial implications for the Australian Government health budget**. Presented as the projected annual net cost per year (Subsection 4.5).

Other less readily quantifiable factors that also influence PBAC decision making are:

* **Uncertainty** – because it reduces decisiveness and increases the likelihood that a risk-averse decision will be made.
* **Equity** – because implicit equity and ethical assumptions, such as age, or socioeconomic and geographical status, may vary for different submissions and need to be re-evaluated on a case-by-case basis.
* **Presence of effective alternatives** – because these help to determine the clinical need for the proposed medicine.
* **Severity of the medical condition treated** – because it relates to any restrictions requested in Subsection 1.4. The emphasis is on the nature and extent of disease as it is currently managed (Subsection 1.2).
* **Ability to target therapy with the proposed medicine precisely and effectively to patients likely to benefit most** – because the cost-effectiveness of the proposed medicine may be greatest in patients likely to benefit the most. Claims of benefits that are greater than the average result from an intention-to-treat analysis should be supported by appropriate trial evidence.

**Development of resistance** (for antimicrobial agents; see Subsection 5.2) – because the PBAC supports the prudent use principles for antimicrobials, and may consider specific advice on the likely extent of the development of resistance to a new antimicrobial agent and appropriate management strategies that might be applied through a PBS listing.

## Key points for preparing a PBAC submission

* Submissions consist of an executive summary, the main text of the submission, and additional information (attachments and technical documents).
* The preferred order for the presentation of information is the executive summary followed by five sections (1–5).
* Each section consists of subsections (1.1, 1.2 …; 2.1, 2.2 … etc), each of which has a series of **information requests** and/or **information requirements**.
* The order of information requests in these guidelines forms a template for your submission. Presenting information in any other order will reduce the PBAC’s ability to evaluate the submission.
* Information requests **should** be followed, if possible; information requirements **must** be followed.
* Use frequent, accurate cross-referencing between the executive summary, main text and other technical documents.
* Use succinct, plain English wherever possible (while maintaining scientific rigour).
* Justify any variations to the requested information.

If using a new analytical technique, present the base case using both the requested methods and the new technique for comparison.

## Associated documents

Documents that should be read in conjunction with the PBAC Guidelines include:

* *Manual of resource items and their associated costs for use in submissions to the Pharmaceutical Benefits Advisory Committee involving economic evaluation* ([PBAC Manual](http://www.pbs.gov.au/info/industry/useful-resources/manual), Department of Health, 2009). The PBAC Manual is revised periodically in the same way as the PBAC Guidelines.
* [Glossary of terms](http://www.pbs.gov.au/info/industry/useful-resources/glossary): key terms for preparing submissions to a health technology assessment (HTA) advisory committee for funding of a medicine, medical service or prosthesis (PBAC, Medical Services Advisory Committee and Prostheses List Advisory Committee, 2013).
* PBAC Guidelines glossary [*in preparation, URL to be provided*]
* [Sources of epidemiological data](http://www.pbs.gov.au/info/industry/useful-resources/sources) for use in generating utilisation estimates (Department of Health, 2011)
* [Highly Specialised Drugs Program criteria](http://www.pbs.gov.au/info/browse/section-100/s100-highly-specialised-drugs)

Standardised utilisation and cost model Excel workbook for PBAC submissions, which is available on the ‘Downloads’ section of the PBAC Guidelines website [URL to be supplied].

# Document table

| Document requested\* | Reference to submission appendix or attachment |
| --- | --- |
| **Regulatory** | [*add*] |
| Most recent version of the (draft) product information | [*add*] |
| Therapeutic Goods Administration (TGA) clinical evaluator’s report | [*add*] |
| TGA delegate’s overview | [*add*] |
| Advisory Committee on Prescription Medicines minutes | [*add*] |
| Australian Public Assessment Report (AusPAR) | [*add*] |
| TGA risk management plan (including Australian-specific appendix) | [*add*] |
| *The following are relevant if the medicine is NOT TGA registered:* | [*add*] |
| Food and Drug Administration assessment reports | [*add*] |
| European Medicines Agency assessment reports | [*add*] |
| **PBAC** | [*add*] |
| Full clinical study report(s) (CSR) of key evidence, including appendixes | [*add*] |
| Trial protocol(s) and amendments *(if not included in CSR)* | [*add*] |
| Publications of all relevant trials | [*add*] |
| Statistical appendix for analyses used in the submission, including any relevant code for statistical software used in the submission | [*add*] |
| Search strategy and literature yield from key bibliographic databases (an Endnote library file would be sufficient), including reasons for exclusion of studies that meet the criteria in Subsection 2.2 | [*add*] |
| Periodic safety update report and development safety update report | [*add*] |
| *If an economic model is presented*, the search strategy and literature yield related to the model structure or variables should be provided (an Endnote library file would be sufficient), including a list of the sources used in the model | [*add*] |
| Full reports of patient or clinician surveys that are used to inform the submission | [*add*] |
| The full economic model or cost-minimisation spreadsheet | [*add*] |
| Financial table workbook | [*add*] |
| **References** (that are additional to the trial publications supplied above) | [*add*] |
| **Other** | [*add*] |

\*Documents cannot be removed from this list. If a document is not available or not relevant, please explain why. Additional relevant documents can be included in the list.

# Part A – Guidelines for preparing the main body of a submission

# Submission executive summary

**INFORMATION REQUESTS**

**Provide an executive summary of no more than 12 pages.**

**Address each key aspect indicated in the checklist provided (see below).**

The executive summary will be included in the agenda papers for the PBAC meeting and is the sponsor’s primary method for communicating with each PBAC member. The executive summary should therefore lay out clearly the key aspects and issues presented in the main body of the submission. It provides the basis for subsequent summary documents relating to the submission, up to and including the public summary document. Checklist 1 lists what needs to be included in the executive summary of a major submission.

Checklist 1 Checklist for the executive summary of a major submission

| Component | Included? |
| --- | --- |
| The Australian approved name, brand name and marketing status of the proposed medicine | [Yes/No] |
| The principal pharmacological action of the proposed medicine | [Yes/No] |
| The form(s), strength(s), pack size(s), maximum quantity(ies), number(s) of repeats and dispensed price(s) requested for PBS listing | [Yes/No] |
| The proposed patient indication(s) and any requested restriction(s) for PBS listing, with a brief rationale | [Yes/No] |
| The inclusion of a diagnostic requirement in a requested restriction, if relevant | [Yes/No] |
| The recommended course of treatment | [Yes/No] |
| The main comparator(s) and the main expected changes in the clinical management algorithm | [Yes/No] |
| Whether the key clinical evidence in the submission comes from direct randomised trials, or from an analysis of two sets of randomised trials involving a common reference (eg placebo or other active therapy), or from nonrandomised studies | [Yes/No] |
| The main results of the clinical evaluation in terms of comparative effectiveness and comparative toxicity | [Yes/No] |
| The therapeutic conclusion that best describes the proposed medicine and therefore the type(s) of economic evaluation presented | [Yes/No] |
| The reasons for, and results of, any transformation studies to generate variables for incorporation into a modelled economic evaluation | [Yes/No] |
| The cost per patient per course (for acute therapy) or the cost per patient per year (for chronic therapy) | [Yes/No] |
| The other types of health care resources affected by the listing of the proposed medicine and the net present value of the overall incremental costs in the base case of the economic evaluation | [Yes/No] |
| The net present value of the overall incremental effectiveness in the base case of the economic evaluation | [Yes/No] |
| The base-case results of the economic evaluation, together with the results of the stepped approach outlined in Section 3, where presented | [Yes/No] |
| The main sources of uncertainty in the structure and variables in the economic evaluation, and the results of associated sensitivity analyses | [Yes/No] |
| The numbers of patients treated, the numbers of packs dispensed and the net costs to the PBS/RPBS of the proposed medicine in each year over five years | [Yes/No] |

# Section 1 Context

Section 1 includes details of the medicine and its proposed use.

## Introduction

Section 1 of a submission to the PBAC establishes the context for the submission.

A description is requested of:

* the clinical issue that the proposed medicine is expected to address (Subsection 1.1)
* the way the medicine will be used (Subsection 1.2)
* the regulatory status of the proposed medicine (Subsection 1.3)
* the proposed PBS listing (Subsection 1.4).

Flowchart 1.1 summarises the information requested for Section 1 of the submission.

*Notes: If the submission is requesting listings for multiple patient indications, present separate Sections 1 to 4 in separate submissions.*

*The singular term ‘comparator’ is used to denote one or more comparators. If there is more than one main comparator, provide all the requested information for each comparator.*

Flowchart 1.1 Overview of information requests for Section 1 of a submission to the PBAC

Section 1: Context
1.1 Clinical issue: What is the clinical claim addressed by this submission? Why should the PBS fund this medicine? Population, intervention comparator; rationale for PBS listing.
1.2 Clinical management algorithms: How will the proposed medicine change clinical management? Flowchart for proposed medicine; flowchart for current practice.
1.3 Regulatory process: What is the regulatory status of the proposed medicine? TGA approval status of proposed medicine; relevant overseas approval status (if not yet TGA approved).
1.4 Proposed PBS listing: What PBS listing are you applying for? Essential elements (name, form, strength, pack size, quantity, repeats etc), restrictions, monitoring requirements, main indication.
Go to Section 2: Clinical evaluation.

## 1.1 Clinical issue addressed by the submission

**INFORMATION REQUESTS**

**Summarise the clinical claim**

Tabulate the proposed population, intervention, comparator and outcomes for the proposed medicine, and present the overall clinical claim.

**Describe the population**

Describe the target Australian population that it is proposed would receive treatment for their disease or condition with the proposed medicine, and identify any relevant population subgroups.

**Describe the proposed intervention and comparator**

* Describe the pharmacological action, therapeutic class and biological plausibility of the proposed medicine.

Identify and justify the main comparator, describe any other relevant comparators (including future comparators), and tabulate key differences between the proposed medicine and the main comparator.

**Provide a brief rationale for PBS listing**

Describe the intended use of the proposed medicine in the target Australian population.

### Clinical claim

Tabulate the proposed population, intervention, comparator and outcome(s), and the overall clinical claim for the proposed medicine in Table 1.1.1.

Table 1.1.1 Components of the overall clinical claim addressed by the submission

| Component | Description | Example |
| --- | --- | --- |
| Population | Briefly state the target population | Patients with type 2 diabetes for whom adequate control with metformin or a sulfonylurea has not been achieved |
| Intervention | Briefly describe the intervention | [medicine XXX] 100 mg mane |
| Comparator | Briefly describe the comparator | [medicine YYY] 25 mg bd |
| Outcomes | Briefly state the critical patient-relevant outcomes | * Change in HbA1c from baseline measured at 6 months * Weight loss from baseline to 6 months * Hypoglycaemic events in 6 months |
| Clinical claim | State the clinical claim that the submission presents: In [population and health issue], [proposed medicine] is no worse than/as effective as/more effective than [main comparator] at improving/reducing [outcome(s)] | In people with type 2 diabetes for whom adequate control with metformin or a sulfonylurea has not been achieved, [medicine XXX] is more effective than [medicine YYY] at reducing HbA1c, and increasing weight loss after 6 months, although this results in more hypoglycaemic events |

### Population

#### Target Australian population

The target population is defined as the people with the specific disease or condition that will be treated with the medicine if it is listed as proposed.

Provide a brief overview of the disease or condition that will be treated by the proposed medicine. Include enough detail of diagnosis, symptoms, prognosis and other related issues to assist the assessment of the submission.

Describe the characteristics of the Australian population who would be treated with the proposed medicine, such as their age, sex, important comorbidities and disease-related characteristics. Sources of data should be provided, and should preferably include Australian datasets, or studies involving Australian participants. Indicate the incidence and prevalence of the disease or condition in Australia using data from a reputable source, such as those listed in ‘[Sources of epidemiological data for use in generating utilisation estimates](http://www.pbs.gov.au/info/industry/useful-resources/sources)’.

Where studies involving Australian participants are not available, discuss whether population or subgroup characteristics are likely to be representative of the Australian setting. Data should be presented as percentages and means with estimates of uncertainty (eg interquartile range, standard deviation and ranges), where possible.

#### Relevant subpopulations

If a specific population group (eg specific age group, sex, comorbidity) is to be targeted for treatment with the proposed medicine rather than the broader population, indicate whether the usual course of the disease – or the available treatment options for that subgroup – differs from that of the broader population. If the broader population is to be targeted, define any important subgroups for which there may be a different use of the proposed medicine, a different comparator or a different treatment effect.

### Intervention and comparator

#### Pharmacological action and therapeutic class of the proposed medicine

Present the therapeutic class, [Anatomical Therapeutic Chemical (ATC) classification](http://www.whocc.no/atcddd) and a description of the pharmacological action of the proposed medicine. Tabulating this information to enable a comparison of the proposed medicine with the nominated comparator would be helpful.

When discussing pharmacological action, ensure that adequate detail is provided to support the targeting of the group of patients described in the proposed listing. If the listing is a subgroup of a broader indication, it is particularly important that the mechanism of action for the particular subgroup is described, and contrasted with the complement for that subgroup.

#### Biological plausibility for the use of the proposed medicine in the intended population

Discuss the pharmacological, biological and clinical plausibility for targeting a subgroup, or state when evidence for any of these is unavailable.

#### Justification for the selection of the main comparator

The PBAC is required under s. 101(3A) of the *National Health Act 1953* to consider the effectiveness and cost of the proposed medicine compared with alternative therapies. When the proposed medicine is substantially more costly than an alternative therapy, the committee will not make a positive recommendation unless it is satisfied that the proposed medicine provides a significant improvement in efficacy and/or reduction in toxicity over the alternative therapy.

Where multiple alternative therapies could be used for the majority of patients, the PBAC cannot recommend a new medicine at a price that is substantially higher than the least expensive alternative medicine unless it is satisfied that the new medicine provides a significant improvement in efficacy and/or reduction in toxicity over that alternative medicine.

In situations where the proposed medicine has more than one alternative therapy and there are distinct groups of patients in whom one alternative therapy, but not the other(s), is appropriate, and those alternative therapies have different prices, then the new medicine’s price can reflect the proportions of the treated population in which the different alternative therapies are appropriate.

Within this context, the main comparator is defined as the therapy that prescribers would most likely replace with the proposed medicine in practice, should it be listed on the PBS. The identification of the therapy most likely to be replaced should be consistent with current Therapeutic Goods Administration (TGA) marketing authorisation and PBS listings for the appropriate patient indication and line of treatment. The main comparator should be consistent with the positioning of the proposed medicine in the intended clinical management algorithm, as presented in Subsection 1.2. Where the medicine most likely to be replaced is not PBS listed or TGA registered, state this and present evidence that it is widely used for the proposed indication.

In general, most comparators are identified in one of the following three categories:

* **Existing pharmacological analogues.** If the proposed medicine is in a therapeutic class for which pharmacological analogues are already listed, the main comparator is usually the analogue prescribed on the PBS for the largest number of patients for the same indication.
* **New therapeutic class.** If the proposed medicine is in a new therapeutic class, but there are other, widely used medicines listed for the proposed patient indication, the main comparator would usually be the medicine prescribed on the PBS to treat that indication for the largest number of patients.

**No currently listed medicine.** If the proposed medicine is for an indication for which there are no currently listed PBS medicines, or the proposed medicine will be used in addition to – rather than replace – a medicine, the main comparator would usually be standard medical management (this could include a nonlisted medicine, a surgical procedure, best supportive care or conservative management). In the absence of a PBS-listed medicine, clinical practice may be to use a medicine that is not PBS listed. In this circumstance, the medicine used in clinical practice may be the appropriate main comparator.

Where possible, the main comparator should be in a similar form to the proposed medicine (eg sustained-release tablets or oral pressurised inhalation); however, this criterion is secondary to the fundamental consideration of which therapy will be replaced in clinical practice.

If a PBS-listed comparator is perceived as having a substantial disadvantage compared with the proposed medicine (ie has a less favourable toxicity profile, is delivered in a less acceptable form or has substantially poorer therapeutic effectiveness), the proposed medicine may be used in a larger number of patients than the currently listed comparator. If there are differences between the currently listed comparator and the proposed medicine, discuss the effect on the number of patients that are likely to be treated. Present:

* a comparison of the proposed medicine with standard medical management (including watchful waiting)

a comparison of the proposed medicine with the nominated main comparator.

When this situation arises, the main comparator should be clearly and consistently defined both in the submission and in the supporting evidence base (ie direct randomised trials).

#### Multiple comparators

Where multiple comparators exist, the PBAC would prefer that all of those that are potentially relevant are included in the submission. Comparisons with multiple comparators may be less relevant when there is convincing evidence of therapeutic equivalence between these comparators.

The presentation of multiple comparators may be required in the following instances:

* when there is no clear market share for one particular comparator
* when it is likely that different comparators are used in different subpopulations of the proposed target population (eg according to disease severity)

when there is a substantial difference in the cost of a treatment course across the comparators.

Where multiple comparators with large disparities in cost are available, and these are equi-effective in the target population, sponsors should be prepared to provide both a comparison against the comparator with the greatest market share and a comparison against the most cost-effective comparator.

The submission should present a comparison against each comparator, rather than a comparison against a weighted or mixed comparator.

#### Future comparator(s)

If there is a reasonable expectation that a medicine will enter the Australian market in the near future for the proposed indication, this may be regarded as a supplementary comparator.

This could include therapies that are currently undergoing TGA registration, or that have recent or current submissions to the PBAC for a PBS listing.

#### Comparison of the proposed medicine and the main comparator

Tabulate evidence that highlights any differences between the proposed medicine and the main comparator (and supplementary comparator, if relevant) in Table 1.1.2. Where characteristics are the same, state this. Provide references to the sources of the data in table notes.

**Table 1.1.2 Comparison of the proposed medicine and the main comparator**

| Comparison | Description for the proposed medicine, main comparator and supplementary comparators (if applicable) |
| --- | --- |
| Course of treatmenta | [Describe the course of treatment for the proposed medicine and the course of treatment for the main comparator (and supplementary comparators, if applicable)] |
| Course of treatmenta for concomitant or subsequent medicines that are included in the economic evaluation | [Describe the course of treatment for concomitant or subsequent medicines for the proposed medicine and the main comparator (and supplementary comparators, if applicable)] |
| Proposed/approved TGA indications (and PBS restrictions, if applicable) | [Describe any differences in the indications or restrictions between the proposed medicine and the comparator] |
| Toxicities that may result in differences in use | [Describe any differences in toxicities between the proposed medicine and the comparator that may result in differences in use] |
| Any differences that may result in changes in patient compliance | [Describe any differences in formulation, pill burden, frequency of dosing etc between the proposed medicine and the comparator that may impact on patient compliance with the treatment course for the condition] |
| Evidence of a difference in time-dependent alteration of dose | [Describe where doses are likely to change over time for the proposed medicine and the comparator, particularly if this is likely to occur for one medicine and not another] |
| Any differences that may result in different populations using the medicine | [Describe any differences (eg mode of administration, metabolism pathways, number of pills) between the proposed medicine and the comparator that may result in different populations using the medicine] |
| Any differences that may result in growth in the market | [Describe differences in the medicines that may result in growth in the market if the proposed medicine is listed] |

**a** When describing a course of treatment, include the following information:

* dose and manner of administration
* dosing frequency per day or other appropriate time interval
* duration of course
* anticipated frequency of repeat courses of treatment.

For the proposed medicine, confirm that these details are consistent with those recommended in the relevant TGA-approved product information or, if this is not available at the time of finalising the submission, in the most recent draft product information, together with the most recent written recommendation(s) of the TGA delegate or Advisory Committee on Prescription Medicines, if available.

### Rationale for PBS listing

Provide a brief rationale for the proposed use of the new medicine in the target Australian population. Under the *National Health Act 1953*, the primary objective of the PBS is to improve health, so the PBAC primarily focuses on health outcomes. Briefly outline the expected impact of the proposed medicine in terms of patients’ health, health-related costs or cost offsets, and the impact on issues such as access or equity. **Limit your response to less than half a page.**

Details of nonhealth-related impacts of the proposed medicine should only be presented as supplementary analyses in Section 3 or discussed in Section 5.

## 1.2 Clinical management algorithms

**INFORMATION REQUESTS**

**Present clinical management algorithms for current practice and the proposed medicine**

Use a flowchart to show the current clinical practice for the disease or condition in the Australian target population, and clinical practice if the proposed medicine is listed.

**Compare the two algorithms**

Describe the changes to Australian practice that would be expected if the proposed medicine is listed.

**List other relevant therapies**

Identify all other therapies commonly used in the current clinical algorithm (PBS subsidised and non–PBS subsidised) and in the intended clinical algorithm (eg comparators, co-administered therapies and other medicines that are likely to be prescribed less often or more often).

### Clinical management algorithms for current Australian practice and the proposed medicine

Present a flowchart that depicts current management of the disease or condition in the target Australian population in the absence of the proposed listing of the new medicine, and a flowchart describing the eligible patients and the circumstances of use of the proposed medicine if the listing is implemented as requested. The two algorithms may be captured on a single flowchart, if appropriate.

The flowchart(s) should be informed by the following sources:

* a literature review of relevant published clinical management guidelines (preferred). The PBAC has a preference for independent, up-to-date evidence-based clinical practice guidelines developed for Australia or relevant to the Australian setting. Include a copy of the literature review and guidelines as an attachment to the submission

an expert panel and/or a well-designed survey (if current clinical management guidelines are not available). Present details of who the survey was sent to, who responded, and the survey questions and responses in an attachment to the submission. See Appendix 1 for further advice on expert panels and surveys.

Identify the following criteria and characteristics in the flowchart(s):

* all relevant diagnostic criteria and/or tests to determine the target population (including tests to exclude patients, or inform continuation criteria or stopping rules). Reference Medicare Benefits Schedule (MBS) items, where appropriate, and state clearly when a test is not currently reimbursed through Medicare
* important characteristics of patients (eg risk factors, severity of disease) and circumstances of use of the medicine
* the prescriber, and whether any special training requirements or specialised facilities are required. Provide a justification for these below the algorithm
* all treatments, including any required previous therapies or required co-administered therapies, and any consequences for subsequent therapy options. Give particular consideration to whether a proposed medicine is likely to replace a currently available option, or whether it is likely to displace that option to a later line of therapy

all streams of health care resource provision, both before and after the point in the algorithm that the proposed medicine is introduced.

It is important that the clinical management algorithms adequately capture the steps (diagnostic and therapeutic) that define the population that would be eligible for treatment, as well as all relevant downstream changes to patient management (such as changes to the use of other medicines). In many cases, an appropriate approach is to extend the clinical algorithm to the expected end of the disease process, capturing all the treatment options. If the clinical algorithm for the proposed medicine and the comparator are expected to be the same after a particular point in the algorithm, the algorithm may be truncated if the submission clearly indicates that clinical management is identical after that point.

It may not be appropriate to capture all relevant details within the flowchart(s). When this is the case, provide a description or justification for the details excluded from the clinical management algorithm.

The population, and the use of the proposed medicine and the main comparator(s) in the clinical management algorithm should be consistent with those described in Subsection 1.1.

The submission should provide a robust justification for the positioning of the proposed medicine in the clinical management algorithm from the options available, and explain why alternative positions for the proposed medicine in the clinical management algorithm are inappropriate.

#### Variation of a current PBS restriction

Submissions can seek a variation of the current PBS listing of a proposed medicine. If the variation represents a new clinical indication, this should be treated in the same way as if the submission were requesting a listing of a new medicine. The clinical management algorithm should represent only patients with the new indication.

If other variations to the PBS restriction are requested, the proposed clinical management algorithm should reflect the change in practice that would occur if the restriction were to change. Such variations could include:

* relaxation or removal of one or more restriction criteria
* relaxation or removal of one or more continuation criteria

request to change the listing to permit patients to access treatment earlier in the management algorithm (ie moving from last line to an earlier line of therapy).

For any proposed change to the listing, the clinical management algorithm should be restricted to patients whose management will change. Patients who receive the same treatment regardless of the proposed change to the listing should be clearly separated, or excluded from the algorithm.

### Comparison of the two algorithms

Summarise the differences between the current and proposed clinical management, as depicted in the algorithm(s). Any changes in the pattern of health care delivery should also be mentioned.

### Other relevant therapies

Identify those medicines and other health care interventions that would be prescribed less or more often as a consequence of listing the proposed medicine.

If relevant therapies are identified as being prescribed more or less often but are excluded from the economic evaluation or financial analyses, provide justification for this exclusion.

## 1.3 Regulatory process

**INFORMATION REQUESTS**

**Tabulate the TGA regulatory milestones for the proposed medicine**

State the date of TGA approval or indicate the progress of the application for registration.

**List the TGA-approved indications**

Provide details of the indication, the dose and method of administration, product information, any concerns raised by the TGA, the risk management plan, and any conditions of registration.

**Indicate whether overseas regulatory approval has been obtained**

Provide information on the overseas registration status of the medicine.

### TGA approval

All new pharmaceutical products must be registered on the Australian Register of Therapeutic Goods (ARTG) by the TGA before being marketed in Australia.

Complete the information requested in Table 1.3.1 and provide relevant documents with the submission. For submissions undergoing parallel processing, provide regulatory documents in Table 1.3.1 to the Pharmaceutical Evaluation Branch as they become available.

Table 1.3.1 Progress of TGA application for registration of proposed medicine

| Regulatory milestone | Date scheduled/received/expected | Reference to attachment |
| --- | --- | --- |
| TGA registration | [insert date] | [insert reference] |
| *If not yet TGA registered:* | [insert date] | [insert reference] |
| * Lodgment of TGA dossier | [insert date] | [insert reference] |
| * TGA clinical evaluator’s report | [insert date] | [insert reference] |
| * TGA delegate’s overview | [insert date] | [insert reference] |
| * ACPM meeting | [insert date] | [insert reference] |
| * Delegate’s decision | [insert date] | [insert reference] |

ACPM = Advisory Committee on Prescription Medicines

### TGA-approved indications

State the indication(s) approved by the TGA. These are identified in the ‘Indications’ section of the product information and are listed in the ARTG.

If TGA approval has not been finalised, provide the proposed indication and the draft product information. These should be consistent with any reports or advice received in the regulatory process to date. Clearly state when the TGA evaluator’s report, delegate’s overview or ACPM advice would impact on the proposed indication or product information.

### Overseas approval status

Provide information on the overseas registration status of the medicine, including registration conditions or boxed warnings that may apply. Provide the unredacted registration reports from the Food and Drug Administration and/or the European Medicines Agency. If the final reports are unavailable, provide the most recent interim reports.

## 1.4 Proposed PBS listing

**INFORMATION REQUESTS**

**List the essential elements of the requested PBS listing**

State the essential elements of the requested listing, including the proposed medicine’s name, restriction, manner of administration, form, maximum quantity, number of repeats, dispensed price, proprietary name and manufacturer.

**Define and justify any restriction(s) in the requested PBS listing**

State the type of restriction and suggested wording. Describe the intention of the requested restriction, discuss the alternative options that were considered, and justify any grandfathering provisions.

**Justify any continuation criteria**

If continuation criteria are proposed, justify their inclusion.

**Describe any assessment or monitoring requirements**

If the requested restriction requires a diagnostic test, indicate whether the test is available and subsidised on the MBS for the intended purpose of the restriction; if not, address the codependency issues that arise (Part B, P4).

**Identify any multiple listing scenarios**

Indicate whether multiple listing scenarios are presented.

**Identify the proposed patient indication(s)**

If an unrestricted listing is requested, identify the proposed patient indication(s).

**Describe any special pricing arrangements**

Explain any proposed special pricing arrangements.

### Essential elements of the requested listing

Complete Table 1.4.1 for the requested listing. If any special pricing arrangements are proposed, complete Table 1.4.1 showing both the published price and the special pricing arrangement (a description of the special pricing arrangement should be provided later in this subsection).

Table 1.4.1 Essential elements of the requested listing

| Name, restriction, manner of administration, form | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Dispensed price for maximum quantity | Proprietary name and manufacturer |
| --- | --- | --- | --- | --- | --- |
| [Australian Approved Name, form(s), strength(s)] | [n] | [n] | [n] | [$] | [Brand name, manufacturer] |

#### Maximum quantities and number of repeats

Demonstrate consistency between the maximum quantities and dosage recommendations using the following principles:

* For an acute-use therapy, demonstrate that the requested maximum quantity is consistent with the likely use of the proposed medicine for a normal course of therapy (in accordance with any clinical practice guidelines identified in Subsection 1.2).

For a chronic-use therapy, demonstrate that the maximum quantity is consistent with the likely use of the proposed medicine for one month of therapy between each dispensing by the pharmacist, and that the number of repeats (usually) permits six months of therapy between each prescription by the prescriber.

Justify proposed deviations from this general approach – for example, to minimise wastage or to facilitate intermittent therapy, as appropriate in particular circumstances (see also Subsection 1.1).

Demonstrate that the requested maximum quantities and the requested numbers of any repeats are consistent with the TGA-approved dosage recommendations (see also Subsection 1.3).

### Requested restriction(s)

Medicines can be listed on the PBS General Schedule (section 85) either as unrestricted benefits (which have no restrictions on therapeutic use for the purposes of subsidy) or as benefits that have restrictions on therapeutic use for the purposes of subsidy. There are different levels of restriction, including:

* ‘Restricted’ benefits, which can only be prescribed for specific therapeutic use

‘Authority Required (streamlined)’ or ‘Authority Required’ benefits, which have restrictions on use, and require authorisation before prescribing by either a streamlined authority code or approval from the Australian Government Department of Human Services or Department of Veterans’ Affairs.

Medicines can also be listed under a section 100 arrangement that provides for different distribution arrangements (such as distribution of highly specialised drugs from hospital outpatient departments).

#### Restricted benefits and Authority Required listings

A submission requesting a Restricted benefit or Authority Required listing is specifically seeking PBAC endorsement of use within the requested restriction and to exclude use beyond that restriction. The wording of the restriction should identify the use that **should** eventuate and be consistent with the TGA-approved indications (and other sections of the product information). The PBAC recognises that restrictions may increase the administrative burden associated with prescribing and would prefer, where a restriction is required, that the complexity of the criteria be weighed against the risk and consequences of use outside the target population.

The PBAC would consider the appropriateness of a request for an Authority Required benefit on initial listing against the following two key principles:

* There is potential for use in a population in which the proposed medicine is not cost-effective or where the PBAC has not yet determined it to be cost-effective.

There is potential for a high cost per patient or high total opportunity cost to the health system.

In addition to the principles above, submissions may need to consider other important factors for an Authority Required listing. These are:

* quality use of medicine factors
* safety factors

administrative burden.

If a Restricted benefit or Authority Required listing is considered appropriate, address the following:

* Describe the intention of the requested restriction.
* When formulating the requested restriction, discuss alternative options that would be acceptable to the sponsor. It may be useful for the PBAC to consider these in order to arrive at the simplest but most effective restriction to administer.
* Discuss the trade-offs between the clinical preference for a simple restriction and a complex restriction to limit the use of the proposed medicine to the target population.

Justify the requested restriction level, method of applying the restriction and criteria proposed in the restriction.

Complete the restriction template from the Department of Health, available at [*link to be inserted when this document becomes available*]. This document provides guidance on how to formulate the restriction wording and justify restriction criteria.

#### Grandfathering

An Authority Required restriction might need to include ‘grandfathering’ provisions for individuals who commence therapy before the requested PBS listing is implemented. When this is likely to be the case, the submission should address the following:

* Provide details of the patients (such as estimated numbers, disease characteristics and information relevant to the requested restriction) currently receiving the proposed medicine and the scheme(s) through which the medicine is available. Where available, provide the eligibility criteria for provision of the medicine through the scheme.
* Explain why patients currently receiving the proposed medicine would not be able to access the proposed medicine according to the requested restriction (where patients would be eligible, no grandfathering clause is required).
* Provide a justification for a grandfathering provision that would enable patients currently receiving the proposed medicine to access it through the PBS. The justification may include
  + evidence that patients cannot cease treatment to ascertain eligibility
  + evidence that patients would have been eligible according to the requested restriction at the time of initiating the medicine
  + any other relevant factors.

Where a grandfathering provision is requested, the estimated number of patients currently receiving the proposed medicine should be clearly identified and counted in Section 4 of the submission.

#### Other issues

If a requested restriction is likely to have implications for the restriction of another PBS-listed medicine (eg its initiation or continuation criteria), discuss these implications.

A number of factors may prompt the PBAC to review the requirement for a pharmaceutical benefit to have an Authority Required listing (eg if the PBAC is considering an application for an additional product for PBS subsidy for the same indication/restriction as an existing listing).

### Justification for continuation criteria

Continuation criteria should only be applied when eligibility criteria alone cannot adequately identify patients for whom use of the proposed medicine would be acceptably cost-effective at the price requested. It is preferable that medicines are cost-effective for the treatment of all patients who continue to receive net benefit from treatment.

Justify the need for continuation criteria and present the proposed wording in a separate restriction for continuing treatment (identified in the ‘Treatment phase’ of the restriction template {*link to be inserted when this document becomes available*}). Each element in the continuation criteria should be justified on clinical grounds, be unambiguous, use objective rather than subjective measures, and explain the thresholds applied with any tests. State whether the continuation criteria are consistent with the clinical evidence presented in Section 2.

Continuation criteria are unlikely to be suitable if there is evidence that breaks in therapy are likely to cause rebound, increase risks of toxicity associated with subsequent recommencement, or reduce the likelihood of benefit from subsequent recommencement. Continuation criteria may not be acceptable where the criteria involve subjective assessments or are likely to result in prescribers seeking to maintain subsidy despite the continuation rules.

Present a risk assessment of the proposed continuation criteria.

### Assessment and monitoring requirements

**Note:** This section may be revised to be consistent with the ‘Codependent technologies’ product type (Part B, P4), which is a section currently being drafted and will be released for public consultation after consultation on the full guideline has commenced.

Indicate whether any assessments or monitoring are required to demonstrate patient eligibility for the proposed medicine. If so, determine what tests are available to make these assessments and whether they are subsidised via the MBS or through another ongoing subsidised arrangement. If listed on the MBS, supply the details of the relevant MBS item. If such a test is not readily or equitably accessible, or has not been assessed for its performance in detecting or monitoring the biomarker, address the codependency issues that arise in the form of an integrated submission (Part B, P4).

If the requisite diagnostic or monitoring test has been assessed for performance and is MBS listed, there are still implications associated with its use in various sections of the submission:

* The implications of misclassification arising from both false positive and false negative tests and assessments should be considered, because these can affect the effectiveness of treatment and the incremental cost-effectiveness of the proposed medicine. Poor test performance can also affect the numbers of treated patients. Information on the performance of relevant MBS-listed tests should be provided in Section 2 of the submission, and inform the economic evaluation (Section 3) and predicted use of the medicine in practice (Section 4).
* If resource use for assessments (eg a diagnostic test or the time to conduct a diagnostic questionnaire) is expected to change as a result of implementing the requested restriction, the costs associated with these changes should be included in the economic evaluation (Section 3) and inform the budgetary considerations for predicted use of the medicine in practice (Section 4). For example, the resources might not be provided routinely in current practice, but would need to be provided to demonstrate eligibility for a requested restriction.

If the assessment involves any risk of harm to the individuals examined (eg by requiring a biopsy), the associated health impairments should be discussed and quantified in Section 2, and the associated provision of any further resources should also be included in the economic evaluation (Section 3).

### Multiple listing scenarios

The clinical management algorithm for the requested restriction specifies the preferred listing scenario for the proposed medicine. However, as part of justifying the requested restriction in response to Subsection 1.4, more than one listing scenario might have been canvassed as being appropriate for PBAC consideration.

If alternative listing scenarios have been proposed, ensure that these scenarios are examined in alternative analyses presented in Sections 3 and 4. The preferred approach would be to present a single model that is capable of presenting multiple scenarios, rather than separate models with different structures.

### Proposed patient indication(s)

The proposed patient indications should be consistent with the (proposed) TGA-approved indications listed in Subsection 1.3, and the population and treatment details described in Subsection 1.1. The proposed patient indication is the indication that is likely to account for the largest proportion of patients treated (as identified in Section 4). If there is no clear ‘main’ indication, the submission should repeat Sections 1 to 4 for each indication, in separate submissions. If a sponsor is in doubt, seek advice from the Pharmaceutical Evaluation Branch.

For an Unrestricted listing, there is no mechanism for the PBS to reinforce consistency between the TGA-approved indications, or to minimise use in indications outside the proposed patient indication. Therefore, the proposed patient indication should be defined as what would eventuate in the absence of a Restricted benefit.

### Special pricing arrangements

Provide details of any special pricing arrangements. Ensure that Table 1.4.1 has been completed to show both the proposed published price and the price associated with any special pricing arrangements.

# Section 2 Clinical evaluation

Section 2 involves providing a systematic review of the clinical evidence.

## Introduction

In Section 2, the submission should identify the requested listing and present the best available clinical evidence to support it; that is, the evidence should describe the effectiveness and safety of the medicine that is intended to treat the proposed patient indication (see Subsection 1.4).

Section 2 has four components:

* a systematic search of the literature to identify relevant clinical trials or studies
* analysis and interpretation of the findings from each included trial, including trial-based estimates of the size of the treatment effect associated with the new medicine (or new use of the medicine) relative to the nominated comparator(s); factors that may influence an assessment of the credibility (internal validity) of the findings are also presented
* analyses (such as indirect comparisons) that are used to estimate the comparative treatment effect and safety of the new medicine (or new use of the medicine) in the absence of direct randomised trials. These analyses are presented in the context of a broader assessment of the quality of the evidence base

an assessment of the applicability of the presented evidence to the Australian setting.

The PBAC considers all levels of evidence, although it has a strong preference for clinical and economic evaluations that are based on direct randomised trials. However, the PBAC recognises that direct randomised trials are not always available, and it will continue to consider all levels of evidence.

The search process described in Subsection 2.1 requests that submissions first search for randomised trials that compare the proposed medicine with the main comparator. If no direct randomised comparisons are located, a second search is requested for randomised trials that would enable an indirect comparison. If no indirect comparison is possible, a third search for nonrandomised studies is requested.

This approach is a pragmatic one. While direct randomised trials are typically less prone to bias than indirect comparisons or nonrandomised studies, it is not always true that indirect comparisons are less prone to bias than well-conducted nonrandomised studies. In some circumstances, the submission may wish to present a well-conducted nonrandomised study alongside an indirect comparison of randomised trials. The approach taken in the submission should be justified.

Flowchart 2.1 gives an overview of all the information requested for inclusion in Section 2.

**Note:** Unless otherwise specified, in the remainder of these guidelines, the term ‘trial’ includes both randomised trials (preferred) and nonrandomised studies.

Flowchart 2.1 Overview of information requests for Section 2 of a submission to the PBAC

Section 2: Clinical evaluation
2.1 Literature search: How was the literature searched? Specify search methods (key terms, databases searched, search criteria for most relevant trials).
2.2 Relevant trials: What trials were identified? How were they used in the submission? PRISMA flowchart, provide a master list of included trials, justify exclusions, describe how the trials were used to support the clinical claim.
2.3 Trial design and execution: How well were the included trials done? Identify risk of bias criteria for each included trial and the quality of any included meta-analyses (internal validity).
2.4 Trial characteristics: What did the trials measure? Describe trial protocols and methods, including participants, treatment details and outcomes studied.
2.5 Trial results: whole trial population: What did the trials show? Present results for the trial population(s).
2.6 Trial results: subgroups and additional analyses: What further analyses were done and what did they show? Describe submission-specific analyses (subgroup analyses, meta-analyses, indirect comparisons, adjustment for treatment switching), present results.
2.7 Applicability of trial evidence: Do the trials reflect the Australian target population and circumstances of use? Effectiveness in Australian target population, extended assessment of comparative harms.
2.8 Interpretation of clinical evidence: How does the proposed medicine compare with the comparator? Compare the benefits and harms for the proposed medicine and the comparator; therapeutic conclusion, justification of economic evaluation.
Therapeutic conclusion can be either superior or noninferior.
Go to Section 3 Economic evaluation.

## 2.1 Literature search methods

**INFORMATION REQUESTS**

**Define the criteria used to search for the most relevant evidence**

Detail the search criteria used to retrieve all relevant direct randomised trials, other randomised trials and nonrandomised studies, as well as relevant systematic reviews and meta-analyses.

**Tabulate the search terms**

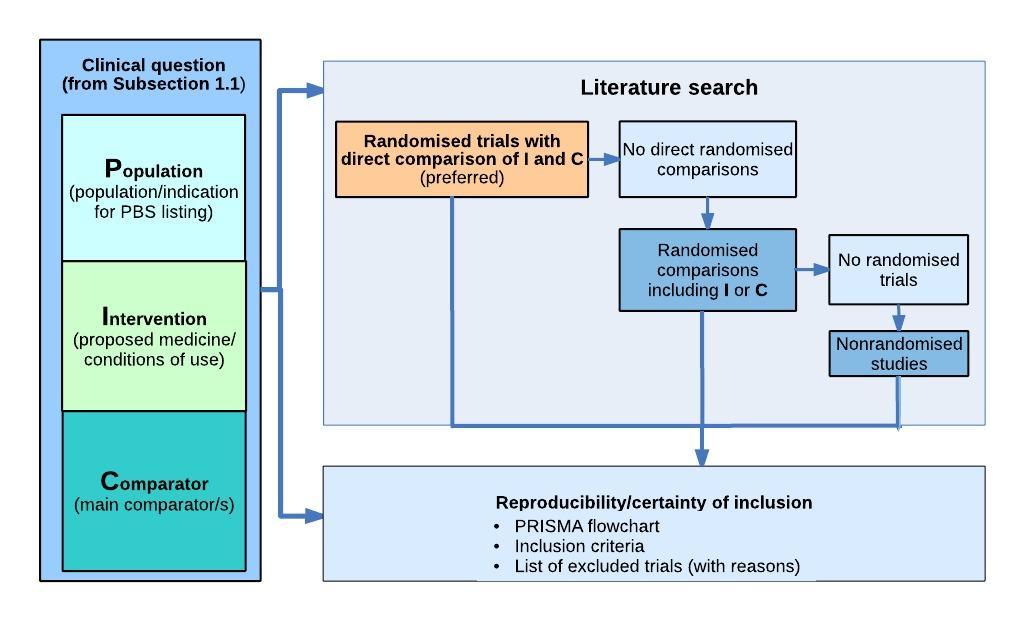
Include the search terms based on the intervention and, if required, population identified in Subsection 1.1.

**Document the search strategy**

Detail the databases searched, search strings used, other sources and dates for the literature searches.

Subsection 2.1 details the search methods that ensure that all relevant randomised trials (or nonrandomised studies) have been included in the clinical evaluation. An overview of the approach is shown in Flowchart 2.2.

Flowchart 2.2 Selection of trials for inclusion in the clinical evaluation



### Search criteria

#### Randomised trials

The primary objective of the literature search is to locate all randomised trials that, for the proposed patient indication, compare the proposed medicine directly with the main comparator for the target Australian population or a population that overlaps with the target Australian population.

Search filters should initially be set to include only randomised trials, as follows:

1. the trial includes a randomisation procedure in its design (use [Cochrane Highly Sensitive Search Strategies](http://handbook.cochrane.org/chapter_6/6_4_11_1_the_cochrane_highly_sensitive_search_strategies_for.htm))
2. the trial contains the proposed medicine (see Table 2.1.1)

the trial recruits participants with characteristics that overlap with those of the target population (see Table 2.1.1; only apply this criterion if the medicine is listed for multiple indications, to avoid excluding potentially relevant trials).

Of these criteria, only (c) requires an element of judgment. If there is any uncertainty about whether to include or exclude a randomised trial, it is usually wiser to include it.

List all randomised trials containing the proposed medicine. If relevant randomised trials are located that directly compare the proposed medicine with the main comparator, trials that compare the medicine with an alternative comparator can be excluded in Subsection 2.2.

If direct randomised trials comparing the proposed medicine with the main comparator are not identified, the search should be performed again, replacing criterion (b) with the main comparator (ie to identify evidence on the main comparator). Present both search strategies (for the proposed medicine and for the main comparator). In this case, the approach taken in the submission would be an indirect comparison of randomised trials.

#### Nonrandomised studies

If neither direct randomised trials nor other randomised trials suitable for an indirect comparison are retrieved, the original search for the proposed medicine should be broadened to identify all nonrandomised studies of the proposed medicine, preferably compared with the main comparator, that recruited participants whose characteristics overlap with the target population.

If the submission is based on nonrandomised studies, present both the search strategy for randomised trials and the search strategy for nonrandomised studies in Table 2.1.1 (detail can be provided in attachments).

#### Systematic reviews and meta-analyses

Separately identify any relevant systematic reviews and meta-analyses of randomised trials.

### Search terms

Use Table 2.1.1 to tabulate search terms based on the intervention and, if required, population identified in Subsection 1.1.

Table 2.1.1 Search terms for the literature review

| Category | Description | Search terms |
| --- | --- | --- |
| Study design | [insert description of category] | [eg Cochrane Highly Sensitive Search Strategies for identifying randomised trials in MEDLINE, or MeSH and text word terms for nonrandomised study designs] |
| Population | [insert description of category] | [Include MeSH terms, text words and synonyms for the target population/disease/condition] |
| Intervention | [insert description of category] | [Include known proprietary and nonproprietary names, MeSH terms and developmental/provisional medicine names] |

The search terms for population should be broad and may only need to be applied if the proposed medicine is used for multiple indications. The search strategy should not include terms for the comparator (unless a search is conducted for trials suitable for an indirect comparison; see Subsection 2.2) or for trial outcomes. Trials that are identified during the search that do not contain a comparison with the most appropriate comparator, or that do not report on an appropriate outcome, may be excluded in Subsection 2.2.

### Search strategy

Describe the methods used to locate all relevant direct randomised trials, and/or other randomised trials or nonrandomised studies. The search should involve at least these four approaches:

* a search of the published literature
* a search of registers of randomised trials
* an examination of the dossier seeking marketing approval submitted to the TGA, supplemented by checks with the sponsor’s head office and subsidiaries of the company (and any other original sponsor or colicensed companies) for any further randomised trials (which may be unpublished)

manual checking of reference lists of all relevant articles that are obtained.

The methods used to search the published literature are key to assessing the completeness of the overall search. Tabulate the characteristics of the search strategy as shown in Table 2.1.2.

The methodological standards for the conduct of new Cochrane Intervention Reviews are an appropriate source of guidance for performing a high-quality systematic literature search;1 however, where the approach recommended in the Cochrane standards differs from that presented below, these guidelines should take precedence.

Provide a complete electronic search strategy for PubMed in an attachment to the submission.

Table 2.1.2 Record of search strategies

| Source | Date searched | Date span of search | Details of search |
| --- | --- | --- | --- |
| MEDLINE (via PubMed) | [insert date] | [insert date] | State where the complete search strategy (search terms, indexing terms, filters, Boolean operators) has been provided in the submission |
| EMBASE (eg Embase.com) | [insert date] | [insert date] | State any key differences from the complete search strategy provided for the PubMed search |
| Cochrane Librarya | [insert date] | [insert date] | State any key differences from the complete search strategy provided for the PubMed search |
| ClinicalTrials.gov | [insert date] | [insert date] | State any key differences from the complete search strategy provided for the PubMed search |
| International Clinical Trials Registry Platformb | [insert date] | [insert date] | State any key differences from the complete search strategy provided for the PubMed search |
| Australian Clinical Trials Registry | [insert date] | [insert date] | State any key differences from the complete search strategy provided for the PubMed search |
| Internal registries | [insert date] | [insert date] | na |
| Other (state other sourcesc) | [insert date] | [insert date] | na |

**a** including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and the Health Technology Assessment database  
**b** [International Clinical Trials Registry Platform](http://www.who.int/ictrp/en)  
c Report on the details of supplementary searches, including manual checking of the references in retrieved papers, searches of the TGA dossier and searches of grey literature.

## 2.2 Identify relevant trials

**INFORMATION REQUESTS**

**Present search results using an adapted PRISMA flowchart**

Present the results of all the literature searches, including trials identified from the literature search, marketing dossier and other sources, using the adapted PRISMA flowchart provided.

**Annotate search results**

Indicate which trials were included in, or excluded from, the submission. Denote the reason for exclusion using a PRISMA code.

**Create a master list of included trials**

Collate all reports of each included trial to create a master list, and allocate an identification code for each trial to be used throughout the submission, for consistency.

**Justify selection of trials for an indirect comparison (if required)**

Identify any trials used in an indirect comparison, and justify the exclusion of any trials.

**Describe how the data were generated to support the clinical claim**

Provide a brief statement of how the included trials were used to support the clinical claim.

**Attach copies of included trials**

Include copies (or sufficient details) of all trials included in the submission as attachments, and identify their location in the document table in Section 1.

### Search results

From the literature searches reported in Subsection 2.1, complete a PRISMA flowchart (Figure 2.2.1) to indicate the number of papers screened at each stage of study selection.

**Figure 2.2.1 PRISMA format for presenting initial search results**

The PRISMA flowchart follows these steps:
Records identified through searching databases = [add number]. Search strategy and databases are provided in Attachment (x).
Records excluded on the basis of title/abstract screening: (A) Not randomised = [add number]; (B) Incorrect intervention = [add number]; (C) Not PBS population = [add number]; (D) Wrong comparator = [add number]. Total excluded = [add number]. Records not able to be retrieved = [add number].
Full-text articles assessed for eligibility = [add number].
Studies identified from other sources: experts = [add number], searching reference lists = [add number], internal databases = [add number], TGA dossier = [add number], other = [add number].
Articles excluded according to selection criteria: (A) Not randomised = [add number]; (B) Incorrect intervention = [add number]; (C) Not PBS population = [add number]; (D) Wrong comparator = [add number]. Total excluded = [add number].
Publications meeting selection criteria = [add number].
Articles excluded for other reasons: (E) Irrelevant dose; (F) Other (state; (G) Other (state). Total excluded = [add number]. Full list of trials and reasons for exclusion provided in Attachment (y).
Publications included in the submission = [add number]. These publications represent (n) studies. Table (z) lists all included studies and the associated publications.

The study selection process should clearly identify those trials to be excluded for the following reasons:

1. not a randomised trial (not relevant when the search is repeated to find nonrandomised studies)
2. incorrect intervention (such as when the intervention is used in combination with another medicine that is outside the use described in the requested restriction)
3. does not include the PBS population (not enough patients are enrolled that can be extracted from the trial who would be eligible for the proposed medicine according to the requested restriction or relevant to the proposed patient indication)

not compared with the main comparator as identified in Subsection 1.1 (this is not relevant for submissions based on indirect comparisons of randomised trials via a common reference arm).

Where multiple reasons for exclusion exist, excluding on the basis of an incorrect comparator should be done last.

The adapted PRISMA flowchart has a three-stage process for study selection, where studies are excluded:

1. on the basis of title and abstract (applying the selection criteria above), or denote when the article cannot be retrieved
2. following the retrieval of full-text articles (applying the selection criteria above)
3. on the basis of clearly specified reasons other than the selection criteria above.

Direct randomised trials that are identified and included will form the basis of the submission.

If no direct randomised trials are identified that compare the proposed medicine with the nominated comparator, present PRISMA flowcharts separately for the proposed medicine and for the main comparator (without excluding studies on the basis of comparator), to enable an indirect comparison of randomised trials. Additional searches may be required to populate more complex networks. Describe the searches and justify the approach. Do not exclude trials on the basis of poor exchangeability at this point. Information on how to present included studies for an indirect comparison of randomised trials is provided in ‘[Further selection of trials for an indirect comparison](#label=Further%20selection%20of%20trials%20for%20an%20indirect%20comparison&name=DocumentView&context=CurrentDocumentID/76,CurrentProjectID/1,CurrentHeadingID/1671)‘.

If no randomised trials are identified that would enable an indirect comparison of the proposed medicine and the nominated comparator(s), present a third PRISMA flowchart depicting screening for nonrandomised studies. If the primary reason for not conducting an indirect comparison of randomised trials is the lack of a common reference arm, consider using statistical methods to compare the intervention with the comparator using a matching-adjusted indirect comparison2,3,4 or a simulated treatment comparison.4,5 If this approach is taken, a search for nonrandomised studies should still be undertaken and relevant studies included in the submission.

### Annotated search results

Indicate which trials were included in, or excluded from, the submission. Denote reasons for exclusion using the appropriate letter defined in the PRISMA flowchart. For example, (A) would indicate that the study was excluded because it was not randomised, and (D) would indicate that the study was excluded because the proposed medicine was compared with an irrelevant comparator.

### Master list of relevant trials

Prepare a master list of all the included trials and relevant systematic reviews or meta-analyses.

Ensure that the list is complete to satisfactorily address publication bias, duplication bias and outcomes reporting bias. The Pharmaceutical Evaluation Branch will run an independent literature search, and if this search retrieves relevant trials that were not listed in the submission, processing of the submission will stop until the matter has been resolved.

Table 2.2.1 provides a suggested format for presentation of a master list of all the trials included in the submission.

Table 2.2.1 Trials (and associated reports) presented in the submission

| Trial | Reports |
| --- | --- |
| Unique identifier (ID) of trial used in submission | * Internal study report title. Date. * Author(s). Title. *Journal* Year; Vol(No):pages * Author(s). Title. *Journal* Year; Vol(No):pages |
| ID of trial used in submission | * Internal study report title. Date. * Author(s). Title. *Journal* Year; Vol(No):pages * Author(s). Title. *Journal* Year; Vol(No):pages |

The exclusion of randomised trials from the master list (either trials that compare the proposed medicine with the appropriate comparator or trials that are used to inform an indirect comparison) is not encouraged at this point. There may be some justification for the exclusion of trials on the basis of quality, patient characteristics or circumstances of use. However, the PBAC would prefer that such trials are initially included and that sensitivity analyses are then conducted that vary the inclusion criteria. Removal of trials that otherwise meet the inclusion criteria will require clear justification.

#### Published systematic reviews and meta-analyses

In most circumstances where the submission has identified a published meta-analysis, it is preferable that the individual trials are also extracted, compared against the study selection criteria and formally included in the submission (where feasible). If some of the trials from the published meta-analysis do not meet the selection criteria, consider presenting the treatment effect estimate from the published meta-analysis in a sensitivity analysis in Subsection 2.6, or perform a meta-analysis using the truncated list of trials.

#### Option to present supplementary evidence

Where data from one or more direct randomised trials are available, the presentation of an indirect comparison or nonrandomised study is generally not encouraged. However, in certain circumstances, it may be reasonable to justify the inclusion of supplementary study data.

If supplementary evidence is to be presented, the literature search should be presented in Subsection 2.1 to show how the supplementary data were located. Separately identify and list the supplementary randomised trials and include reports of the trials with other references to the submission. Indicate how these supplementary trials are used in Subsection 2.2, ‘[Approach taken to support the clinical claim](#label=Approach%20taken%20to%20support%20the%20clinical%20claim&name=DocumentView&context=CurrentDocumentID/76,CurrentProjectID/1,CurrentHeadingID/1181)‘, and present relevant analyses in Subsections 2.3–2.6. Clearly label this supplementary information to distinguish it from the information from the relevant direct randomised trial(s).

### Further selection of trials for an indirect comparison

Where the submission has not identified direct randomised trials or is seeking to present a supplementary analysis, including an indirect comparison of randomised trials, further selection of trials may be required. The approach to selecting trials for the presentation of an indirect comparison is discussed in Appendix 2. A general approach is summarised here:

* Step 1. Follow the approach outlined in Subsection 2.2 to identify all trials involving the proposed medicine (irrespective of comparator arm) and all trials involving the main comparator (irrespective of comparator arm).
* Step 2. Draw a network diagram to show all the possible links.
* Step 3. Where pairwise comparisons are possible, the submission may seek to exclude linkages requiring multiple steps, or include these as a supplementary analysis.
* Step 4. Examine heterogeneity within trial sets and across trial sets, and justify the exclusion of trials with differences in factors that may result in heterogeneity of treatment effect.
* Step 5. Examine the event rates in the common reference arms and justify the exclusion of trials on the basis of differences in baseline risk.

Step 6. Present a list of the trials included in the main analysis, the trials included in supplementary or sensitivity analyses, and the trials excluded from the analysis.

### Approach taken to support the clinical claim

Describe which of the included trials were analysed in the submission (whole trial population) and how they were combined or compared to provide data or increase the statistical precision of the clinical claim (subgroups and additional trial analyses, such as meta-analyses or indirect comparisons; see Subsection 2.6).

EXAMPLE: *The submission is based on a meta-analysis of 3 trials of medicine X compared with medicine Y, which is then compared indirectly to a single trial of medicine Z compared with medicine Y. A claim of noninferiority is made on the outcomes of time to progression and quality of life.*

If the approach taken to support the clinical claim relies on subgroups (either prespecified in the trials or analysed in the submission), justify why the randomised (intention-to-treat) population is not appropriate in the context of the proposed listing, in terms of relevant evidence and biological plausibility.

### Copies of included trials

Include sufficient details of the relevant trials as attachments to the main body of the submission. The location of the trials in the submission should be provided in the document table in Section 1.

Where there is more than one report of a randomised trial (eg one or more published papers and one or more trial reports internal to the sponsor), provide both the published paper(s) and key extracts from the sponsor’s internal trial report (see the *Pharmaceutical Evaluation Branch checklist for submissions* [URL to be supplied] for details on how to do this). The results might vary between reports of the same randomised trial. If so, justify, and cross-reference the source of, results extracted for the submission. Provide a copy of each other publication reporting data from a listed randomised trial.

For any relevant trial identified from a meta-analysis, include the individual trial report or publication(s) as above.

Provide reputable translations of trial reports that are not published in English.

## 2.3 Trial design and execution

**INFORMATION REQUESTS**

**Assess risk of bias (internal validity)**

For each trial, describe the factors that are likely to affect its credibility (internal validity) according to the study type. Specify the source and location of the information.

### Internal validity

The purpose of assessing risk of bias is to provide the PBAC with a clear idea of which trials are of greater scientific rigour. The PBAC is most likely to be persuaded by data that are robust. Information needed to inform an assessment of the risk of bias can be broadly assessed according to study type:

* Approach 1 – randomised trials. Relevant to trials that directly compare the proposed medicine with the nominated comparator, and trials that compare the proposed medicine and nominated comparators with a common reference used as part of an indirect comparison.

Approach 2 – nonrandomised studies. Relevant to study types such as cohort studies, case-control studies and quasi-experimental studies.

Where the rarity of the disease prohibits the use of a traditional parallel-group randomised controlled trial, alternative trial designs may be acceptable (such as randomised crossover trials, including n-of-1 trials, and trials with a randomised adaptive design). Such trials require a protocol, a clinical trial registry number or identifier, and a design that involves a randomisation procedure. Where a submission is based on such a trial, risk of bias can be addressed according to Approach 1.

### Approach 1: randomised trials

Table 2.3.1 is based on Chapter 8 of the [*Cochrane handbook for systematic reviews of interventions*](http://handbook.cochrane.org/) (version 5.1.0) and is the preferred approach for presenting study characteristics that inform an assessment of the risk of bias in the included trials. Complete the table for **each** included trial. The table should present factual information regarding the design and conduct of the trial, rather than judgments (ie do not include judgment statements such as low risk, unclear risk or high risk; such judgments will be made by the submission evaluator). After the table, provide additional information regarding the following aspects that may influence an assessment of risk of bias (state if this information is not relevant or not available):

* **Unmasking.** Discuss whether the medicine or comparator have any effects (such as adverse events) that may result in the participant, the investigator or the outcome assessor ‘guessing’ the treatment allocation of the participant.
* **Treatment decisions.** Describe the decision-making processes (including responsible personnel), such as cessation of treatment as a result of failure or adverse events, or commencement of a new treatment or a concomitant treatment for adverse events or inadequate treatment response. Discuss whether these decisions could affect the measurement of any of the key outcomes.
* **Testing decisions.** Discuss whether the investigator, or other person caring for the participant, can request tests that are not part of the protocol or that occur at different times than prescribed in the protocol. Discuss whether these tests may affect the measurement of key outcomes or adverse events.
* **Nature of outcomes.** Regardless of whether the trial is blinded or open-label, discuss whether any of the key outcomes could be affected by a participant’s, investigator’s or outcome assessor’s knowledge of treatment allocation.

**Missing data.** Discuss the reasons for any loss to follow-up or missing data. Summarise how missing data have been imputed and the assumptions surrounding the use of these methods (cross-reference to Subsection 2.4). Discuss whether the characteristics of the participants who were lost to follow-up are similar to, or different from, those remaining in the trial, and state whether there is a differential loss to follow-up or discontinuation across the arms. Discuss whether missing data are expected to affect the treatment effect, and if the effect is likely to be overestimated or underestimated.

Table 2.3.1 Information required to assess the risk of bias in randomised trials

| Type of bias | Trial | Description | Source(s): page number(s) of clinical study report/publication |
| --- | --- | --- | --- |
| Selection bias: random sequence generation and allocation concealment | Trial 1 | [Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. Describe the method used to conceal the allocation sequence in sufficient detail to allow an assessment of whether intervention allocations could have been foreseen in advance of, or during, participant enrolment.] | [insert source] |
| Trial 2 | [insert description] | [insert source] |
| Trial 3 | [insert description] | [insert source] |
| Performance bias: blinding of participants and personnel | Trial 1 | [Describe all measures used, if any, to blind trial participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.] | [insert source] |
| Trial 2 | [insert description] | [insert source] |
| Trial 3 | [insert description] | [insert source] |
| Detection bias: blinding of outcome assessment | Trial 1 | [Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.] | [insert source] |
| Trial 2 | [insert description] | [insert source] |
| Trial 3 | [insert description] | [insert source] |
| Attrition bias: incomplete outcome data | Trial 1 | [Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), and the reasons for attrition/exclusions, where reported.] | [insert source] |
| Trial 2 | [insert description] | [insert source] |
| Trial 3 | [insert description] | [insert source] |
| Reporting bias: selective reporting | Trial 1 | [State how the possibility of selective outcome reporting was examined, and what was found.] | [insert source] |
| Trial 2 | [insert description] | [insert source] |
| Trial 3 | [insert description] | [insert source] |
| Other sources of bias | Trial 1 | [State any important concerns about the study design and execution that are not addressed elsewhere in this table.] | [insert source] |
| Trial 2 | [insert description] | [insert source] |
| Trial 3 | [insert description] | [insert source] |

Adapted from the Cochrane Collaboration’s tool for assessing risk of bias ([Chapter 8 of the *Cochrane handbook*](http://handbook.cochrane.org/chapter_8/table_8_5_a_the_cochrane_collaborations_tool_for_assessing.htm))

Where the information provided in the submission implies a risk of bias, describe the likely effect that the bias may have on the direction of the comparative treatment effect.

Present the flow of participants in Table 2.3.2.

Table 2.3.2 Flow of participants through the trials

| Trial ID | Intervention arm | No. randomised | Did not receive intervention | Lost to follow- up | Discontinued | Analysed | Source of information |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Trial 1 | Proposed medicine | *N* | *n* (%) | *n* (%) | *n* (%) | *n* (%) | Reference the source of this information |
| Main comparator | *N* | *n* (%) | *n* (%) | *n* (%) | *n* (%) | Reference the source of this information |
| Trial 2 | Proposed medicine (high dose) | *N* | *n* (%) | *n* (%) | *n* (%) | *n* (%) | Reference the source of this information |
| Proposed medicine (low dose) | *N* | *n* (%) | *n* (%) | *n* (%) | *n* (%) | Reference the source of this information |
| Main comparator | *N* | *n* (%) | *n* (%) | *n* (%) | *n* (%) | Reference the source of this information |
| Trial 3 | [etc] | [etc] | [etc] | [etc] | [etc] | [etc] | [etc] |

#### Systematic reviews and meta-analyses

Where a published systematic review or meta-analysis has been identified in the literature search conducted in Subsection 2.2, the preferred approach is to complete Table 2.3.2 for each of the key trials included in the paper that meet the eligibility criteria outlined in Subsection 2.2. Where individual trials are not able to be retrieved and the submission relies on a pooled treatment effect from the published systematic review and meta-analysis, the submission should clearly report the risk of bias assessment undertaken by the authors of the systematic review, and also assess the quality of the systematic review using a validated tool (such as AMSTAR6 or ROBIS7).

### Approach 2: nonrandomised studies

Because of the nonrandom allocation of participants to treatment arms, nonrandomised studies are prone to a high risk of bias. Although methods are available for mitigating some of the risks associated with the differential distribution of **known** confounders due to nonrandom treatment allocation, these methods cannot adjust for the differential distribution of **unknown** confounders. The PBAC has a preference for high-quality randomised controlled trials for determining the incremental treatment effect. Nonrandomised studies can, however, provide useful information in the following situations:

* when it is unethical to conduct randomised trials (ie when the treatment effect is extraordinarily large in observational studies and so equipoise is not achieved)
* when randomised trials are not feasible (ie when the disease/condition is rare)
* when rare adverse events cannot be feasibly captured within the duration of a randomised trial (provide nonrandomised study data **in addition** to randomised trial data)

when eligibility criteria for the trial are very restrictive, meaning that the applicability of the treatment effect to the target population is unknown (provide nonrandomised study data **in addition** to randomised trial data).

The assessment of risk of bias in nonrandomised studies may differ according to study design and conduct, and cannot be captured in a single checklist. The preferred approach is to provide information relating to the nonrandomised study that will allow the PBAC to judge the likelihood of bias, and the direction and magnitude of that bias. The submission may wish to address possible sources of bias according to the domains described by the Cochrane Collaboration’s ACROBAT-NRSI tool8 (adapted in Table 2.3.3).

Table 2.3.3 Information required to assess the risk of bias in nonrandomised studies

| Domain (detailed guidance in ACROBAT-NRSI8)a | Signalling questions | Source(s): page number(s) of clinical study report/publication |
| --- | --- | --- |
| Confounding | * Were participants analysed according to their initial intervention group? Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome? Were the methods for adjusting for important confounders (baseline and time varying) appropriate? Were the confounders that were adjusted for measured validly and reliably by the variables in the study? Were there any adjustments for postintervention variables? * Where there is a possibility of bias, what is the predicted direction of bias due to confounding (provide supporting evidence)? | Reference the source of this information |
| Selection of participants into the study | * Cohort-type studies: Was selection into the study unrelated to intervention or unrelated to outcome? Does the start of follow-up and start of intervention coincide for most subjects? Were adjustment techniques used that are likely to correct for the presence of selection biases? * Case-control studies: Were the controls sampled from the population that gave rise to the cases, or using another method that avoids selection bias? * Where there is a possibility of bias, what is the predicted direction of bias due to selection of participants (provide supporting evidence)? | Reference the source of this information |
| Measurement of interventions | * Is intervention status well defined? Was information on intervention status recorded at the time of intervention? Was information on intervention status unaffected by knowledge of the outcome or the risk of the outcome? * Where there is a possibility of bias, what is the predicted direction of bias due to measurement of outcomes or interventions (provide supporting evidence)? | Reference the source of this information |
| Departures from intended treatment allocation | * Were the critical co-interventions balanced across intervention groups? Were numbers of switches to other interventions low? Was implementation failure minor? * Cohort-type studies: Were adjustment techniques used that are likely to correct for these issues? * Where there is a possibility of bias, what is the predicted direction of bias due to departures from the intended interventions (provide supporting evidence)? | Reference the source of this information |
| Missing data | * Cohort-type studies: Are outcome data reasonably complete? Was intervention status reasonably complete for those for whom it was sought? * Case-control studies: Was outcome status reasonably complete for those for whom it was sought? Were data on intervention status reasonably complete? * Are data reasonably complete for other variables in the analysis? * Are the proportion of participants and reasons for missing data similar across interventions (for cohort-type studies), or cases and controls (for case-control studies)? * Were appropriate statistical methods used to account for missing data? * Where there is a possibility of bias, what is the predicted direction of bias due to missing data (provide supporting evidence)? | Reference the source of this information |
| Measurement of outcomes | * Cohort-type studies: Were the outcome measures objective? Were outcome assessors unaware of the intervention received by study participants? Were the methods of outcome assessment comparable across intervention groups? Were any systematic errors in measurement of the outcome unrelated to the intervention received? * Case-control studies: Was the definition of case status (and control status, if applicable) based on objective criteria? Was the definition of case status (and control status, if applicable) applied without knowledge of the intervention received? * Where there is a possibility of bias, what is the predicted direction of bias due to measurement of outcomes (provide supporting evidence)? | Reference the source of this information |
| Selection of the reported result | Is the reported effect estimate unlikely to be selected on the basis of the results, from:   * 1a. multiple outcome measurements within the outcome domain (cohort-type studies)? * 1b. multiple definitions of the intervention (case-control studies)? * 2. multiple analyses of the intervention–outcome relationship? * 3. different subgroups? | Reference the source of this information |
| Where there is a possibility of bias, what is the predicted direction of bias due to selection of the reported outcome (provide supporting evidence)? | Reference the source of this information |

**a** Version 1.0.0 of the ACROBAT-NRSI publication includes detailed guidance on each of the domains included in the tool. The guidance discusses sources of confounding or bias within nonrandomised studies and how to identify them, and is an appropriate reference for ensuring that the risk of bias within nonrandomised studies is adequately discussed in the submission.

Types of information that may be required for each domain are discussed at length in ACROBAT-NRSI.8

The submission should present factual information rather than judgments of the risk of bias; such judgments will be made by the submission evaluator. For example, it is not appropriate to state that there is no risk of bias due to confounding; rather, state that measured baseline characteristics are similar across the study arms (reference the study report) and that patients did not switch between treatment arms during the observation period of the study when the outcome was measured.

## 2.4 Trial characteristics

**INFORMATION REQUESTS**

**Present the characteristics of participants in each trial**

Describe the eligibility criteria, baseline demographics and clinical characteristics of trial participants, and discuss any differences across trial arms. Provide details for the whole trial population and any relevant subgroups.

**Provide details of the treatments in each trial**

Describe the treatment regimens for each trial and discuss any differences in duration of treatment or follow-up. Provide details for the whole trial population and any relevant subgroups.

**Describe the outcomes in each trial**

List the outcomes measured in each trial and describe any differences. Identify the minimal clinically important difference. If appropriate, specify the noninferiority margin, describe composite outcomes and provide details of patient-reported outcome measures. Provide details for the whole trial population and any relevant subgroups.

**Cross-reference the source documents**

For each response, specify the source document in the reports or papers accompanying the main body of the submission, together with the page or table number from which the information was extracted.

**Note:** Where the submission has included a systematic review containing multiple studies, it is expected that the submission would present the trial characteristics for the individual studies, as presented either in the individual publications or, where these are unavailable, as presented in the systematic review.

### Participants

Identify any differences in the baseline demographic or clinical characteristics across arms in the trials. Report whether differences are statistically significant, but note that important differences may not always be statistically significant, particularly for subgroups.

For each of any identified differences, discuss the likely impact on the magnitude and direction of the treatment effect. Any differences across arms or across relevant subgroups, whether in prognostic variables or not, may be an indication that randomisation was unsuccessful and should be noted in Subsection 2.3.

In an attachment to the submission, provide the following details about the trial participants for each trial:

* eligibility criteria for participants considered for recruitment into the trial
* baseline demographic and clinical characteristics for each randomised group

median duration (and range) of follow-up for each group and for the entire trial (also indicate whether the trial is ongoing).

Where there are differences between treatment arms in terms of the extent or timing of patients lost to follow-up, patient withdrawals, or missed or refused assessments, the PBAC would also find it helpful if baseline demographic and clinical characteristics were available for the following groups:

* patients who were lost to follow-up compared with those who were not
* patients who withdrew from the trial compared with those who did not

patients who missed an assessment compared with those who were assessed (this comparison is critical when the assessment is for the purpose of measuring an outcome that is related to the disease or medicine).

If the submission relies on prespecified or post hoc subgroups, present the participant information requested in this section for the whole trial population, the relevant subgroups and their complement.

### Treatment details

If available, provide the intended treatment regimen (for both arms) as outlined in the study protocol. Include details on dose, method of administration, dose timing and frequency, dose titration and criteria for titration, intended treatment duration, continuation criteria or stopping criteria, and prespecified use of subsequent active therapy following treatment completion or failure.

Provide details of how the interventions actually occurred in the trial (across each arm). These details should include an average dose that incorporates the frequency (and/or proportion of participants taking particular doses) and average duration of treatment.

If participants received concomitant treatments for the same indication (such as a background therapy), provide details of these treatments as above.

State whether the doses and dose regimens of the proposed medicine, the main comparator and the concomitant treatments are supported by high-quality clinical practice guidelines and by the product information for each of the medicines. It is particularly important to determine whether the comparator arm is dosed appropriately. Where available, present the doses and dose regimens for the main comparator from recent trials where the main comparator is the investigational medicine.

If participants received active treatments following cessation of the proposed medicine or comparator, provide details on dose and duration of these treatments across the trial arms.

Identify differences in the duration of treatment and duration of follow-up across the trial arms for the randomised population. Provide an explanation for any differences observed.

If the submission relies on subgroups, present the information requested in this section for the whole trial population, relevant subgroups and their complement.

### Outcomes

The PBAC prefers that outcomes presented in the submission are relevant, and any differences in observed outcomes are meaningful to the individual patient. Most trials will measure multiple outcomes. The PBAC considers the following outcomes to be relevant, and these should be listed and clearly defined for each included trial:

* the primary outcome specified in the trial protocol
* secondary outcomes that are patient relevant
* outcomes that are not patient relevant but are deemed to be appropriate surrogates for patient-relevant outcomes

outcomes that are used in the economic evaluation.

For each outcome relevant to the submission, state the units of measurement and the method of statistical analysis, describe and justify the population in which the analysis is performed (i.e. intention to treat, per protocol), and describe the timing of the outcome assessment. Summarise the power calculations for outcomes for which the trial was designed to detect a change, and state how missing data were dealt with.

Where there are multiple trials, it is important that any differences in the definition of outcomes or the method of statistical analysis are clearly presented. An example of how outcomes may be presented is shown in Table 2.4.1.

Table 2.4.1 Example presentation of differences in trial outcomes or analyses

| Outcome | Trial | Definition of outcome, units of measurement and timing of outcome assessment | Method of statistical analysis | Basis of analysis |
| --- | --- | --- | --- | --- |
| Progression-free survival | Trial 1 | Primary study outcome was defined as the time from randomisation to first documented progression or death. Progression was measured using RECIST v1.1 (see RECIST criteria presented in text below) and was determined by the study site investigator. Target lesions were measured at baseline using CT or MRI scanning within 28 days of randomisation. Target lesions were measured on treatment using CT or MRI every other cycle, starting from cycle 2. Investigator-initiated CT or MRI scans were permitted between scheduled measurements. | A stratified Cox model was used to generate hazard ratios (and 95% CIs). The stratification variables were disease stage, performance status and previous cisplatin therapy (stratification variables are discussed further in the statistical appendix). Patients who were lost to follow-up (including those who withdrew consent) were censored at the last tumour assessment. | Per protocol analysis, including only patients who received at least one dose of the medicine. |
| Trial 2 | [add description] | [add description] | [add description] |
| Trial 3 | [add description] | [add description] | [add description] |
| Overall survival | Trial 1 | [add description] | [add description] | [add description] |
| Trial 2 | [add description] | [add description] | [add description] |
| Trial 3 | [add description] | [add description] | [add description] |

Source: *Primary CSR, pages 70–72, 75–77 and Statistical Appendix 3 to the submission.*

The definition of the outcome should include a description of the instrument used to measure the outcome (eg questionnaire, criteria such as RECIST,9 blood test), the threshold for categorisation as an outcome, the timing of the measurement of the outcome, the personnel who administered the instrument (eg investigator, study nurse, patient) and the personnel who determined whether the outcome had been achieved (or the magnitude of the outcome). For each instrument, state whether the instrument is validated in the population and the circumstances in which it is applied in the study, and provide a reference for its validation.

The description of the method of statistical analysis should include the name of the statistical test and sufficient details to allow the PBAC to ascertain how the analysis was performed. Where possible, a statistical appendix – including the statistical code and statistical output – should be provided, with notation explaining the variables used in the analysis. The description should include a description of the analysis set (total randomised population, per protocol), as well as a description of the extent of missing data and how missing data were handled (eg censored, imputed). Comment on the likely effect of missing data on the estimate of the treatment effect. Clearly describe the assumptions for the approach to dealing with missing data.

Ensure that each outcome is reported as being truly independent, or that the statistical analysis appropriately adjusts for clustering. This issue most often occurs when a single patient can experience multiple events (eg fractures, hypoglycaemic events, hospitalisation episodes) during follow-up.

Where the submission has identified multiple trials, clearly indicate how many trials reported on each relevant outcome. If some trials have not reported on relevant outcomes, indicate this in a footnote when presenting results.

#### Minimal clinically important difference

For each outcome relevant to the submission, nominate and justify the minimal clinically important difference (MCID). The source of the MCID may be:

* defined in the protocol for the purposes of powering the study
* a commonly accepted MCID in the literature relevant to both the trial population and the proposed indication
* an internal study performed by the sponsor (anchor-based analysis, expert consensus, statistically based analysis)

a commonly accepted MCID in the literature for a similar indication that can reasonably be expected to be generalisable to the proposed indication.

In all cases, the MCID should be adequately justified to show that the detected difference in patients from baseline is perceptible and meaningful to a patient, or the difference between arms would likely translate to a perceptible and meaningful difference from baseline for the majority of patients in the trial.

For all MCIDs identified for each outcome, present:

* a reference to the source
* the method for determining the MCID (anchor, Delphi, distribution, other)
* a comparison of the definition of the outcome used in the MCID study with the identified studies

the estimate of the MCID (this is usually presented in absolute units, such as millimetre change in visual analogue scale or points change in patient-reported outcome measures).

For guidance on the presentation and justification of the choice of MCID, see Appendix 3.

#### Noninferiority margin

Where the submission aims to demonstrate that the proposed medicine is not inferior to a comparator by more than a clinically meaningful margin, that margin (called the noninferiority margin) must be justified. State the outcomes for which noninferiority is to be tested and justify when an outcome is excluded from the assessment of noninferiority.

Suggested approaches for nominating a noninferiority margin are presented in Appendix 4.

#### Composite outcomes

If one or more of the reported outcomes is a composite, discuss and compare the clinical importance of each of the components of this composite. Report whether the definition of the composite outcome was explicitly prespecified. Justify the inclusion of the components in the composite outcome, and the exclusion of any components that were considered but subsequently rejected. Disaggregate the composite outcome and present the results (eg comparative rates) of each component as a secondary outcome in Subsection 2.5.

To avoid double counting, a composite outcome is usually defined as having been experienced when the trial participant experiences the first component outcome in the composite (such as disease progression), even though other component outcomes in the composite (such as death) might occur subsequently. This needs to be appropriately handled when disaggregating the composite outcome so that, where possible, all subsequent first experiences of any other component outcome in the composite are also included.

#### Patient-reported outcome measures (quality-of-life instruments)

Patient-reported outcome measures (or quality-of-life instruments) include generic (‘global’) and condition-specific (eg for respiratory conditions, depression or arthritis) measures that patients complete to assess their own health. Patient-reported outcome measures are a patient-relevant outcome and therefore relevant to present in the submission.

Where a patient-reported outcome measure is used, provide a discussion of:

* the domains of quality of life that are covered by the instrument
* the scoring method of the instrument
* the validity of the instrument
* the reliability of the instrument
* the responsiveness of the instrument to differences in health states between individuals and to changes in health states over time experienced by an individual

the clinical importance of any differences detected by the instrument (see guidance on MCID, above).

Patient-reported outcome measures may include multi-attribute utility instruments (MAUIs; eg EQ-5D, SF-6D, AQOL) in which the scoring method for the instrument is anchored on a quality-adjusted life year (QALY) scale of 0 (death) to 1 (full health). Where the measurement of quality of life uses a MAUI, provide details of the selected MAUI.

​Include any data and references that support the selection of the MAUI in a technical document or an attachment to the submission (provide clear cross-references between these data and the main body of the submission).

In terms of how the patient-reported outcome measure is used within the study, the submission should report on:

* the timing of assessments, including how often and at what points in the study the instruments were administered
* a description of who administered the questionnaire and in what setting

why assessments were missed and how missed assessments were dealt with.

The submission should seek to provide the characteristics of the patients who missed or refused to complete patient-reported outcome measures and compare them with those patients who completed the questionnaires. If an investigator assessment of patient wellbeing (or performance score) is captured for all patients, this may be an appropriate metric to compare patients who completed the questionnaire with those who did not. Describe any methods that were used to adjust for response bias, or describe the effect of missed assessments on the comparison of patient-reported outcome measures across the arms of the study.

### Cross-references to source documents

For each trial, specify the source document in the reports or papers accompanying the main body of the submission. For each of the responses provided above, provide adequate cross-referencing to page, table or figure numbers of the relevant trial report(s) – if necessary, in a separate technical document or attachment.

## 2.5 Trial results: whole trial population

**INFORMATION REQUESTS**

**Present the results on effectiveness for each trial (primary analysis)**

Present the results of each trial for the randomised, intention-to-treat or per-protocol population – that is, the whole trial population. (Present the results for subgroups in Subsection 2.6.) Provide a tabulated analysis of each patient-relevant outcome, including results of patient-reported outcome measures.

**Present adverse event data**

Report and analyse adverse event data from each trial.

**Cross-reference the source documents**

For each response, specify the source document in the reports or papers accompanying the main body of the submission, together with the page or table number from which the information was extracted.

Subsection 2.5 is intended to capture the results from the studies for the whole trial population. Where the submission is based on a subgroup, meta-analysis or indirect comparison, or requires adjustment for treatment switching, this will be addressed in Subsection 2.6. Regardless of the overall approach taken in the submission, the results for the whole trial population should be presented.

### Effectiveness

For each study identified in Subsection 2.2, present the results of the primary outcome, and other relevant outcomes identified in Subsection 2.4, for the whole trial population. Results from meta-analyses, subgroups and indirect comparisons are presented in Subsection 2.6.

The presentation of results will differ according to the nature of the outcome, but, in general, the submission should present the following details (where permitted by the data):

* the number of patients at risk or providing data to the results
* the number of patients experiencing the event (if appropriate)
* the percentage of patients with the event, and means or medians within groups
* confidence intervals of the outcomes within groups
* relative and absolute differences between groups, and confidence intervals
* an interpretation of the results

a discussion of the results in the context of the nominated MCID.

Example tables for presenting different data types are provided in Tables 2.5.1–2.5.4.

Although the outcomes are defined in Subsection 2.4, it is important to present the timing of the outcome assessment (eg EORTC-QLQ C30, change from baseline at six weeks), either in the table heading or as a footnote to the table. If there are multiple studies that differ in timing of the measurement of the outcome or length of follow-up over which the outcome can be observed, clearly present this below each results table. Justify and discuss any early stopping of a trial or reliance on interim analysis in the interpretation of the results.

The results of nonrandomised comparative study designs (cohort studies, case-control studies) may be presented in this section.

#### Dichotomous data

Table 2.5.1 Results of [outcome] across the studies: dichotomous data

| Trial ID | Proposed medicine *N* = | Main comparator *N* = | Relative risk (95% CI) | Risk difference (95% CI) |
| --- | --- | --- | --- | --- |
| Trial 1 | *n* with event (%) | *n* with event (%) | [add] | [add] |
| Trial 2 | *n* with event (%) | *n* with event (%) | [add] | [add] |
| [etc] | [etc] | [etc] | [etc] | [etc] |

CI = confidence interval; *n* = number of participants with event; *N* = total participants in group

#### Continuous data

Table 2.5.2 Results of [outcome] across the studies: continuous data (with outcome presented as an endpoint)

| Trial ID | Proposed medicine *N* = | Proposed medicine *N* = | Main comparator *N* = | Main comparator *N* = | Mean difference (95% CI) |
| --- | --- | --- | --- | --- | --- |
| Trial 1 | *n* reporting data (%) | End point mean (SD) | *n* reporting data (%) | End point mean (SD) | [add] |
| Trial 2 | [add] | [add] | [add] | [add] | [add] |
| [etc] | [etc] | [etc] | [etc] | [etc] | [etc] |

CI = confidence interval; *n* = number of participants reporting data; *N* = total participants in group; SD = standard deviation

Table 2.5.3 Results of [outcome] across the studies: continuous data (with outcome presented as change from baseline)

| Trial ID | Proposed medicine (mean values) *N* = | Proposed medicine (mean values) *N* = | Proposed medicine (mean values) *N* = | Main comparator (mean values) *N* = | Main comparator (mean values) *N* = | Main comparator (mean values) *N* = | Mean difference (95% CI) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Trial 1 | Baseline (SD) | End point (SD) | Change (SD) | Baseline (SD) | End point (SD) | Change (SD) | [add] |
| Trial 2 | [add] | [add] | [add] | [add] | [add] | [add] | [add] |
| [etc] | [etc] | [etc] | [etc] | [etc] | [etc] | [etc] | [etc] |

CI = confidence interval; *N* = total participants in group; SD = standard deviation

When presenting continuous data, it is reasonable to present both the weighted mean difference at end point (Table 2.5.2) and the weighted mean difference of the change (usually from baseline) (Table 2.5.3). If the outcome was measured at more than one time point, justify the selection of the particular end point presented. Discuss whether the treatment effect differs across other time points, and present these results in an appendix, or provide a clear reference to where they are presented in the sponsor’s study report.

Where continuous data are translated to dichotomous data in the economic evaluation or to support the clinical claim, justify the use of the threshold to convert the data. Present sensitivity analyses using different thresholds, or present a cumulative distribution function of the continuous outcome separated by treatment arm and clearly show the effect of the choice of threshold to determine the dichotomous outcome.

#### Time-to-event data

Table 2.5.4 Results of [outcome] across the studies: time-to-event data

| Trial ID | Proposed medicine *N* = | Proposed medicine *N* = | Main comparator *N* = | Main comparator *N* = | Difference in median | *P* value (log rank test) | Hazard ratio (95% CI) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Trial 1 | *n* with event (%) | Median time to event (95% CI) | *n* with event (%) | Median time to event (95% CI) | [add] | [add] | [add] |
| Trial 2 | [add] | [add] | [add] | [add] | [add] | [add] | [add] |
| [etc] | [etc] | [etc] | [etc] | [etc] | [etc] | [etc] | [etc] |

CI = confidence interval; *n* = number of participants reporting data; *N* = total participants in group

Present relevant Kaplan–Meier curves for each included study. If the sponsor cannot access the study data or cannot request a Kaplan–Meier curve, and it has not been published, clearly state this.

Where the analysis is based on a Cox proportional hazards model, present the hazard ratios, together with their 95% confidence intervals. Discuss whether the results are consistent with the assumption of constant proportional hazards. Present results of testing for proportional hazards. Where the assumption of constant proportional hazards is not reasonable, present alternative methods for estimating comparative effectiveness. Where restricted mean survival time is used, present estimates of the restricted mean (and the difference in restricted means) calculated at several time points over the duration of the trial.

#### Ordinal or categorical data

A similar approach to the above for continuous data should be attempted if the trial results are available as ordinal or categorical data (eg a Likert scale for patient-reported outcome measures). Expert biostatistical advice will be helpful in such circumstances, particularly to meta-analyse such data.

#### Multi-attribute utility instrument data

Ideally, report MAUI results as the difference (with 95% confidence interval) in the integrals between the mean utility weights obtained over time up to the median period of follow-up in the trial for the proposed medicine and its main comparator. This directly estimates the incremental QALYs gained. Also report the results analysed as specified in the trial protocol, particularly if the difference between integrals cannot be generated directly.

If the scoring algorithm has not been derived from the general population in Australia, consider presenting sensitivity analyses using alternative scoring algorithms. If more than one MAUI has been used in the included study, compare the results from the two MAUIs.

Discuss the interpretation of these QALY results. Assess the results against other outcomes measured in the trial. In particular, discuss the consistency or inconsistency with any concomitantly assessed disease-specific patient-reported outcome measure and/or generic patient-reported outcome measure.

Also assess:

* whether the technique of measurement at baseline and during the trial is valid and likely to be free from bias (eg whether the results correlate with clinical or other measures of health outcomes in the trial)
* whether the results of the exercise are reliable (eg whether there is a high variance in results or inconsistencies in responses, or a high number of missing observations)

what attributes of health-related quality of life and other patient attributes are being valued.

### Adverse events

As a minimum, the following categories of adverse events should be reported:

* any adverse event
* any adverse event resulting in discontinuation of the randomised treatment
* any serious adverse event (including hospitalisations)
* any adverse event resulting in death

each and every other type of adverse event where the frequency or severity differs substantially across groups, for each study listed in Subsection 2.2.

Adverse event data should be reported as both the number of patients reporting an adverse event in each category and the absolute number of adverse events in each category. The absolute number of events in each category may be a more appropriate estimate for costing adverse events in an economic or financial analysis, rather than the number of patients who experience an adverse event, because the latter will not capture patients who experience two events in the same category.

For each important adverse event, present these results as for dichotomous data above, with relative risks and risk differences with their 95% confidence intervals across the groups for each study, separately.

Where the average period at risk per participant varies substantially between treatment groups, the relative adverse event rates (events per period at risk) should also be analysed using Poisson regression.

See Subsection 2.7 for further discussion of adverse reactions reported from other sources.

### Cross-references to source documents

For each trial, specify the source document in the reports or papers accompanying the main body of the submission. For each of the responses provided above, provide adequate cross-referencing to page, table or figure numbers of the relevant trial report(s) – if necessary, in a separate technical document or attachment.

If statistical approaches are used that cannot be replicated using the data provided in this section, present the statistical code (including adequate explanation of covariates) and the statistical outputs in a separate technical document.

## 2.6 Trial results: additional analyses

**INFORMATION REQUESTS**

**Present the results of any relevant additional analyses**

Describe and justify the use of analyses that were not prespecified in the included studies but are relevant to the submission, including:

* subgroup analyses
* meta-analyses
* indirect comparisons

adjustment for treatment switching.

### Subgroup analyses

The purpose of a subgroup analysis in Subsection 2.6 is to select, from the whole trial population, patients who match the proposed listing. Where the whole trial population would be eligible for treatment according to the proposed listing, a subgroup analysis should not be presented in Subsection 2.6.

Ensure that the participant characteristics and treatment details have been presented in Subsection 2.4 for the whole trial population, relevant subgroups and their complement.

#### Justification for the use of subgroups

The PBAC prefers submissions based on the whole population of a randomised trial. If a submission seeks listing of a medicine for a particular subgroup within a trial, the reasons for this should be made clear. The submission should discuss why the trial enrolled a broader population than the subgroup, and why the proposed medicine should not be available to the patients in the complement of the subgroup.

Provide the following information to support a subgroup analysis:

* Discuss the plausibility of a variation in treatment effect, including the pharmacological, biological or clinical plausibility, to justify the use of results of the subgroup. An unexplained variation is difficult to interpret in the absence of such plausibility (if this has been addressed in Subsection 1.1, state this and cross-reference).
* Clearly indicate whether the subgroup analysis was prespecified and whether randomisation was stratified by the subgroup. Cross-reference the appropriate section in the trial protocol (or other source) that discusses prespecified subgroups, justification for the selection of subgroups, the precise method for defining subgroups and a clear justification for any threshold used to define subgroups.

Describe the number of subgroup analyses originally conducted and any statistical adjustment for multiple comparisons.

#### Results of subgroup analyses

For **each** of the outcomes relevant to the submission, present the results of the subgroup, the complement to the subgroup and the whole trial population. The presentation of data will differ according to the type of outcome; example tables are provided in Subsection 2.5, which may be adapted to report subgroups (see Table 2.6.1 for an example using dichotomous outcomes).

Results should include relative and absolute treatment effect measures for the subgroup, the complement of the subgroup and the total trial population, and a test for interaction between the subgroup and its complement. The test for interaction should support and quantify the association between the treatment effect and the covariate defining the subgroup. If a continuous variable has been used to define the subgroup, particularly if the subgroup is not prespecified, perform a sensitivity analysis on the threshold value chosen to define the subgroup and present results for different thresholds.

Pooling should be done using a random effects meta-analysis (see ‘Meta-analyses’, below, for guidance on performing and presenting meta-analyses). Present the forest plots for the meta-analyses in an attachment to the submission and provide adequate cross-referencing.

**Table 2.6.1 Results of [outcome] within the studies: dichotomous data**

| Population | Trial ID | Proposed medicine [*n* with event/*N* (%)] | Main comparator [*n* with event/*N* (%)] | Relative risk or odds ratio (95% CI) | Risk difference (95% CI) |
| --- | --- | --- | --- | --- | --- |
| Whole trial population | Trial 1 | [add] | [add] | [add] | [add] |
| Trial 2 | [add] | [add] | [add] | [add] |
| Meta-analysis of overall trial results | [add] | [add] | RR (95% CI)  (k = ) | RD (95% CI) (k = ) |
| I2 statistic with 95% uncertainty interval | – | – | [add] | [add] |
| Identified subgroup | Trial 1 | [add] | [add] | [add] | [add] |
| Trial 2 | [add] | [add] | [add] | [add] |
| Meta-analysis of identified subgroup | [add] | [add] | RR (95% CI)  (k = ) | RD (95% CI) (k = ) |
| I2 statistic with 95% uncertainty interval | – | – | [add] | [add] |
| Complement of subgroup | Trial 1 | [add] | [add] | [add] | [add] |
| Trial 2 | [add] | [add] | [add] | [add] |
| Meta-analysis of complement of subgroup | [add] | [add] | RR (95% CI) (k = ) | RD (95% CI) (k = ) |
| I2 statistic with 95% uncertainty interval | – | – | [add] | [add] |
| Test for treatment effect variation | – | – | – | *P* = | *P* = |

CI = confidence interval; k = number of studies contributing to the pooled estimate of effect; *n* = number of participants with event; *N* = total participants in group; RD = risk difference; RR = relative risk

Present adverse event data as for dichotomous data above. Refer to Subsection 2.5, ‘Adverse events’, for further guidance on presenting adverse events. Particular care should be taken when performing a test for interaction where the average period at risk per participant varies substantially between the relevant subgroup and its complement.

### Meta-analyses

Where there is more than one trial reporting a particular outcome, presentation of a meta-analysis, which statistically combines (pools) results across the studies, is generally preferred, if feasible. Justify any decision **not** to present a pooled result whenever there is more than one relevant trial reporting a common patient-relevant outcome (eg justification could include the presence of significant clinical heterogeneity between studies).

Input the aggregated results of each trial that reported the relevant outcome into a meta-analysis and present the pooled results in a table and as a forest plot. [RevMan](http://tech.cochrane.org/revman), the software from the Cochrane Collaboration, quickly and succinctly conveys the requested array of meta-analysed information in a format suitable for inclusion in the main body of the submission. An alternative approach could be to use meta-analysis output from Stata.10

When pooling group-level study data, a DerSimonian–Laird random effects model is generally preferred. Explain and justify any other method used for statistically combining the results of the direct randomised trials and any additional statistical tests used. Clearly document and reference the methods used in order to make them independently reproducible and verifiable. Provide adequate detail of all sources of information relied on for these analyses, then present the results.

Where individual patient data are meta-analysed or used in a pooled analysis, ensure that the trial in which each individual was randomised is included as a covariate in the analysis.

#### Publication bias

Present an assessment of the risk of publication bias.11 Where there are sufficient trials, this may be assisted by the presentation of a funnel plot and statistical tests such as the Begg test12 and Egger test.13

#### Assess the clinical and statistical heterogeneity in the meta-analyses

Assessing heterogeneity is an important aspect of interpreting meta-analyses. Such an assessment should ideally consider the factors in Appendix 5**.** It may be appropriate to present the table from this appendix in the submission, briefly indicating where trials are similar and describing where they differ.

If there is a risk of heterogeneity because the trials have different periods of follow-up, it may be useful to present the pooled incidence rate differences.

#### Results of meta-analyses

For each submission-relevant outcome, statistically combine the results using the DerSimonian–Laird random effects model (or alternative method justified above) and include the pooled results in each table, together with their 95% confidence intervals. The presentation of the results will differ according to the type of data presented. Example tables are provided in Subsection 2.5, which may be adapted to include pooled estimates (Table 2.6.2a and 2.6.2b). For dichotomous outcomes, separately present analyses for the relative risk, odds ratio and risk difference.

Report results for the extent of statistical heterogeneity observed in the form of a Cochran *Q* statistic*,* degrees of freedom, chi-square test for heterogeneity, and the I2 statistic with its 95% uncertainty interval. This should be provided for the whole trial population and for each subgroup.

For each outcome, it is important to clearly state the number of trials providing data to that outcome as a proportion of the total number of trials identified in Subsection 2.2. If there are substantial differences in duration of follow-up, or time at which patients are at risk of an event, discuss the implications of this.

Table 2.6.2a Adapting results tables to include relevant information on pooled results

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trial ID | Proposed medicine *N* = | Main comparator *N* = | Relative risk (95% CI) | Risk difference (95% CI) |
| Trial 1 | *n* with event (%) | *n* with event (%) | RR (95% CI) | RD (95% CI) |
| Trial 2 | *n* with event (%) | *n* with event (%) | RR (95% CI) | RD (95% CI) |
| [etc] | [etc] | [etc] | [etc] | [etc] |

CI = confidence interval; *n* = number of participants with event; *N* = total participants in group

Table 2.6.2b Adapting results tables to include relevant information on pooled results

| Measurement | Outcome |
| --- | --- |
| Pooled result from random effects model (RR, 95% CI, k) | [add] |
| Pooled result from random effects model (RD, 95% CI, k) | [add] |
| Chi-square (*Q*) for heterogeneity: Q | [add] |
| Chi-square (*Q*) for heterogeneity: df | [add] |
| Chi-square (*Q*) for heterogeneity: p | [add] |
| I2 statistic with 95% uncertainty interval | [add] |

CI = confidence interval; k = number of studies contributing to the pooled estimate of effect

Comment on the consistency of treatment effects across the trials, the heterogeneity in the meta-analysis and the I2 statistic. In an attachment, provide a forest plot for each outcome (examining both relative treatment effects and absolute treatment effects). Discuss the results.

With reference to identified factors in Table 2.6.2, discuss and explain any heterogeneity of treatment effect across trials. Unexplained heterogeneity, depending on its direction and magnitude, generally makes the summary estimator less meaningful. Where there are strong biological or methodological grounds for heterogeneity, consider presenting sensitivity analyses that explore the impact of these factors. Discuss any implications of factors that may cause heterogeneity of treatment effect with regard to the proposed target population.

Where there are multiple trials reporting on a time-to-event outcome, present the pooled results across the trials, together with the number of trials contributing to the forest plot and the proportion of the trials among the total number of trials included in the submission. Data from multiple trials involving a particular time-to-event outcome may be statistically combined in a number of ways. Justify and reference the method(s) selected for pooling time-to-event data. Specify and describe this method in a short technical document as an attachment to the submission, and provide sufficient data to allow the results to be reproduced and verified independently.

The preferred method is to pool individual patient data from a Cox proportional hazards model, ensuring that the pooling method includes the trial as a covariate. If individual patient data are not available, pool the hazard ratios from the trial-level data to present the pooled hazard ratio with its 95% confidence interval. If hazard ratios with their standard errors are not all available, it might be possible to pool dichotomised data based on a common duration of follow-up. Expert biostatistical advice will be helpful for pooling the integral between Kaplan–Meier curves.

#### Adverse event data

Meta-analysis of adverse event data can be presented as for dichotomous data (see Table 2.6.1). Ensure that the duration over which adverse events were recorded is reported for each trial. If events per period at risk have been analysed using Poisson regression, pool these results across trials.

#### Meta-analyses of subgroups

When the submission relies on a subgroup analysis, this analysis will have been performed in Subsection 2.6, ‘Subgroup analyses’. The PBAC prefers that meta-analyses be presented for the subgroup, the complement of the subgroup and the whole trial population. It may be difficult to interpret results when subgroups have been included for only some of the trials, or where other included trials have enrolled a population that wholly reflects the subgroup. If this is the case, the meta-analysis of whole trial populations would be expected to elicit substantial heterogeneity due to the differences in populations across the trials. This should be presented and discussed.

If a meta-analysis of the whole trial population or of the complement to the subgroup has not been presented, but there are enough trials to make this feasible, justify the omission.

### Indirect comparisons

Baseline characteristics, treatment details, outcomes and outcome definitions that are relevant to the assessment of an indirect comparison are presented in Subsection 2.4 for the included studies. When relevant, cross-reference to where these have been presented and discussed in the submission.

#### Indirect comparison methodology

Describe the method(s) used for performing the indirect comparison, such as the Bucher single pairwise method, matching-adjusted indirect comparison (MAIC), simulated treatment comparison (STC), network meta-analysis (NMA) or mixed treatment comparison (MTC).

Where there are multiple common comparators in the network, pairwise comparisons should be performed for each of the possible pathways in the network. The Bucher method for performing indirect comparisons14 is widely used and describes how to indirectly compare the odds ratios from randomised trials that share a common reference arm. This method has been extended to include other treatment effect measures, such as relative risk, absolute risk and hazard ratio.15

More complex methods, such as NMA, may be presented as a supplementary analysis. Where an NMA is presented, ensure that the results of pairwise comparisons are presented for each link in the network. While methods exist that enable the consideration of nonrandomised studies in a network, the inclusion of nonrandomised studies is not preferred. Where nonrandomised studies are included, present the results of the NMA both with and without the nonrandomised studies.

Indirect comparisons that are unadjusted (such as a comparison between single arms) are not preferred by the PBAC and are difficult to interpret. MAICs and STCs are useful for single-arm studies, or where there are likely to be differences in baseline risk or in the event rates of the common reference arms.

Provide a statistical report addressing the approach(es) used in the submission. For complex approaches, such as MAIC, STC, NMA or MTC, provide sufficient detail that the analysis could be repeated. This may include programming code for statistical software such as Stata or WinBUGS. For methods that require individual patient data (MAIC or STC), the PBAC prefers that the individual patient dataset is provided in a spreadsheet and attached to the submission. Discuss and justify where this is not possible.

#### Transitivity assumption

Table 2.6.3 provides guidance on the key steps in assessing the transitivity assumption for indirect comparisons. Transitivity in an indirect comparison implies that the treatment comparisons within the indirect comparison do not differ with respect to the distribution of treatment effect modifiers. These steps are further described below.

Table 2.6.3 Steps in assessing the transitivity assumption

| Comparison | Issues to consider |
| --- | --- |
| A vs C direct randomised trials | 1. Assess the trials for factors that may cause heterogeneity of the A vs C comparative treatment effect 2. Assess the event rates in the medicine C populations 3. Assess the impact of the measure of comparative treatment effect for A vs C 4. Assess statistical homogeneity of the A vs C comparative treatment effect across trials |
| B vs C direct randomised trials | 1. Assess the trials for factors that may cause heterogeneity of the B vs C comparative treatment effect 2. Assess the event rates in the medicine C populations 3. Assess the impact of the measure of comparative treatment effect for B vs C 4. Assess statistical homogeneity of the B vs C comparative treatment effect across trials |
| A vs B indirect comparison | 1. Assess the sets of trials (ie the A vs C and the B vs C trials) for factors that may cause heterogeneity of the A vs B comparative treatment effect 2. Assess the event rates in the medicine C populations across the sets of trials 3. Assess the impact of the measure of comparative treatment effect for A vs B 4. Assess statistical homogeneity of the synthesised comparative treatment effect A vs B across the sets of trials (only possible if A vs B has been compared via multiple common references) |

##### Assessing factors that may cause heterogeneity of comparative treatment effects

Studies with substantial heterogeneity may have been excluded in Subsection 2.2. For studies retained in the analysis, identify any differences in trial characteristics or patient characteristics. For more information, see Appendix 5. If this table was completed during an assessment of heterogeneity for the inclusion of studies in Subsection 2.2, cross-reference the table; otherwise, it is preferable that the table be presented in an attachment to allow a comparison of factors within and across trial sets. Cross-reference to the baseline characteristics, treatment details and outcome definitions presented for the individual trials in Subsection 2.4, and discuss any differences.

Summarise any differences within and across trial sets, and briefly state the likely effect, if any, of differences on the comparative treatment effect. Where trials are heterogeneous for characteristics that have no impact on treatment effect, these differences do not affect the transitivity of the indirect comparison.

If confounders are present in an indirect comparison, it is possible to adjust for them using meta-regression. However, this would be an unusual situation because at least 10 trials per adjustment variable are required to achieve stability in the meta-regression results. An alternative may be to present a matching-adjusted indirect comparison or a simulated treatment comparison, in addition to the pairwise comparisons adjusted for the common reference arm (Bucher method).

##### Assessing event rates in the common reference groups

Compare the event rates across the common reference arms of the pairwise comparisons. If this has been presented in Subsection 2.2 or within an attachment to the submission, provide a cross-reference here. Report and discuss the implications of any differences in the event rates. Where event rates differ, and this is likely to be due to differences in patient baseline risk, it may be appropriate to present evidence of a constant relative (or sometimes absolute) treatment effect across baseline risks. This may improve the validity of the indirect comparison.

##### Assessing the impact of the measure of comparative treatment effect on statistical heterogeneity

Describe and justify the outcome measures used for the indirect comparison(s). It is preferable to perform the indirect comparison using an odds ratio, and convert this to an estimate of relative risk and absolute risk difference (although this will depend on the nature of the outcome).16 Present both relative and absolute treatment effect measures, and discuss the impact of the choice of the measure of comparative treatment effect. The most appropriate comparative treatment effect would be the one that minimises the variation in comparative treatment effect within each and all sets of included randomised trials. Specify this treatment effect measure.

##### Assessing statistical homogeneity of the comparative treatment effect across trials

Where the indirect comparison is based on multiple A vs C and/or B vs C trials, discuss the statistical heterogeneity within the meta-analyses of each trial set. Evidence of statistical heterogeneity using an absolute measure of comparative treatment effect, together with evidence of statistical homogeneity using a relative measure of comparative treatment effect (especially if this was explained by varying baseline risk), would provide reassurance that the general assumption of a constant relative treatment effect was applicable in the indirect comparison.

#### Results of the indirect comparison

Present the results of the indirect comparison as follows:

* For dichotomous outcomes, present the results of each individual randomised trial as the odds ratio, relative risk and absolute risk difference with 95% confidence interval between the common reference and the proposed medicine and the main comparator (this will likely require three separate tables).
* For time-to-event outcomes, present the results of each individual randomised trial as the hazard ratio with its 95% confidence interval between the common reference and the proposed medicine and the main comparator, as well as reporting the median event-free survival in each of the arms of the common reference, proposed medicine and main comparator.
* Where there is more than one randomised trial in a set, separately pool the treatment effect results between the common reference and the proposed medicine, and between the common reference and the main comparator. Present the relevant outcome measures with 95% confidence intervals, using the random effects model (presentation of meta-analyses is discussed in Subsection 2.6, ‘Meta-analyses’).
* Calculate the indirect estimate of effect, and present the estimate as a relative risk and odds ratio (or the ratio of hazard ratios) with its 95% confidence interval.
* Where there are multiple common reference arms that allow multiple pairwise indirect comparisons, present these and compare the indirect comparative treatment effects. Discuss any differences, noting that unexplained differences in treatment effects are difficult to interpret. It may be appropriate to present a supplementary network meta-analysis to synthesise the data available.

Where trials or trial sets have been excluded in Subsection 2.2, consider including sensitivity analyses in which these trials are included. Similarly, if trials or trial sets have been included that may be increasing heterogeneity, consider including sensitivity analyses in which these trials are excluded.

The presentation of the results will differ according to the type of data presented. Example tables for presenting results are provided in Subsection 2.5. These may be adapted to include indirect comparisons (Table 2.6.4).

Table 2.6.4 Summary of results of the indirect comparison

| Trial ID | Trial(s) of proposed medicine: treatment effecta OR (95% CI) | Trial(s) of proposed medicine: proposed medicine *n* with event/*N* (%) | Trial(s) of proposed medicine: common reference *n* with event/*N* (%) | Trial(s) of main comparator: common reference *n* with event/*N* (%) | Trial(s) of main comparator: comparator *n* with event/*N* (%) | Trial(s) of main comparator: treatment effectb OR (95% CI) | Indirect estimate of effectc OR (95% CI) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Trial 1 | [OR (95% CI)] | *[n* with event/*N* (%)] | *[n* with event/*N* (%)] | *[n* with event/*N* (%)] | *[n* with event/*N* (%)] | [OR (95% CI)] | – |
| Trial 2 | [OR (95% CI)] | *[n* with event/*N* (%)] | *[n* with event/*N* (%)] | *[n* with event/*N* (%)] | *[n* with event/*N* (%)] | [OR (95% CI)] | – |
| [etc] | [etc] | [etc] | [etc] | [etc] | [etc] | [etc] | – |
| Pooledd | [OR (95% CI)] | – | – | – | – | [OR (95% CI)] | [OR (95% CI)] |

CI = confidence interval; *n* = number of participants with event; *N* = total number of participants in group; OR = odds ratio  
**a** Proposed medicine over common reference  
**b** Main comparator over common reference  
**c** Inferred as proposed medicine over main comparator  
**d** Pooled using the random effects model

#### Indirect comparisons of subgroups

When the basis of the submission relies on a subgroup analysis, an analysis of these subgroups will have been performed in Subsection 2.6, ‘Subgroups’. The PBAC prefers that indirect comparisons are presented for the subgroup, the complement of the subgroup and the whole trial population. When this approach is not possible, the submission should attempt to present an alternative approach that does not require subgroups from trials. Where no meaningful alternative approach can be devised, clearly state why an indirect comparison that relies on whole trial populations cannot be performed.

#### Additional methods to quantify results

Clearly document and reference any additional methods used to quantify the results of the indirect comparison in terms of the magnitude of effect and its 95% confidence interval. These additional methods may include network meta-analyses or mixed treatment comparisons, meta-regressions, matching-adjusted indirect comparisons, or simulated treatment comparisons.

When documenting and referencing any additional methods, ensure that the methods are reproducible and can be independently verified.

In general, when presenting methods for establishing the comparative treatment effect using indirect data, the submission should present:

* an explanation of the method
* the statistical code used to perform the comparison, as well as an explanation of the variables included in the model. Where continuous variables have been translated to categorical or dichotomous covariates for the model, explain and justify the choice of threshold. Where the choice is arbitrary (eg median age, reduction of 10 mmHg), present a sensitivity analysis where the threshold is varied
* the assumptions required for each approach, how the assumptions were tested and the results of such testing
* where Bayesian methods have been used, a description and justification of the priors
* the results of the method and confidence intervals or intervals to capture the uncertainty in the approach
* heterogeneity statistics or bias statistics
* an interpretation of the results and the uncertainty in the results
* a comparison with the results from the simple indirect comparison method (Bucher’s method) and an explanation of any difference

where individual patient data are required by the statistical approach (eg matching-adjusted indirect comparison), the individual patient data, or a justification if these are not available.

Where appropriate, assess the implications for the conclusions of the indirect comparison if trials considered to be less comparable (eg in terms of trial populations or doses) are excluded.

### Adjustment for treatment switching

Adjustment for treatment switching is not necessary when the switching that occurs in the included studies either represents clinical practice or would represent clinical practice if the proposed medicine were to be listed on the PBS as requested. It is important that such switching is captured in Subsection 1.2 (‘Clinical management algorithms’) and appropriately dealt with in the economic evaluation in Section 3 and when estimating the budgetary implications in Section 4.

Where one or more of the included studies has participants that switched treatments, and the pattern of switching is inconsistent with current clinical practice for the comparator arm or future clinical practice for the intervention arm, the observed comparative treatment effect may not reflect the expected treatment effect in the Australian population. In these cases, adjustment may be appropriate.

Methods for adjusting the treatment effect for treatment switching may have limitations, introduce bias into the treatment effect estimate, and rely on assumptions that are difficult to validate. Therefore, if adjustment for treatment switching is appropriate, the PBAC prefers that the approach results in an estimate of comparative treatment effect that has a low risk of overstating the true comparative treatment effect.

#### Preferred approach

Describe the mechanism of treatment switching in the relevant treatment arms and whether treatment switching occurred in all relevant trial arms. Include the following points for each arm:

* the medicine(s) to which switching occurred
* the extent of the switching (see Table 2.6.5)
* current Australian clinical practice and the likely clinical practice if the proposed medicine is listed as requested
* whether the treatment switching from the comparator arm reflects current clinical practice (or how it differs)

whether the treatment switching from the intervention arm will reflect clinical practice if the proposed medicine is listed.

If switching (and the likely proportion of patients switching) from the comparator arm resembles current clinical practice, adjustment for treatment switching in this arm is **not** appropriate. If switching (and the likely proportion of patients switching) from the intervention arm resembles future clinical practice if the proposed medicine is listed, adjustment for treatment switching in this arm is **not** appropriate. If switching (or the extent of switching) does not reflect clinical practice, clearly describe the differences and address the following:

* State whether treatment switching and/or specific analyses to adjust for treatment switching were prespecified/allowed in the protocol. Reference the section of the protocol that discusses this.
* Present the baseline characteristics of switchers and nonswitchers, as well as the characteristics of participants just before switching. If this has been presented and discussed in Subsection 2.4, provide a cross-reference to the appropriate table and summarise the differences here. If participants switched primarily as a result of disease progression, present the characteristics of the participants who were at risk of switching (progressed) but did not switch and compare them with those who did switch.
* Provide the reasons for switching (eg disease progression, toxicity) and the patient numbers for each category.

To report the extent and timing of treatment switching, complete Table 2.6.5.

Table 2.6.5 Extent of treatment switching in the randomised controlled trials (cumulative across follow-up periods)

| Trial arm | Characteristic | Time point 1 | Time point 2 | Time point 3 |
| --- | --- | --- | --- | --- |
| Proposed medicine arm, number randomised = *N* | Number at risk of switchinga | s1 | s1 + s2 | etc |
| Number of treatment switches to the comparator arm | (m – c)1 | (m – c)1 + (m – c)2 | etc |
| Number of treatment switches to any subsequent active treatments (comparator or nonstudy therapies) | (m – t)1 | (m – t)1 + (m – t)2 | etc |
| Proportion of randomised patients who switched to the comparator arm (%) | (m – c)1/N | (m – c)1 + (m – c)2/N | etc |
| Proportion of randomised patients who switched to any subsequent treatments (comparator or nonstudy therapies) (%) | (m – t)1/N | (m – t)1 + (m – t)2/N | etc |
| Proportion of patients at risk of switching who actually switched to the comparator arm (%) | (m – c)1/s1 | (m – c)1 + (m – c)2/s1 + s2 | etc |
| Proportion of patients at risk of switching who actually switched to any subsequent treatments (comparator or nonstudy therapies) (%) | (m – t)1/s1 | (m – t)1 + (m – t)2/S1 + S2 | etc |
| Comparator arm | [As for proposed medicine arm] | [As for proposed medicine arm] | [As for proposed medicine arm] | etc |

(m–c)1 = number switched from the medicine to the comparator at time point 1; (m–t)1 = number switched from the medicine to any subsequent therapy at time point 1; *N* = number randomised; s1 = number at risk of switching at time point 1

**a** Patients at risk of switching are usually those who stop the assigned treatment and remain in the study (eg disease progression or medicine intolerance).

Several methods can be used to adjust survival estimates for treatment switching.17 The use of simple methods is acceptable when the estimate of comparative treatment effect is clearly towards the null. More complex methods, such as inverse probability of censoring weights (IPCW) or a rank-preserving structural failure time (RPSFT) model, have assumptions that are difficult to validate. If complex methods are used, the PBAC prefers to see the results of several commonly used methods, and clear justification where a method is not used. Where more complex methods are presented, also present the results of simpler methods as a reference.

In a technical document presented with the submission, provide a detailed discussion of the methods used, the assumptions underlying each method and whether the assumptions have been tested in the included trials. Clearly state whether the estimate of comparative treatment effect following adjustment for treatment switching is conservative, and provide evidence to support this claim. Where it is unclear whether the estimate is conservative, consider using the most conservative end of the 95% confidence interval for the treatment effect in an economic analysis, if presented. If the most conservative method is not used, present a detailed discussion of why the chosen method has a very low risk of overstating the treatment effect that would have occurred in the absence of treatment switching.

#### Results of adjustment for treatment switching

For each of the methods used to adjust the treatment effect for treatment switching, present the adjusted treatment effect and the 95% confidence interval. Explain any heterogeneity of treatment effects across the different methods for adjustment. Present the treatment effect and 95% confidence interval for the intention-to-treat analysis or per-protocol analysis for comparison.

Where a statistical analysis has been done to adjust overall survival estimates following switching from randomised treatment, present a Kaplan–Meier graph with curves for each treatment arm with adjustments for treatment switching. Display the 95% confidence intervals for each arm, and include a risk table with the graph to display the number of patients still at risk in each arm across regular time points for the follow-up period of the trial.

Where complex statistical approaches for adjusting for treatment switching have been used, perform a literature search for studies that report on the treatment arms in the absence of switching (eg historical controls). Discuss the applicability of the findings from the identified studies to the key trials in the submission. Compare the Kaplan–Meier curves of the non-switched studies with the modelled Kaplan–Meier curves and discuss where they differ.

In addition, where there is a largely uncontaminated estimate of progression-free survival, the submission may wish to present a discussion of whether progression-free survival is a valid surrogate for overall survival in Subsection 3.4. Where progression-free survival is a justifiable surrogate for overall survival, present a comparison of the estimate of overall survival by transforming progression-free survival with the overall survival determined by statistical methods used above to adjust for switching.

In general, the greater the number of approaches that converge on a similar result, the more certain the PBAC can be of the success of the statistical approaches used to adjust for switching. Where results can be ‘validated’ by comparison with historical controls or with overall survival calculated from a surrogate measure, this will also improve confidence in the statistical approaches. The presentation of only one or two approaches for adjusting for treatment switching, and the absence of corroborating evidence, will act to increase decision-maker uncertainty.

#### Adjustment for treatment switching in trials that rely on subgroups or indirect comparisons

There is a risk of bias associated with the use of subgroups, indirect comparisons and adjustment for treatment switching. Approaches that combine adjustment for treatment switching with either subgroup analyses or indirect comparisons (or both) may be regarded as poor-quality evidence. It is preferable to present evidence that does not combine these approaches, or ensure that the results of analyses combining these approaches can be clearly interpreted by the PBAC as conservative.

## 2.7 Applicability of the trial evidence

**INFORMATION REQUESTS**

**Identify treatment effect variation**

Identify any treatment effect variation in subgroups, compare the subgroups with the Australian population, and discuss how this is reflected in the therapeutic claim and economic analysis.

**Conduct an extended assessment of comparative harms**

Identify any evidence for delayed or rare adverse reactions, or dependence or abuse potential, and compare the proposed medicine with the main comparator in the Australian context.

**Describe any postmarketing surveillance studies**

Present details of any proposed studies (eg pharmacovigilance studies) to reduce uncertainty relating to the safety of the proposed medicine.

Subsection 2.7 explores possible differences between the observed comparative benefits and harms in the trial setting, and the benefits and harms that are likely to occur in the Australian setting should the proposed medicine be listed on the PBS. The PBAC is concerned when, compared with the trial evidence, the expected benefits of treatment with the proposed medicine over the comparator may be reduced in the Australian setting, or the expected adverse effects or harms of the proposed medicine may be greater in the Australian setting.

Where possible, the PBAC prefers to rely on estimates of the treatment benefits and harms derived from the whole population of a randomised trial that is applicable to the Australian setting. However, there may be some circumstances in which differences in treatment effect (benefits or harms) across subgroups may provide relevant information in a submission.

Subsection 2.7 is split into two parts. The first part addresses issues of effectiveness (and sometimes safety) by establishing whether there is any evidence of treatment effect variation across subgroups in the included studies. Where there is likely treatment effect variation, the PBAC is concerned if the variable defining the subgroups is more or less prevalent in the Australian setting than the trial setting, such that the average benefit of the proposed medicine for the whole trial population may not reflect the average benefit in the Australian setting.

The second part is concerned with establishing a more extensive safety assessment of the proposed medicine. Commonly, the main comparator has been available for longer than the proposed medicine, and its safety profile in terms of rare and serious adverse events may be better understood. To address this potential asymmetry, Subsection 2.7 requests the presentation of additional safety data and an overall conclusion on the safety of the proposed medicine compared with the main comparator.

### Treatment effect variation

For relevant outcomes (those on which the therapeutic claim is based, and those included in the economic evaluation), present an assessment of prespecified subgroups that indicate a treatment effect variation. The submission should seek to present subgroups (and their complements) according to Table 2.6.1.

Comparative treatment effects are often presented as relative or absolute measures. It is preferable that both relative and absolute comparative treatment effects are presented. Treatment effect variations across subgroups may be identified for only the absolute measure of comparative treatment effect or, less commonly, only the relative measure of comparative treatment effect. When determining whether to present a treatment effect variation that is identified only for relative or only for absolute comparative treatment effects, the submission should consider whether:

* the absolute or relative treatment effect is relevant to the therapeutic claim

the absolute or relative treatment effect is used in the economic analysis.

For example, where there is an identified difference in the absolute treatment effect across subgroups, yet the relative treatment effect remains constant, and the relative treatment effect is applied in the economic analysis, it may not be necessary to present the treatment effect variation. However, if the absolute treatment effect varies such that the anticipated benefit in the Australian population may no longer be considered meaningful, this is likely to be relevant to present.

#### Subgroups showing treatment effect variation

Where a subgroup analysis (indicating a treatment effect variation) is presented, the submission should seek to address the following:

* Discuss the pharmacological, biological and clinical plausibility of the treatment effect variation. Unexplained variation is difficult to interpret. Where the subgroup has been defined by a threshold value for a continuous covariate, justify the threshold used. An arbitrarily selected threshold (such as dichotomising a continuous measure) is difficult to interpret. Where subgroups are defined by a threshold of a continuous covariate, present sensitivity analyses of this threshold.
* Cross-reference to where the trial protocol discusses the prespecification of subgroups and the explicit hypothesis relating to the proposed subgroup. State whether treatment allocation was stratified by the subgroup. State whether the patient characteristics were balanced across the subgroups for all covariates, with the exception of the covariate defining the subgroup.
* Present the outcomes of statistical analyses for treatment effect variation, including uncertainty intervals, where appropriate.

State how many prespecified subgroup analyses were performed and whether there was any statistical adjustment accounting for multiple subgroups.

#### Comparison of trial setting and Australian setting

Where there is an identified treatment effect variation across subgroups, the results for the whole trial population may still be an appropriate estimate for the Australian population. However, where the proportion of patients in the subgroup of the trial is different from the proportion of patients in the Australian population that are represented by that subgroup, the results for the whole trial population may overestimate or underestimate the likely treatment effect in the Australian setting.

Present the distribution of Australian patients by the covariate used to define the subgroup, or cross-reference to Section 1, Section 3 or Section 4 where this is presented. Provide details of the sources of information and the methods used for identifying the sources of information. Subsection 4.1 discusses appropriate sources for epidemiological data. Where data are not presented elsewhere, present a summary of the Australian data and relevant publications or sources in an attachment to the submission. Ensure that the definition of the subgroup in the trial matches the definition used in the Australian setting, and discuss any discrepancies.

Present a comparison of the trial setting and the Australian setting for the covariate used to define the subgroup. An example is shown in Table 2.7.1.

Table 2.7.1 Example comparison of trial setting and Australian setting for subgroups

| Covariate | Treatment effect (observed in the trial) | Trial setting (reference) | Australian setting (reference) |
| --- | --- | --- | --- |
| Whole of trial | 0.77 [0.60, 0.98] | – | – |
| Mild/moderate disease | 0.85 [0.63, 1.14] | 60% (CSR, Table 14) | 80% (disease registry, Appendix 5) |
| Severe disease | 0.65 [0.43, 1.00] | 40% (CSR, Table 14) | 20% (disease registry, Appendix 5) |

CSR = clinical study report

#### Implications of treatment effect variation

Where the overall treatment effect in the trial differs from that expected in the Australian setting, discuss how this affects the therapeutic claim.

State how the treatment effects are applied in the economic analysis. It is preferable that the economic analysis considers the treatment effect of each of the subgroups individually. Where a cost-utility analysis is presented, the PBAC prefers that incremental cost-effectiveness ratios are presented for each subgroup.

### Extended assessment of comparative harms

Clinical trials are often inadequate for providing data on comparative harms for two key reasons:

* Trials tend to enrol patients who are healthier, have fewer comorbidities or concomitant medications, and have more stringent monitoring than the target population.

Trials are usually underpowered and of insufficient duration to detect important adverse events.

The submission should describe the adverse event profile of the proposed medicine and determine whether there is a potential for greater harm in the Australian population if the proposed medicine is listed as requested.

#### Trial applicability to the Australian setting

In some circumstances, trials may be adequately powered to detect differences for some adverse events, particularly if this difference is a key benefit of the proposed medicine over the main comparator. Where this is the case, it may be appropriate to address applicability issues for safety outcomes as performed above for effectiveness outcomes.

Discuss whether there are differences between the settings that may affect the comparative safety of the proposed medicine if used in the Australian setting. The extent to which the submission attempts to quantify the effect of the differences across settings depends on the prevalence and severity of the adverse event. In general, the submission should explore applicability issues for safety outcomes to reduce the PBAC’s concern that the comparative safety will be meaningfully worse in the Australian setting than in the trial setting. Factors that may influence the decision to present analyses for exploring applicability issues related to safety may include the following:

* The trial evidence identified a serious adverse event that is likely to be related to the medicine.
* There is a difference in the rate of this serious adverse event between the patients receiving the proposed medicine and the main comparator.

The factors in which the trial setting differs from the Australian setting may affect the expected rate of the serious adverse event.

Where the submission intends to present analyses exploring applicability issues related to safety outcomes, follow the approach described above for treatment effect variation.

#### Extended safety of the proposed medicine

Identify sources of evidence of comparative harms beyond the results of clinical trials. This broader assessment is especially important for serious adverse reactions that might occur in the long term or rarely, or when the proposed medicine has a new mechanism of action, or when the mechanism of action or evidence of early physiological or biochemical changes suggests an increased potential for subsequent harms.

The following sources of evidence on harms should be identified:

* any randomised trials against the nominated comparator that were excluded in Subsection 2.2
* any randomised trials against other comparators that were excluded in Subsection 2.2
* the most recent periodic safety update report for the proposed medicine
* the most recent development safety update report for the proposed medicine
* any pharmacovigilance studies

any studies identified in a separate search, including nonrandomised study designs (such as registry data or observational studies) and studies involving the proposed medicine in other indications (or justify why this may not be appropriate).

Describe the search strategy for identifying nonrandomised studies and studies involving the proposed medicine in other indications. Provide any identified publications, the periodic safety update report and the development safety update report in an attachment to the submission. Some sources of evidence will be inappropriate or provide little additional value. The submission should not attempt to report on case studies, small case series or studies of short duration. In this case, some judgment may be required regarding the presentation of the most relevant studies, which will tend to be larger or longer than the studies included in Subsection 2.2. Where the number of studies found is large and studies are excluded on the basis of study size, state the threshold for exclusion.

Present a summary of the findings from each source of evidence, with additional detail or tabulated data provided in an attachment to the submission, if relevant. Where the source of evidence does not report safety, or the safety conclusions are no different from those in the included studies, state this. Provide a brief synthesis of all the sources and propose an overall conclusion of comparative safety against the nominated comparator.

The extended assessment of comparative harms should not form the basis of a claim of superiority for safety of the proposed medicine over the nominated comparator where superiority cannot be adequately justified on the basis of trial data included in Subsection 2.2.

### Postmarketing surveillance

Where long-term safety is uncertain, or there are concerns regarding rare events, it is preferable that a postmarketing surveillance study is proposed. Where the efficacy of the drug in the Australian population or maintenance of a response beyond the clinical trial period is uncertain, a pharmacovigilance study designed to monitor the clinical event rates predicted in the economic evaluation is appropriate.

Present the details of any proposed postmarketing surveillance study (pharmacovigilance study), including the method of data capture, the outcomes of concern and how the results of the study will be communicated. Assess whether the interpretation of the results would be affected by the subsequent listing of another medicine in a similar population.

## 2.8 Interpretation of the clinical evidence

**INFORMATION REQUESTS**

**Interpret the evidence**

Provide a summary assessment of the overall clinical trial evidence presented.

**Classify comparative effectiveness and safety (therapeutic conclusion)**

State the therapeutic conclusion for the proposed medicine.

### Evidence interpretation

Provide a summary assessment of the clinical evidence presented in the submission (without re-presenting evidence presented in other sections). Include consideration of:

* the level of the evidence, taking account of the directness of the comparison (Subsection 2.2)
* the quality of the evidence (Subsection 2.3)
* the clinical importance and patient relevance of the effectiveness and safety outcomes (Subsection 2.4)
* the statistical precision of the evidence (Subsections 2.5 and/or 2.6)
* the size of the effect (Subsections 2.5 and/or 2.6)

the consistency of the results across the clinical trials presented (Subsections 2.5 and/or 2.6).

**Example:**

*The submission is based on two randomised trials of [proposed medicine] versus [comparator]. One trial was open-label, and one trial was blinded. However, as the primary outcome is overall survival and there was little cross-over, knowledge of allocation is unlikely to affect the results. The primary outcome and several secondary outcomes are highly patient relevant. The results showed that [proposed medicine] resulted in a statistically significant improvement in survival compared with [comparator]. The improvement in median survival was 4.5 months, and this is considered to be clinically important and patient relevant. Both trials reported a similar improvement in survival. For most patient-relevant outcomes (use of pain medication, tumour-related symptoms), [proposed medicine] showed an improvement compared with [comparator], with the key exception of quality of life, where the differences were not statistically different but favoured [comparator] early in the trials. This may be explained by the more commonly reported nausea and bowel symptoms reported by patients in the [proposed medicine] arm.*

### Therapeutic conclusion

The interpretation of the clinical data presented in Section 2 of the submission is crucial in determining the success of the submission. It is important to classify the therapeutic profile of the proposed medicine in relation to its main comparator (ie whether it is therapeutically superior, inferior, equivalent or noninferior to the comparator).

The therapeutic conclusion should be a simple and unequivocal statement that is supported by evidence provided in the submission. An example of such a statement would be:

*[Proposed medicine] is superior/noninferior/equivalent/inferior in terms of comparative effectiveness over [comparator].*

*[Proposed medicine] is superior/noninferior/equivalent/inferior in terms of comparative safety over [comparator].*

It may be appropriate to describe the treatment regimen rather than simply the proposed medicine or the comparator, particularly if either or both are delivered in combination with other treatments or for differing durations. The description should be short, yet capture important aspects of the proposed treatment (eg the proposed medicine in combination with X and administered for 18 cycles (or until recurrence) is superior in terms of comparative effectiveness over the comparator given in combination with X administered until recurrence).

# Section 3 Economic evaluation

Section 3 presents an economic analysis of substituting the proposed medicine for the main comparator.

## Introduction

Section 3 of a submission to the PBAC presents an economic evaluation of substituting the proposed medicine for the main comparator in the context of the listing requested. Requests are made for a full and transparent description of the economic evaluation, with sensitivity analyses to validate the evaluation.

The economic evaluation initially depends on whether the therapeutic conclusion shows that the proposed medicine is:

* therapeutically superior to the main comparator, or
* noninferior (equivalent) to the main comparator, or
* therapeutically inferior to the main comparator.

When the proposed medicine is concluded to be therapeutically superior or noninferior **and** is anticipated to provide cost savings to the health system, a cost-minimisation approach is appropriate.

When the proposed medicine is concluded to be (i) therapeutically superior but will result in additional costs to the health system, or (ii) therapeutically inferior but will result in lower costs, the preferred type of economic evaluation is a cost-utility analysis (CUA) or cost-effectiveness analysis (CEA). Where there are uncertainties or trade-offs across health outcomes (eg both increased effectiveness and reduced safety or differing safety profiles), or where the proposed medicine has an inferior therapeutic conclusion, a cost-consequences analysis should be presented (in addition) to clarify the nature of all health effects.

Economic evaluations of therapeutically inferior medicines are rare; therefore, there is less experience in interpreting and comparing results of this type of economic evaluation.

Flowchart 3 gives an overview of these options for Section 3 of the submission.

Flowchart 3 Overview of the options for Section 3 of a submission to the PBAC

Section 2: Clinical evaluation leads to a therapeutic conclusion of superior, inferior or noninferior. If the therapeutic conclusion is superior or inferior, then Section 3: Economic evaluation should use a cost-effectiveness or cost-utility analysis (or similar), which is found in Section 3A (follow guidance for cost-effectiveness analysis). Then go to Section 4: Budgetary implications.
If the therapeutic conclusion from Section 2 is noninferior, then Section 3: Economic evaluation should use a cost-minimisation approach, which is found in Section 3B (follow guidance for cost minimisation). Then go to Section 4: Predicted use of the medicine in practice.

Go to the relevant Section 3 for your submission:

* **Section 3A** – guidance for preparing a cost-utility or cost-effectiveness analysis

**Section 3B** – guidance for presenting a cost-minimisation approach.

# Section 3A Cost-effectiveness analysis

This section provides information requests for preparing Section 3 of a submission when there is a therapeutic conclusion of superiority but use of the proposed treatment will potentially result in additional costs to the health care system.

The PBAC’s preferred approach is for the economic evaluation to be based on results from direct comparisons of randomised trials (see Section 2), with any translations presented transparently in a stepped manner. For economic evaluations that rely on results from either indirect comparisons or comparisons based on nonrandomised studies, the modelled evaluation should adapt the stepped approach.

Flowchart 3A shows the key flow of information in Section 3 when there is a superior therapeutic conclusion leading to a cost-effectiveness analysis (or similar).

Flowchart 3A Overview of information requests for Section 3 of a submission to the PBAC based on a cost-effectiveness analysis (or similar)

Section 3A: Cost-effectiveness analysis (for a superior or inferior therapeutic conclusion from Section 2)
3.1 Overview and rationale: What are the key features of the economic evaluation? Summary description, decision addressed by the evaluation, perspective, discounting, generation of base case.
3.2 Methods and structure: How was the economic model developed? What modelling technique was used? Review the economic literature, describe the conceptual structure of the model, describe the computational methods used in the model.
3.3 Population in the model: Does the model population reflect the Australian population? Describe demographic and patient characteristics in the model, and consistency across the submission; perform translation studies as required.
3.4 Transition probabilities: What probabilities are used in the model? Is transformation or extrapolation required? Define all event transition probabilities, identify values used in sensitivity analyses, transform surrogate to final outcomes, describe any extrapolation of the time horizon.
3.5 Health outcomes: How are health outcomes incorporated in the model? Specify intermediate and final outcomes.
3.6 Resource use and costs: What health care resource items and costs will change if the proposed medicine is listed? Define direct health care resource items and costs.
3.7 Model validation: Are all aspects of the model valid? Tabulate variable and discuss any deficiencies.
3.8 Uncertainty analysis: What are the areas of uncertainty in the model? Define and justify any uncertainty relating to model input parameters, including sensitivity analysis.
3.9 Results: Is the proposed medicine cost-effective? Provide stepped presentation of results, disaggregated and aggregated results, and base-case incremental cost-effectiveness ratio.
3.10: Summary of model inputs and key assumptions. Present a table of key variables and assumptions.
Go to Section 4: Predicted use of the medicine in practice.

## 3.1 Overview and rationale of the economic evaluation

**INFORMATION REQUESTS**

**Summarise the key components of the economic evaluation**

Complete the summary table provided to describe the economic evaluation.

**State the type of economic evaluation**

Identify whether the submission uses a cost-utility analysis, cost-effectiveness analysis, cost-consequences analysis or cost-benefit analysis.

**Describe the decision that the economic evaluation is addressing**

Identify the objective and primary decision addressed by the evaluation, with cross-reference to Subsection 1.1. Include a decision tree or analytic diagram.

**Define the perspective(s) taken for analysis**

Confirm that the base-case analysis is from a health care system perspective, and describe any alternative perspectives taken in any supplementary analyses.

**Describe the discounting methodology**

For analyses exceeding one year, confirm the discounting methodology for costs and outcomes in the base case (prespecified variable). Justify any additional sensitivity analyses other than those recommended.

**Describe the generation of the base case**

Describe whether the base case is trial based or modelled using a stepped approach.

### Summary table of economic evaluation

Complete Table 3.1.1 to summarise the key components of the economic evaluation.

Table 3.1.1 Key components of the economic evaluation

| Component | Description |
| --- | --- |
| Type(s) of analysis | [eg cost-effectiveness analysis, cost-utility analysis] |
| Outcomes | [eg events avoided, life years gained, quality-adjusted life years] |
| Time horizon | [x] days/months/years in the model base case (vs [y] weeks/years in the key trial(s))  Sensitivity analyses, include time horizons of [...] |
| Method(s) used to generate results | [eg cohort expected value, Markov, microsimulation, discrete event simulation] |
| Health states | [If a state transition model, provide number of health states and brief description] |
| Cycle length | [x] days/weeks/months/years |
| Transition probabilities | [Describe the source(s)] |
| Software | [eg Excel 2010, @RISK, TreeAge Pro Suite] |

### Type of economic evaluation

If the proposed medicine has been shown to be therapeutically superior to the main comparator, an economic evaluation to estimate cost-effectiveness is required. This would generally take the form of a cost-effectiveness analysis (CEA) and/or a cost-utility analysis (CUA). Both of these should identify the incremental health outcomes (as nominated for the CEA, or as quality-adjusted life years [QALYs] in the case of a CUA) and incremental health costs, and the incremental cost-effectiveness ratio (ICER), for the proposed treatment compared with the comparator.

Alternative types of economic evaluation (eg cost-benefit analysis or cost-consequences analysis) are not preferred. (See Glossary for definitions.)

#### General guidance on preferred and supplementary types of economic evaluation

The various types of economic evaluation are not necessarily mutually exclusive. It may be appropriate to present more than one analysis to make a stronger case for cost-effectiveness (eg both CEA and CUA, or cost-consequences analysis and CUA).

##### Cost-utility analysis

CUA is generally preferred where:

* there is a claim of incremental life-years gained in the economic evaluation, to assess the impact of quality adjusting that survival gain

relevant direct randomised trials report results using a multi-attribute utility instrument (MAUI).

The preference for a full CUA is less clear where:

* there is a claim of quality-of-life or disability improvements but no reliable estimate of utility or utility change associated with the relevant health states or treatment, despite an exhaustive search

there are differential quality-of-life impacts arising from the therapies being compared in a submission to derive a common outcome across submissions.

In the situation of an improvement in quality of life but not in quantity of life, a submission should present a CUA or justify the decision to not transform the quantified health outcomes via a utility valuation.

There might be a trade-off between the most theoretically appealing approach and the degree of uncertainty in the estimate of incremental cost-effectiveness. For example, estimating the cost-effectiveness based directly on the outcome from a trial might be relatively robust. However, in moving to a CUA (which is theoretically easier to interpret and compare across submissions and medical conditions), additional sources of uncertainty might be introduced to determine utility weights for various health states. Submissions should make these trade-offs and their implications explicit.

Where transformations or external data sources are required, presentation of a CEA and/or cost-consequences analysis, with a stepped adjustment to a CUA, is recommended to transparently indicate the implications of the transformation and/or use of external data.

##### Cost-effectiveness analysis

Where a CEA is presented as the primary economic analysis, the incremental health outcome (eg life-years, other health events etc) presented in the analysis should be representative of overall health in the context. Justify the choice of outcome and describe the extent to which the outcome captures relevant health considerations. Justify why the outcome cannot be reliably translated into QALYs.

Detail whether the health outcome was reported directly in the clinical evaluation (Section 2), and/or whether it required transformation from a surrogate and or translation for the economic evaluation setting. Justify any translations required.

##### Cost-consequences analysis

Cost-consequences analysis compares the incremental costs of the proposed medicine with the comparator and describes the various incremental differences (consequences) in a range of relevant (nonaggregated) outcomes that would occur with use of the proposed medicine. It can be presented if the proposed medicine is demonstrated to have a different profile of effects that are not adequately captured by a single outcome measure. There might be trade-offs between the two medicines in terms of the directions of the changes in effectiveness and safety (and within effectiveness and safety).

A cost-consequences analysis presented alone is generally less helpful for PBAC decision making, but may be useful as a supplementary or preliminary analysis to either a CEA or a CUA. Disaggregated analysis may provide transparency in identifying changes in patterns of health care resource provision or specific health outcomes of interest that are not obvious in an aggregated evaluation.

##### Cost-benefit analysis

Cost-benefit analysis (see Glossary) is not preferred. It is unlikely to be helpful to most PBAC deliberations (further reasons are given in Appendix 6). Thus, although monetary valuation of health outcomes is allowed, it is considered to be supplementary to utility valuation. If a cost-benefit analysis is presented in the absence of a CUA, the PBAC is less likely to regard it as a convincing basis for a claim of cost-effectiveness.

### Decision addressed by the economic evaluation

By definition, the economic evaluation is intended to inform a decision. Therefore, the structure of the evaluation needs to allow comparison of the streams of outcomes and resources following the use of either the proposed medicine or its main comparator, in order to calculate the incremental outcomes and costs between these streams.

The included decision-tree diagram should characterise the primary decision that the economic evaluation addresses, based on the information provided in Subsection 1.1. This diagram is to provide a conceptual overview rather than the complete computational structure of the economic model. However, following the decision point, the tree should also define alternative choices, uncertain events (and probabilities, if practical) and outcomes. For readability, where the model is particularly complex, branches can be collapsed and summarised, provided that this is clearly indicated, and the detail of collapsed branches or a more suitable complete diagram of the model structure (eg a health state transition diagram) is provided in Subsection 3.2.

Ensure that the pathways depicted in the decision tree are consistent with the existing and proposed clinical management algorithms presented in Section 1. If the diagram(s) of the clinical management algorithms detailed in Section 1 contain sufficient information to represent the decision analytic of the economic model, do not reproduce the diagrams, but cross-reference to Section 1.

Ensure that codependent diagnostic decisions and outcomes are included, if relevant (Part B, P4).

### Perspective of the economic analysis

The PBAC seeks a ‘health care system’ perspective in economic analyses, and this should be the perspective of the base-case analysis presented.

This perspective includes health and health-related resource use (costs and cost offsets) and health-related outcomes. Costs and outcomes that are not specifically related to ‘health and/or provision of health care’ should not be included in the base case. Further detail is provided in Subsections 3.6 and 3.7.

If the sponsor wishes to present an economic analysis from a broader societal perspective and quantitatively incorporate considerations beyond the patient and the health care system, this should be presented as a supplementary analysis in addition to (not in place of) the base case that uses a societal health care system perspective.

Supplementary analyses may be appropriate where the proposed intervention has important societal implications extending beyond the health outcomes of the patient receiving the medicine and the health care system. This may be with respect to either resources or outcomes – for example, costs/savings or socially relevant outcomes in domains such as education, housing or justice, or economic productivity impacts. In circumstances where the beneficiaries of health or other relevant outcomes are broader than the treated patient population (eg community, carers, dependants), include these as supplementary analyses.

### Discounting

Consistent with standard economic evaluation, the values of costs and benefits incurred or received in the future are expected to be discounted to reflect the present value. The PBAC requires base-case economic analyses to incorporate discounting of both costs and outcomes at a uniform, annual (compounding) rate of 5% per year for all costs and health outcomes that occur or extend over a time period beyond one year.

Present sensitivity analyses using a fixed 3.5%, 2.5% and 0% discount rate for both costs and outcomes. If the results of the economic evaluation are sensitive to discounting, and the sponsor wishes to present analyses using other discounting methodologies (eg a different uniform rate, differential rates, time-varying rates), present these as supplementary analyses, and explain and justify the alternative approach.

### Generation of the base case

#### Trial-based economic evaluation

If the trial(s) recruited patients who are directly representative of those for whom listing is sought, trialled the proposed medicine in the circumstances of use expected to apply to the requested PBS listing, and directly measured and reported patient-relevant end points over an appropriate time horizon, a trial-based evaluation is sufficient to provide the base case of the economic evaluation.

#### Modelled economic evaluation (including stepped adjustments to a trial-based evaluation)

If the evidence obtained directly from trials is insufficient to measure the full clinical and economic performance of the proposed medicine compared with its main comparator in the Australian setting, additional adjustments to the trial data, or modelling, will be needed to generate the base-case economic evaluation.

Any translations of the primary effectiveness data and applications of additional assumptions in the model should be fully justified and transparent in their application. It is strongly recommended that economic models are constructed in a manner that allows the sequential presentation of results before and after key translational steps.

The stepped approach may include some or all of the following stages:

1. Begin with the key trial(s), and present the outcomes and costs as identified in the key trial(s).
2. Apply treatment effects on health care resource use and health outcomes to the intended PBS population and the circumstances of use identified by the requested restriction. This may involve one or more steps – for example:
   * re-estimation of the treatment effect in the PBS population (eg use of selected subgroups or weighted trial outcomes to improve applicability to the Australian demographic)
   * incorporation of Australian circumstances of use or clinical practice (eg with respect to patterns of resource use)
   * incorporation of other necessary and justifiable assumptions to improve the representativeness of the model (eg incorporation of resource use or outcomes associated with adverse event data, or subsequent treatment lines that are not captured in the trial data or previous translations).
3. ​Extrapolate health care resource use and health outcomes (for the proposed PBS use) as required over the appropriate time horizon (detailed in Subsections 3.2 and 3.5).
4. Transform health outcomes, if necessary, to final economic outcomes (eg using utility weights to obtain QALYs) (detailed in Subsection 3.6).

The base-case result is represented by the final incremental costs, outcomes and ICER after the translation of the evidence from the main trial(s) has been completed.

## 3.2 Computational methods and structure of the economic analysis

**INFORMATION REQUESTS**

**Review the literature**

Present the results of a review of relevant economic literature and any additional clinical literature relevant to the model that has not been presented in Sections 1 or 2.

**Describe the conceptual model structure**

Report and justify the conceptual model and its development process, define and justify the time horizon, and describe any modifications to the implemented model.

​**Describe and justify the computational method (modelling technique) used**

Define and justify the choice of modelling technique used to implement the conceptual model. If an individual-level modelling technique is selected, explain why the conceptual model could not be implemented as a state transition model.

**Provide a fully accessible electronic copy**

Ensure that all variables in the electronic copy of the economic evaluation can be changed independently during the evaluation.

**Attach copies of relevant economic studies and original sources of data**

Provide copies of all papers identified in the economic evaluation (from the literature review and original sources of all data or opinion).

### Literature review

Present the results of a literature search for reports of economic evaluations of similar treatment algorithms, or the proposed and similar medicines, focusing on the structure of the existing models.

Present any additional clinical literature (eg additional clinical trials, guidelines, natural history studies, burden of disease studies) that informs the conceptual model structure and has not already been presented in Subsection 1.2 or Section 2.

### Structure of the conceptual economic model

The conceptual model represents all relevant and important health states or clinical events along the disease pathway, and should be consistent with the treatment and disease algorithms presented in Subsection 1.2 of the submission.

The model structure should be informed by the results of the literature review of economic evaluations, as well as other relevant clinical and economic literature, including clinical trials, clinical guidelines, natural history studies and burden-of-disease studies.

Important clinical events should be disaggregated where there are important differences with respect to mortality, disease progression, associated costs, or quality-of-life effects, and the distribution of the disaggregated clinical events differs between the intervention and comparator.

The process for development of the conceptual model should also inform whether any event experienced in the model should influence the risk of experiencing subsequent events – this may inform the choice of computational method.

Multiple plausible model structures may be defined, which may be tested as part of a structural sensitivity analysis.

The conceptual model structure(s) should be assessed by experts in the field to establish face validity. The structure of the conceptual model, including the exclusion of potentially relevant states or events, should be justified with reference to relevant data sources and expert input. The potential impact of any exclusions on the model outputs should be discussed. Where the model structure differs from existing models, explain the basis for the selection of the submission’s approach.

Structural uncertainty should be examined and addressed in Subsection 3.8.

#### Time horizon of the evaluation

Define and justify the time horizon over which the costs and outcomes of the proposed medicine and its main comparator are estimated. The time horizon should be sufficient to capture all important differences in costs and outcomes between the intervention and the comparator. The default is a lifetime horizon, although shorter horizons may be used for interventions that do not affect mortality and have temporary quality-of-life effects.

The validity of a model with a lifetime horizon is determined by the population of the model, not the choice of a lifetime horizon. A model that predicts that 50% of patients with an advanced cancer survive for 10 years is not invalid because a lifetime horizon was selected, but because the input data predict implausible outputs. Uncertainty regarding the extrapolation of costs and outcomes over a lifetime is presented in Subsection 3.4.

#### Input data and the structure of the implemented model

The methods used to identify data to populate the model’s input parameters should be described – for example, whether systematic or ad hoc reviews of the literature were undertaken, or how relevant primary data sources, including registries and observational studies, were identified.

The identified data may not inform the population of the defined conceptual model structure. In such cases, it is acceptable to review the conceptual model structure in the light of the available data to assess the face validity of alternative model structures that better conform to the available data. If a valid alternative model structure can be defined, the revisions to the structural model should be described and any potential effects on the model outputs discussed.

If an alternative valid model structure cannot be defined, expert opinion may be used to estimate input parameters for which empirical data were not identified (Subsection 3.4)

### Computational methods

If a trial-based economic evaluation is being undertaken using individual patient data on costs and outcomes from a clinical trial(s), describe the software in which the analysis was undertaken.

For model-based economic evaluations, identify the most appropriate modelling technique for the implementation of the final model structure(s).18 General advice is to select the least complicated modelling technique for which it is feasible to implement the specified model structure, moving from decision trees to cohort-based state transition models to individual-level modelling techniques.

#### Decision trees

Decision trees are useful for models with short time horizons and may be implemented in general spreadsheet software such as Excel, or in specialist software, such as TreeAge. Good-practice guidelines for the use of decision trees should be followed.19

#### Cohort-based state transition (or Markov) models

Cohort-based state transition models should be used to represent longer time horizons for models that can be represented using a manageable number of health states under the constraints of the Markovian (memoryless) assumption. These models may also be implemented in general spreadsheet software such as Excel, or in specialist software, such as TreeAge.

Good-practice guidelines for the use of state transition models should be followed.20 In particular, the following factors should be considered when implementing a cohort-based state transition model:

* Is it reasonable to assume that transition probabilities from each defined health state are independent of states that may have been experienced before entering each state? Health states that describe pathways through the model are required to represent the effects of previous events on subsequent transition probabilities.
* Do transition probabilities vary according to how long individuals have remained in each health state? Tunnel states are required to represent time-varying transition probabilities.
* Is the eligible population homogeneous, or is variation in patient variability normally distributed? This issue most commonly refers to the age of the eligible population, but may include other factors. If relevant factors are not normally distributed, separate analyses of the model may be run and the outputs aggregated.

What is the likely impact of alternative cycle lengths on the model outputs? The factors determining the selected cycle length should be described.

A half-cycle correction is the default approach to representing the time of transition between states, although an alternative correction factor may be proposed with justification.

#### Individual-level (or microsimulation) models

Individual-level modelling approaches are appropriate when a defined model structure cannot be feasibly implemented as a cohort-based model. The most common approaches include Markov microsimulation and discrete event simulation (DES) models.

The justification for a more complex model structure that requires an individual-level model should reference the characteristics of the model structure that reduce the feasibility of implementing the structure as a cohort-based model. The justification should also describe how these features are expected to produce a more accurate representation of disease pathways, costs and patient outcomes.

Individual-level models are generally implemented in specialist software, such as TreeAge, Simul8 or AnyLogic. Methods for the application of individual-level models should follow published guidelines on good research practices.21,22

The submission of an individual-level model should be accompanied by a cohort-based model that implements a nested, less complex model structure. A nested model requires no additional data collection, and provides a basis for model verification. It also provides quantitative estimates of the value of an individual-level model, and objective justification for the use of such models.

The mechanism and rationale for any significant differences in the outputs of an individual-level model and a nested cohort-based model should be clearly discussed.

#### Other modelling techniques

If the results from simpler models are robust to plausible sensitivity and scenario analyses, use of more complex modelling techniques is unnecessary.23 If an alternative modelling technique is used, describe and justify how the approach leads to more accurate and valid results. For example, in the clinical area of infectious diseases, the use of dynamic transition models or agent-based models to represent herd immunity may be justified if a simple nondynamic model does not demonstrate cost-effectiveness.

Note that more complex modelling techniques may be less transparent, and the model assumptions may be less certain, which may result in the PBAC having less confidence in the cost-effectiveness claim. It is preferable that the Pharmaceutical Evaluation Branch is forewarned of the use of more complex modelling techniques.

### Fully accessible electronic copy of the economic evaluation

Provide access to the electronic copy of the economic evaluation. Make sure that all variables can be changed independently, including allowing the base case of the economic evaluation to be completely respecified and a new set of sensitivity analyses to be conducted with each respecified base case. Make sure that the economic evaluation is able to produce results following respecification of variables within reasonable running times.

Software packages that support decision analyses and can be readily evaluated by the Pharmaceutical Evaluation Branch currently consist of:

* TreeAge Pro Suite

Excel 2010, including @RISK®, but not necessarily including all advanced features and plug-ins (eg Crystal Ball).

Economic evaluations constructed using any of these may be submitted without earlier arrangement with the Pharmaceutical Evaluation Branch.

### Sources of data

Provide copies of the original sources of all data (beyond those already presented in Section 2) or expert opinion used in the model, in an attachment or technical document. Cross-reference the extraction of data from each source to the page, table or figure number of the source document.

## 3.3 Population in the model or analysis

**INFORMATION REQUESTS**

**Describe the demographic and patient characteristics**

Use summary statistics (where appropriate) to describe the characteristics of the population entering the economic model.

**Assess the consistency of the population characteristics across the submission**

Identify any inconsistencies between the indicated Australian population and the clinical study population(s) that inform the parameters in the economic analysis. Discuss how these might affect the relevance of the cost-effectiveness analysis.

**Provide translation studies, if required**

Undertake translation studies as required so that the modelled population reflects the Australian population who are likely to be treated as per the proposed listing.

### Demographic and patient characteristics

The demographic and clinical characteristics of the indicated population should be described using summary statistics, including information on distributions around the central estimate (eg standard deviations, confidence intervals). Relevant patient and clinical characteristics may include age, sex, ethnicity, medical condition, severity of the medical condition, and comorbidities.

Provide details of any additional circumstances of use relating to the proposed medicine that are relevant to the definition of the eligible population. These may include:

* restrictions on the position of the proposed medicine in the clinical management algorithm (eg first-line treatment or second-line treatment)

specific requirements of the proposed medicine in terms of geography, facilities or location of delivery (including any limitation to the hospital or other approved setting, or any specification of equipment or facilities that need to be available during or soon after administration).

Describe and justify the heterogeneity in patient characteristics that is represented in the cost-effectiveness analysis.

### Consistency and translation of the evidence on clinical effectiveness

Assess the consistency between the demographic and patient characteristics of the target population reflected in the requested restriction and the clinical management algorithms presented in Section 1, and the study populations and circumstances of use described in Section 2.

Compared with the trial population and setting, would a difference in response to the proposed medicine or comparator be expected in the indicated Australian population?

The PBAC is particularly concerned if the baseline risk (ie prognostic characteristics) of patients differs between the trial evidence and the target population, or if patients could be expected to respond better to the proposed medicine or the main comparator in one setting than in another setting. Caution should be taken when converting relative treatment effects across jurisdictions with different baseline risks.

Assess whether any differences are likely to influence the treatment effect or any other variables in the model. In each case, justify the choice of the following conclusions:

* Differences are immaterial with respect to the cost-effectiveness of the proposed medicine.
* Differences are relevant but methods of translation can appropriately apply the trial data to the indicated Australian population.

There is uncertainty with respect to how the trial data should be applied.

For each translation study, provide an analytical plan that clearly describes:

* the issue and the specific question to be addressed by a translation study
* the data to be used and their sources (and justification for the choice of data where there are multiple possible sources)
* the methods of the translation study (with sufficient details to enable independent verification of the analysis)

the results of the translation study, including an estimate of the comparative treatment effect (both relative and absolute) and the 95% confidence interval.

Common methods for the analytical plan may include subgroup analysis, regression analysis, meta-regression or use of other published studies. The selected approach should be justified.

Where uncertainty remains, identify and describe sensitivity analyses that will be undertaken to examine the impact of the uncertainty on the base-case cost-effectiveness results.

### Translation across different populations

#### Subgroup analysis

Subgroup analysis may be a reasonable approach to estimate differences in treatment effect, particularly if a randomised clinical trial was stratified by the relevant characteristics and only a small number of characteristics differ. In other cases, care should be taken in constructing and drawing conclusions from subgroup analyses because of the potential for confounding and spurious statistical significance.

The submission should discuss the clinical rationale and plausibility of any observed variation in treatment effect (or the lack of variation) across subgroups. If multiple trials are used in a subgroup analysis, assess the reason for any observed heterogeneity of treatment effect within a subgroup across studies.

#### Regression or meta-regression

Regression analysis has an advantage over stratified analyses based on subgroups because it can examine more than one covariate (or difference between the clinical trial participants and the target PBS population) simultaneously. Where multiple trials are available, a meta-regression may be appropriate.

Meta-regression may be performed at the study level or at the individual patient level (where the study is entered as a covariate). When meta-regression is performed at the study level, it is only useful if the number of trials is large (5–10 trials for each covariate examined).

Where a regression analysis is used, provide the following in a technical attachment to the submission:

* a clear description of the regression method, the associated assumptions, how these assumptions were tested and the results of the tests
* the statistical commands or syntax used to perform the analysis, with a description of the variables (including a description of the thresholds used to define categorical variables)
* the direct output from the statistical program

the dataset used in the statistical program (or a justification, where this is not provided).

Present the results in the main body of the submission and provide an interpretation.

#### Published studies

If it is not possible to inform translation using the direct clinical evidence for the intervention, describe the reasons and seek relevant published data. Published studies concerning the proposed medicine (or comparator) or the same class of medicines in the proposed eligible population should be identified systematically. Present the search strategy, selection criteria and PRISMA flowchart in an attachment to the submission.

Report the relevant findings from the included studies in the main body of the submission. Describe the interpretation of the findings in relation to the proposed medicine and the application of the findings to inform the translation.

## 3.4 Transition probabilities

**INFORMATION REQUESTS**

**Present transition probabilities**

Systematically define and describe all transition probabilities incorporated into the base-case economic model, and identify values used in sensitivity and scenario analyses.

**Justify and describe the transformation of surrogate to target clinical outcomes**

Justify the use of a surrogate outcome(s) and describe how this measure(s) was transformed to estimate treatment effects on a target clinical outcome.

**Explain any requirements for extrapolation**

Compare the time horizon for the economic analyses with the time horizon of the available clinical data, and describe any extrapolation methods used. Present sensitivity or scenario analyses.

### Presenting transition probabilities

Transition probabilities inform the movement of patients between health states in decision trees or state transition models. In a discrete event simulation, time-to-event parameters are analogous to transition probabilities. Transition probabilities or time-to-event parameters may differ by treatment or by how long a patient has been in a particular health state (time-varying probabilities).

Transition probabilities that differ by treatment are generally estimated using the clinical evidence described in Section 2 (with translation as appropriate). Cross-reference the relevant subsections of the submission for the clinical evidence and translation studies.

Other transition probabilities describe the progression of a disease following the experience of an intermediate outcome event, after which the same transition probabilities are applied to all individuals, regardless of treatment allocation. The methods used to identify and analyse relevant data to derive these transition probabilities should be clearly described and justified.

For each transition probability, present the point estimate and interval estimates (eg 95% confidence intervals). The methods used to derive interval estimates should follow good-practice guidelines (eg using probability distributions based on agreed statistical methods for alternative types of input parameters).24

Potential correlation between alternative transition probabilities should also be assessed. Describe and justify any assumed correlation, and the methods used to represent correlation and present the resulting correlation parameters.

Correlation should generally be represented between disease progression probabilities in the intervention and comparator groups. The application of a relative treatment effect parameter to comparator transition probabilities links the transition probabilities. If a relative treatment effect parameter is not applicable, bootstrapping can be applied to individual patient data to represent correlation. Otherwise, expert elicitation may be used to inform a correlation parameter, noting that the PBAC is likely to take a conservative view of the resulting estimates.

### Transforming surrogate health outcomes to target clinical outcomes

In some cases, the clinical evidence presented in Section 2 provides no data (or underpowered or premature data) on comparative treatment effects in a relevant health outcome that is used in the model (referred to as a target clinical outcome). Studies may provide stronger evidence of a comparative treatment effect in a proposed surrogate measure, which is claimed to represent a relevant comparative health outcome. The claimed relationship between the change in treatment effect in the proposed surrogate measure and the change in treatment effect in the target clinical outcome used for the economic evaluation should be justified and quantified.

The transformation of a change in proposed surrogate measure to predict a change in target clinical outcome should follow the framework for assessing a proposed surrogate measure, as detailed in Appendix 7.

It may not be necessary to fully detail the transformation of a proposed surrogate measure to a target clinical outcome when the PBAC has previously accepted the surrogate outcome as valid and **all** of the following apply:

* The proposed treatment effect is within the range of the comparative treatment effect previously identified in the clinical evidence associated with transformation.
* The proposed medicine will be used in the same population as the previously accepted transformation.

The medicines in the evidence used to previously validate the surrogate, the main comparator and the proposed medicine are all in the same class or have a similar mechanism of action.

There is no general principle regarding the extent to which underpowered or premature treatment effect data for a target clinical outcome justify the transformation of a proposed surrogate measure. However, if a proposed surrogate measure is transformed and direct treatment effect data for the corresponding target clinical outcome are also available, the surrogate and direct data should be applied separately to populate the model. Application of both approaches provides a form of model validation if both approaches provide similar estimates of the comparative treatment effect on the target clinical outcome over the longer term.

If a proposed surrogate measure is transformed, sensitivity analyses should represent both the uncertainty in the estimation of the comparative treatment effect on the proposed surrogate measure and the uncertainty of the transformation. This is therefore more complex than where direct measures of comparative treatment effect for a target clinical outcome are used.

### Extrapolation

Extrapolation may be justified when all important differences in costs and outcomes between the intervention and comparator(s) groups are not represented over the time horizon for which observed data are available.

Generally, transition probabilities should be derived from observed time-to-event data to the time point at which the observed data become unreliable as a result of small numbers of patients remaining event-free. Beyond this point, extrapolated transition probabilities should be derived from appropriately estimated parametric survival curves based on observed data. Describe and justify the selected time point beyond which extrapolated transition probabilities are applied. External data may be used to justify the selected time point – for example, the point at which one or more of the curves fitted to the clinical trial data deviates from a curve fitted to observational data from a similar patient cohort with a larger sample over a longer follow-up period. Alternative truncation points should be tested in the sensitivity analysis.

If available, individual patient data should be used to extrapolate survival or time-to-event data beyond the horizon of a trial. The following sections represent current literature on extrapolation for economic evaluation,25,26,27 noting that gaps remain.

#### Extrapolating individual patient time-to-event data

Survival analysis is used to extrapolate individual patient time-to-event data. The extrapolation process should comprise the following three stages, which should be described and justified:

1. Decide whether an assumption of proportional hazards is appropriate beyond the observed data.

If proportional hazards are assumed, survival curves are fitted to the time-to-event data for the comparator, and a relative treatment effect parameter is applied to the derived transition probabilities to estimate transition probabilities for the intervention group.

To inform assumptions around proportional hazards, visually inspect relevant plots of the data, including cumulative hazard plots and log-cumulative hazard plots, and assess the clinical rationale for continued proportional hazards. Generally, nonproportional hazards should be assumed in the extrapolation period unless an assumption of proportional hazards is strongly supported by all forms of visual inspection and an a priori clinical rationale.

If proportional hazards are assumed, sensitivity analysis should be undertaken to test the effects of this assumption.

2. Fit alternative survival models to the available data and assess their relative goodness of fit.

A range of alternative survival models should be fitted to the observed data. The range of models to be tested should include more flexible extrapolation approaches with multiple points of inflexion (eg piecewise spline models28), which better facilitate extrapolation based on the section of the Kaplan–Meier curve that is most representative of long-term survival.

Akaike’s information criterion (AIC) and the Bayesian information criterion (BIC) statistical tests should be used to compare the relative goodness of fit of alternative parametric models. The AIC and BIC statistics trade off the improved fit of more flexible models with the potentially inefficient use of additional distribution parameters. Model residuals should also be presented to assess the absolute goodness of fit of the models to the available data.

A range of the best-fitting models should be tested in the sensitivity analysis.

3. Assess the plausibility of the predictions in the unobserved period.

The extrapolated treatment effect needs to be clinically plausible in the context of the treatment effect demonstrated in the key trial. Older randomised trials, observational studies or registries may report time-to-event data for similar patient groups and medicines over a longer time horizon than the clinical trial data used to fit the extrapolated survival curves. If comparable, the extended data from the older study(ies) can inform the validity of the fitted extrapolation curves by comparing predicted survival probabilities with those observed in the older data over a longer time horizon. Established methods for the calibration of model parameters could be used to weight alternative extrapolation curves.29,30

The hazard ratio between the intervention and comparator groups resulting from the independent extrapolation of the survival curves should be plotted over the time horizon of the model. If the extrapolated hazard ratio remains significantly less than 1, and this is not considered to be clinically plausible, two general scenarios should be tested:

* Apply a hazard ratio of 1 to estimate transition probabilities in the intervention group beyond a time point at which the treatment effect is assumed to cease.

Apply a hazard ratio such that the intervention and comparator curves converge at a plausible time point.

When considering the extrapolated treatment effect, explicit consideration should be given to clinical decisions regarding the cessation or continuation of treatment. Ensure that all assumptions in this regard are stated and justified, and are applied consistently in the modelling of respective treatment costs.

Parametric uncertainty should be assessed by bootstrapping the clinical trial data, stratified by treatment group. For each bootstrapped sample, the best-fitting extrapolation curves for the intervention and comparator should be selected. The bootstrapped set of paired intervention and comparator curves can be analysed to identify relevant ranges to be used in deterministic sensitivity analyses (eg based on the difference in the areas under the paired intervention and comparator curves).

#### Other individual patient extrapolation issues

For categorical data that describe the experience of multiple intermediate or outcome events, use a two-stage process of modelling the time to any event, combined with a multinomial logistic model to define the probabilities of the aggregate event being each of the competing events. A time covariate can be included in the multinomial logistic model to represent time-varying probabilities. The other option is to fit independent competing risks time-to-event models for each event, but this approach is likely to overestimate parameter uncertainty as a result of the assumed independence of the multiple events modelled.

For continuous variables, data can be formatted into categories, or a generalised estimating equation (GEE) model could be used.

#### Extrapolating published time-to-event data

If individual patient time-to-event data are not available, published Kaplan–Meier curves should be extrapolated.

Using graph digitiser software, extract survival probabilities from the published curves. Alternative constant (ie exponential) or monotonically increasing and decreasing (eg Weibull or Gompertz) hazard functions should be fitted to the extracted survival data beyond the last point of inflexion to the time point at which the observed data become unreliable as a result of small numbers of patients remaining event-free.

Tests of the relative and absolute goodness of fit of the alternative curves should be presented, and the best-fitting curve should be used in the base case. The alternative models should be tested in the sensitivity analyses.

## 3.5 Health outcomes

**INFORMATION REQUESTS**

**Justify and describe the intermediate and final health outcomes**

Define and justify the final health economic outcome used in the model.

**Apply utility weights to health outcomes (where applicable)**

Provide details of how all utility weights were identified and applied. Where the measurement of quality of life uses a MAUI, provide details of the selected MAUI, including whether Australian-based preferences were used to map utilities. If other patient-reported outcome measures are used, describe these fully.

### Intermediate and final health outcomes and economic outcomes

Nominate and justify the final health economic outcome that is considered to best reflect the comparative clinical performance of the interventions and will be presented as the denominator unit in the base-case ICER. This should generally be based on the outcome measure that most closely and validly estimates the final health outcome from a patient perspective (eg survival, decreased events, overall quality-of-life improvement).

Where a combination of outcomes (either intermediate or final outcomes, or both) are relevant to the patient, it is desirable to capture these collectively. These should be transformed and summed as QALYs, rather than presenting cost-effectiveness analyses for multiple outcomes.

If QALY gains are not estimated using utility weights derived from data collected in the clinical trials reported in Section 2, the outcomes reported in Section 2 should be transformed to estimate QALY gains. This generally involves applying utility weights to time spent in different health states that represent the experience of target clinical outcomes.

The transformation of surrogate outcomes to inform the experience of target clinical outcomes, and the estimation of transition probabilities to inform the time spent in different states are presented in Subsection 3.4.

If a claim is made for a change in nonhealth outcomes, or the submission identifies health-related outcomes in people other than the patient receiving treatment (eg quality-of-life benefits for family, decreased carer burdens), these should not be included in the base-case evaluation, but may be presented as supplementary analyses (see Appendix 8).

### Applying preference-based (utility) weights to health outcomes to generate QALYs

Estimates of the utility from the within-trial evidence (presented in Section 2) may inform direct estimates of QALY gains in the intervention and comparator populations, or inform utility values applied to health states in a cost-effectiveness model.

Additional studies may be needed to estimate appropriate utility weights, either to map utility values to nonpreference-based patient-reported outcome measures that are available from the clinical evidence reported in Section 2, or to estimate utility weights for health states included in a cost-effectiveness model.

#### Use of quality-of-life data from the clinical trials to estimate QALYs

In all instances when incorporating trial-based patient-reported outcome data into the economic model, the following broader issues should be explicitly addressed in the context of the submission:

* Are the trial participants representative of the population for whom listing is requested? Refer to Subsection 3.3, as needed.
* If quality of life is not the primary outcome, is the trial adequately powered to detect a difference in the survey results? As with all secondary outcomes, the results would need to be assessed with reference to the conclusion from the primary analysis of the trial.
* ​Is there a ‘healthy cohort effect’? This is where the patients who are sickest or progressing fastest are least likely to complete patient-reported outcome data forms, particularly in postprogression states in fatal conditions. Consider the responder numbers and drop-outs. The healthy cohort effect generally results in an overestimate of utility weights. The direction of any associated bias may depend on whether the treatment and comparator are associated with different utility weights, the relative extent of the effect across different arms and health states, and the time spent in different health states. Any impact on the overall ICER should be identified.
* Is there potential for systematic bias where progressed health states are defined by nonsymptomatic events (ie identified by investigations that may or may not reflect clinical practice)? Provide details.

Is it appropriate to pool patient-reported outcome data across arms of a trial? This may be appropriate where patient numbers are small and for post-treatment states, but not in other circumstances where treatment (rather than disease) directly affects quality of life (eg due to serious adverse events and any associated long-term implications, or imposed limitations). Justify the approach taken.

##### Multi-attribute utility instruments

The PBAC considers that estimation of QALYs by delivering an acceptable MAUI to participants in a randomised double-blind trial, together with an appropriate scoring algorithm, is an accepted methodology.

Acceptable MAUIs are the Health Utilities Index (HUI2 or HUI3), the EQ5D (‘EuroQol’), the SF-6D (a subset of the Short Form 36, or SF-36) or the Assessment of Quality of Life (AQoL) instrument. Use of other MAUIs should be well justified. If other patient-reported outcome measures are used, these should be detailed in Subsection 2.4.

If a MAUI has been used in an included study to estimate utility weights, clearly state where and when the scoring algorithm was derived, and consider how applicable it is to the general Australian population. It is preferred that Australian-based preference weights are used in the scoring algorithm used to calculate utility weights.

Consider the duration over which the MAUI was administered compared with the duration of the condition of interest. Also, if a generic MAUI is used, consider whether it captures all important disease-specific factors that might be relevant for the particular disease pathways and treatments.

##### Mapping of patient-reported outcome measures to MAUIs

If the initial patient-reported outcome measure is not a MAUI, present details of a validated method of mapping the results into preference weights. State whether Australian-based value sets are incorporated.

If there is no reliable method of transforming the patient-reported outcome data into utility weights for the model, describe why this is not possible and detail whether the patient-reported outcome data from the trial can still be used to inform or validate the economic model.

#### Scenario-based methods to indirectly elicit utility weights

Scenario-based methods involve the use of vignettes describing the symptoms of a health state to a sample population, usually a representative general population sample, from whom utility weights are elicited using an accepted preference-based method.

Where utility weights cannot be estimated from data collected in the clinical studies reported in Section 2, or there are significant concerns regarding the reliability and relevance of trial-based utility weights, scenario-based methods may be used to estimate utility weights that can be applied to health states in a cost-effectiveness model.

Methods to elicit preferences include the standard gamble, time trade-off and discrete choice experiments, and other conjoint analysis methods.

It is difficult to minimise the many sources of analyst bias that are intrinsic to the scenario-based utility approach, including in the unblinded nature of the construction and presentation of the scenarios (eg incomplete inclusion and differential focus on alternative aspects of quality of life), the design of the methods to elicit values, and the analysis and interpretation of the results. Describe all stages of a scenario-based study in detail and explain efforts to minimise potential bias.

​Present the results of the utility study as the point estimate of the mean elicited utility weight for each health state with its standard deviation and 95% confidence interval.

##### Supplementing trial-based weights

If trial-based utility weights were obtained, justify the inclusion of scenario-based health state utilities. Present both sets of methods and results, and compare the interpretation.

If using a scenario-based utility valuation to value health outcomes beyond the time horizon of the trial, include one or more health states captured and valued within the trial in the scenario-based study to validate the commonality of the trial-based and scenario-based utility weights.

Present supporting evidence for any claim of increased sensitivity of a scenario-based approach to identify real differences in utility.

#### Population matching studies

Another form of utility study involves the recruitment of a separate sample of patients with characteristics similar to those enrolled in the clinical trials reported in Section 2. These matched patients complete a MAUI reflecting their current health state, which informs the estimation of utility weights for the health states in the cost-effectiveness model.

Potential sources of bias for such studies include the possibility of systemic differences between the clinical study participants and the matched patients, and the inability to blind the sampled patients from the objectives of the study. If there are important symptomatic medicine toxicities, it might be important that the sampled patients are exposed to the medicine and its toxicities at the time the MAUI is completed.

Matched patients should complete other patient-reported outcome measures that were completed by the trial participants, and the results of this concurrent instrument should be used to more closely match utility study participants to the clinical study population.

#### Use of external published sources of utility weights

Utility estimates are sometimes available from the literature. The validity of the derived utility weights depends on the applied elicitation methods and the relevance of the study populations.

Present details of search strategies, and inclusion and exclusion criteria used to identify relevant utility studies. Assess the validity of all identified studies, including:

* how representative the health state in each identified study is of the health state in the economic evaluation (including the type and severity of symptoms, and the duration of the health state)
* how the health state was captured (eg MAUI, scenario based)
* how the preference was elicited (eg standard gamble or time trade-off)
* what sample was chosen to respond to the MAUI questionnaire or scenario (eg the general public, patients, carers, health care professionals)
* what assessment was made of the nature and direction of bias that might arise, given the sample and methods

how the sensitivity analyses examined variation in the identified utility options.

The use of different published studies to inform utility weights for alternative health states is discouraged because of the potential for inconsistency in the methods and populations from which utilities were derived.

## 3.6 Resource use and costs

**INFORMATION REQUESTS**

**List and detail health resource use and costs**

Identify and define the direct health care resource items for which there would be a change in use if the proposed medicine is substituted for the main comparator.

**Where a special pricing arrangement is proposed, the submission should detail costs with and without the proposed arrangement. The details of any special pricing arrangement should be described in Subsection 1.4.**

### Direct health care resource use and costs

For within-trial analyses, identify the health care resource items for which there is a change in use associated with substituting the proposed medicine for the main comparator.

For model-based evaluations, estimate cost weights representing the resources used within a relevant time period (eg a model cycle for a state transition model) for every health state. Alternative health state costs may be defined for patients receiving the intervention and the comparator – for example, to account for differences in adverse event rates.

See the *Manual of resource items and their associated costs* for additional detail regarding all aspects of this section.

#### Health care resource items

The following resource items should be considered, where appropriate:

* medicines (direct costs of treatment and medicines used to treat adverse reactions)
* medical services, including procedures
* hospital services
* diagnostic and investigational services
* community-based services

any other direct medical costs.

For each resource item, define the natural units and quantify the number of natural units provided to patients in each treatment group, or to patients remaining in a health state for a relevant time period (eg number of packs of medicine dispensed, number of general practitioner consultations, number of episodes of hospital admission).

Use of the intervention and comparator therapies is generally derived from the clinical studies reported in Section 2. However, in some studies with incomplete follow-up, this may represent a truncated mean and require adjustment. For therapies used episodically, calculation of the cost per patient per year would also require additional calculations. Justify and explain any calculations, as necessary.

The amount of a medicine or other resource provided (eg dispensed) is the relevant economic measure, rather than the amount of resource consumed. Wastage still represents a consumption and incurred cost, and should be incorporated in the model.

Describe and justify the basis for these estimates, specifying the source of the information. The pattern of provision of health care resources may be measured prospectively in the course of a clinical study, by retrospective review of relevant records, by administration of a questionnaire or survey, or through the use of diaries. Distinguish between data on resource use that are directly derived from the primary evidence, and extrapolations or modelling of resource use beyond that available from the primary evidence. Justify any choice to use data that are not consistent with data from the primary evidence, particularly where this has an important impact on incremental costs, as revealed in the sensitivity analyses.

It might be reasonable to exclude types of health care resources that have such a small impact on incremental costs that they would not have a material influence on the conclusion of the economic evaluation. If resources are excluded for this purpose, state this explicitly and justify their exclusion.

#### Allocation of prices (cost values) to resources

Present all unit prices and costs in Australian dollars, and ensure consistency with respect to the price year of analysis. The price year should be explicit and as close as possible to the date of the submission.

Section 3 adopts a broad perspective for the valuation of health care resources, so all contributions to the costs of health care resources – including those paid for by patients, governments, health insurance agencies and any other part of society – should be considered for inclusion in the economic evaluation. Where available, use the source of costs recommended by the *Manual of resource items and their associated costs*. If there are important reasons to use different unit prices from those recommended, present these as a sensitivity analysis, justify each and describe its source or generation. Ensure that any different unit price is consistent with the broad perspective of including all contributions to the costs of health care resources.

Fully detail all other sources of costs, alternatives identified and any assumptions relating to them. If multiple estimates are identified, justify the estimate used in the base case and present alternative plausible estimates in sensitivity analyses.

If historical estimates of costs are used, detail all information sources and the methods used in their estimation. Justify the use of the historical cost source as relevant and the best estimate available. Use the most relevant available Australian price index (eg total health and health industry–specific price indexes published by the Australian Institute of Health and Welfare) to make adjustments for inflation and estimate current prices.

Value future costs at current prices (ie do not make allowance for future inflation in the calculations), consistent with using constant prices in the economic evaluation.

#### Presentation of resource use and cost information

A format for summarising the minimum dataset of health care resource items and their associated unit costs relevant to the economic evaluation is suggested in Table 3.6.1. These are samples for each identified category, which are consistent with the manual but are not comprehensive of all types of health care resource items, natural units of measurement, or sources of unit costs.

Table 3.6.1 Indicative list of health care resource items, unit costs and usage included in the economic evaluation

| Type of resource item | Subtype of resource item | Natural unit of measurement | Unit cost (AUD) | Source of unit cost | Usage for the proposed medicine | Usage for the comparator |
| --- | --- | --- | --- | --- | --- | --- |
| Pharmaceutical products | Proposed medicine | Dispensed price for maximum quantity of item | x | Proposed | [add usage] | [add usage] |
| Comparator | Dispensed price for maximum quantity (if a medicine) | x | PBS item code if PBS-listed medicine | [add usage] | [add usage] |
| Medical services | Type of medical practitioner attendance | Consultation | x | MBS item code according to current MBS, as schedule fee | [add usage] | [add usage] |
| Hospital services | Hospital admission | Episode for identified AR-DRG | x | DRG Item code according to current AR-DRG Public Sector Estimated Cost Weights, as average cost | [add usage] | [add usage] |
| Diagnostic and investigational services | Type of service | Visit | x | MBS item code according to current MBS, as schedule fee | [add usage] | [add usage] |

AR-DRG = Australian Refined Diagnosis Related Group; AUD = Australian dollars; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme

All steps taken to calculate costs in the economic evaluation should be presented in a way that allows independent verification of the calculations.

If a complete presentation of costs is very large, the calculations may be presented in an accompanying technical document. Provide clear cross-references between the calculations and the main body of the submission, and include an electronic version of the detailed calculations.

## 3.7 Model validation

**INFORMATION REQUESTS**

**Describe and justify methods used to validate a model-based cost-effectiveness analysis**

Describe efforts made to assess alternative forms of model validation and provide justification for not reporting on particular forms of validation.

**Present model traces over time**

For extrapolation models, present model traces (eg Markov traces) describing the proportion of patients in each health state over time.

### Validation of the economic model

The submission should address the following questions to validate the economic model. These are derived directly from the validation tool for cost-effectiveness models published by the Assessment of the Validation Status of Health-Economic Decision Models (AdVisHE) Study Group.31 Some of these questions may not be applicable to a particular model; in this case, justify why the question is not applicable.

#### A. Validation of the conceptual model

1. Face validity (concept): Have experts been asked to judge the appropriateness of the conceptual model? (If yes, who are they? why are they expert? to what extent do they agree that the conceptual model is appropriate? If no, why not?)
2. Cross-validity testing: Has this model been compared with other published conceptual models? (If yes, cross-refer to this comparison. If no, why not?)

#### B. Input data validation

1. Face validity: Have experts been asked to judge the appropriateness of the input data? (If yes, who are they? why are they expert? to what extent do they agree that the conceptual model is appropriate? If no, why not?)
2. Model fit testing: When input parameters are based on regression models, have statistical tests been performed? (If yes, cross-reference to this analysis. If no, why not?)

#### C. Validation of the computerised model

1. External review: Has the computerised model been examined by modelling experts? (If yes, who are they? why are they expert? are they independent? what were the results of the review? If no, why not?)
2. Extreme value testing: Has the model been run for specific, extreme sets of parameter values to detect any coding errors? (If yes, detail the tests and outcomes or cross-reference to the relevant attachment. If no, why not?)
3. Testing of traces: Have patients been tracked through the model to determine whether its logic is correct? (If yes, detail the tests and outcomes or cross-reference to the relevant attachment. If no, why not?)
4. Unit testing: Have individual submodels of the computerised model been tested? (If yes, was a protocol describing test, criteria and acceptance norms predefined? Detail or cross-reference to the relevant attachment. If no, why not?)

#### D. Operational validation

1. Face validity (outcomes): Have experts been asked to judge the appropriateness of the model outcomes? (If yes, who are they? why are they expert? to what extent do they conclude that the outcomes are reasonable? If no, why not?)
2. Cross-validation testing (outcomes): Have the model outcomes been compared with outcomes of other similar models? (If yes, was the comparison to published information only? can differences be explained? Detail or cross-reference to the relevant attachment. If no, why not?)
3. Validation against outcomes using alternative input data: Have model outcomes been compared with outcomes obtained using alternative input data? (If yes, detail or cross-reference to the relevant attachment. If no, why not?)
4. Validation against empirical data: Have model outcomes been compared with empirical data? Consider both data sources used in the model (ie dependent validation) and data sources not used in the model (ie independent validation). A more specific request for a comparison of model trace outputs with empirical data is also detailed below. If this is not undertaken, explain why.

#### E. Other validation techniques

1. Have any other validation techniques been performed? If yes, detail these.

### Model traces over time

Model traces for the proposed medicine and its comparator can inform the face validity and the validity of the computerised model. Present traces representing the proportions of the cohorts in each health state over time, and the cumulative sum of the undiscounted costs and outcomes (eg QALYs) over time. Comment on whether each of the model traces makes sense.

Where possible, model traces should be compared with corresponding empirical data to inform either dependent or independent model validation (eg compare predicted clinical events with observed data on the natural history of the medical condition). Comment on, and explain, any differences indicated by this comparison.

## 3.8 Uncertainty analysis

**INFORMATION REQUESTS**

**Define parameter uncertainty and structural uncertainty**

Estimate the uncertainty around the parameters in the model and assess any structural uncertainties.

**Describe and justify sensitivity and scenario analyses**

Explain and justify the methods used to represent the uncertainty around the model’s input parameters. Describe the analyses to be reported and justify the omission of potential analyses that are not reported.

### Defining parameter uncertainty

The following recommendations are based on good-practice guidelines for model parameter estimation and uncertainty analysis.32

Use commonly adopted statistical standards to represent the uncertainty around the true value of each uncertain input parameter. Beta distributions are a natural match for transition probabilities and utility values, gamma or log normal for costs or utility decrement parameters, log normal for relative risks or hazard ratios, and logistic distributions for odds ratios. The use of alternative distributions should be justified.

Where there is very little information on a parameter, adopt a conservative approach by defining a broad range of possible parameter values. Never exclude parameters from uncertainty analysis on the grounds that there is insufficient information to estimate uncertainty.

Correlation among parameters should be considered. Jointly estimated parameters, such as those from a regression analysis, will have direct evidence on correlation that should be reflected in the analysis. In the absence of empirical evidence of correlation, correlation coefficients may be defined to test the effects of elicited correlation estimates on the incremental cost-effectiveness results.

### Examination of structural uncertainty

If multiple plausible model structures are defined, assess the potential impact of the alternative structures on the model outputs. If a substantial impact is predicted, use a formal approach to characterise the structural uncertainty. Parameterisation is recommended where there is sufficient clinical evidence or expert opinion to parameterise structural assumptions. Scenario analyses assess the impact of model assumptions, most commonly around the structure of the economic model. Scenario analyses are recommended if there is insufficient clinical evidence, and results should be reported under each set of plausible structural assumptions.

### Defining sensitivity analyses to be undertaken

Interval estimates (eg 95% confidence intervals) derived from fitted probability distributions should be used to define the ranges of the parameter values tested in the deterministic sensitivity analyses.

Univariate deterministic sensitivity analyses should be undertaken for all uncertain input parameters, or natural groups of input parameters (eg cost or utility weights for all target clinical outcomes). Multivariate sensitivity analyses should test the combined effects of the uncertainty around the true values of input parameters to which the base-case incremental cost-effectiveness result was shown to be sensitive in the univariate analyses.

Describe the multivariate sensitivity analyses to be undertaken, and justify the inclusion and exclusion of parameters in these analyses.

If undertaking a probabilistic sensitivity analysis on a cohort-based state transition model, the number of iterations (sets of randomly sampled input parameter values included in the analysis) should provide stability in the model outputs across multiple analyses using alternative random number seeds.

If undertaking a probabilistic sensitivity analysis on an individual-level model (eg a discrete event simulation), the number of iterations may be selected to balance stability of model outputs and a reasonable time required to undertake a probabilistic sensitivity analysis (eg a few hours, rather than a few days).

### Defining scenario analyses to be undertaken

Describe and justify the inclusion and exclusion of potential scenario analyses that are undertaken to assess the impact of alternative model assumptions on the base-case incremental cost-effectiveness results.

If multiple plausible model structures have been defined and the uncertainty around the true model structure has not been parameterised, scenario analyses should be run for each alternative model structure.

Other scenario analyses may assess the effects of substantial use of the proposed medicine beyond the intended population and circumstances of use defined in the requested restriction. This wider population or circumstances would be expected to have demographic and patient characteristics and circumstances that differ from the target population and circumstances.

## 3.9 Results of the economic evaluation

**INFORMATION REQUESTS**

**Calculate the cost per patient**

Present an estimate of the cost per patient for the proposed medicine.

​**Provide a stepped presentation of the cost-effectiveness results**

Present the incremental cost, incremental effectiveness and incremental cost-effectiveness results after sequential stages of the economic evaluation, culminating in the presentation of the base-case incremental cost-effectiveness ratio.

**Present disaggregated and aggregated costs and outcomes**

Provide fully disaggregated estimates and aggregated summaries of modelled costs and outcomes for both the proposed medicine and its main comparator.

**Present and discuss sensitivity and scenario analyses**

Present the results of sensitivity and scenario analyses.

### Intervention costs per patient

Present the expected costs of the proposed medicine and comparator (individually) per patient per course for an acute or self-limited therapy, or the cost per patient per year for a chronic or continuing therapy. This estimate should be consistent with estimates of per-patient use in Section 4.

### Stepped presentation of results

If the model translates clinical data, present the results of the key steps involved in transforming the comparative data (from Section 2) into the modelled base-case estimate of incremental cost-effectiveness.

Begin with an analysis of costs and outcomes that are directly associated with the comparative data presented in Section 2. Where the following procedures are undertaken to estimate the base case, sequentially present re-estimated costs and outcomes (and interim results) for each step:

* transformation(s) for applicability
* transformation of surrogate outcomes to final clinical outcomes
* extrapolation of data over longer time periods
* additional data or assumptions

transformation of clinical outcomes to economic outcomes (QALYs).

Identify the steps or assumptions of the model that have important impacts on the ICER, and cross-reference the related variables or assumptions identified in Subsection 3.8.

Table 3.9.1 shows an example of how to present this analysis.

Table 3.9.1 Presentation of the stepped derivation of the base case economic evaluation from the clinical study data

| Data | Outcomes: proposed medicine | Outcomes: comparator | Costs: proposed medicine | Costs: comparator | Incremental effectiveness | Incremental costs | Incremental cost-effectiveness |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Comparative study data (as presented in Section 2)  Setting: (trial setting)  Time horizon: (trial follow-up) | [A] (surrogate outcome)a | [B] (surrogate outcome)a | [C]b | [D]b | [A – B] (surrogate outcome) | [C – D] | $[C – D]/[A – B] per [surrogate outcome] |
| Study evidence **transformed from surrogate to clinical outcome** (A→E, B→F)c | [E] (clinical outcome) | [F] (clinical outcome) | [C] | [D] | [E – F] (clinical outcome) | [C – D] | $[C – D]/[E – F] per [clinical outcome] |
| Study evidence transformed to clinical outcome e **Australian population and/or Australian setting** (may need multiple steps) | [modified E]d | [modified F]d | [modified C]e | [modified D]e | [modified E – modified F] | [modified C – modified D] | $[modified E – modified F]/[modified C – modified D] per [clinical outcome] |
| Study evidence transformed to clinical outcome, translated to the Australian population/setting, and **extrapolated to the appropriate time horizon** | [modified & extrapolated E] = [G] | [modified & extrapolated F] = [H] | [modified & extrapolated C] = [I] | [modified & extrapolated D] = [J] | [G – H] | [I – J] | $[G – H]/[I – J] per [clinical outcome] |
| Study evidence transformed to clinical outcome, translated to the Australian population/setting, extrapolated and **with additional assumptions or modelled information** | *(G + w)* = [K]f | *(H + x)* = [L]f | *(I + y)* = [M]g | *(J + z)* = [N]g | [K – L] | [M – N] | $[K – L]/[M – N] per [clinical outcome] |
| Study evidence translated to clinical outcomes, the Australian population/setting, extrapolated, with additional modelling and **transformed into an economic outcome** (eg QALYs)(K→O, L→P) | [O] | [P] | [M] | [N] | [O – P] | [M – N] | $[O – P]/[M – N] per QALY |

**a** Key outcome(s) from comparative data (presented in Section 2) used to generate ‘treatment effect’ in the economic evaluation, without any modification  
**b** If resource data are not provided, estimate resource use and apply costs (Australian $) within the study period.  
**c** Evidence to justify the transformation of the surrogate outcome to the clinical outcome and the method employed should be fully documented in Subsection 3.5.  
**d** Include here any transformations to estimated outcomes to increase applicability to the Australian population or setting.  
**e** Include here any modelled changes in the provision of resources as would occur in the Australian health care setting.  
**f** Re-estimate of outcomes after including additional data or assumptions that were not captured in the key comparative clinical data (eg adverse events or second-line treatments)  
**g** Re-estimate of costs after including additional data or assumptions that were not captured in the key comparative clinical data (eg adverse events or second-line treatments)

The order of considering the translation of the trial-based economic evaluation may vary. It is suggested to firstly incorporate the patient-relevant health outcome if the study outcome is a surrogate, and then translate the effect as necessary to match the Australian population.

The final row of Table 3.9.1 incorporates all translation studies and additional modelling to complete the impacts of translation of the trial-based economic evaluation into a modelled economic evaluation, and should correspond to the base-case incremental cost-effectiveness ratio.

The stepped presentation informs the face validity of the results, and identifies assumptions and approaches to be examined in more detail in the sensitivity analyses. For example, if the main impact is achieved by extrapolating the final outcome over time, it is important to undertake comprehensive sensitivity analyses around the extrapolation methods.

Present the base-case incremental cost, incremental effectiveness, and ICER (calculated as the incremental costs divided by the incremental health outcomes).

Discuss and justify a proposed conclusion that the base-case ICER demonstrates that the proposed medicine provides value for money.

If the ICER is based on an outcome other than life-years or QALYs gained, compare the presented results with any previous PBAC decisions based on the same measure of outcome.

### Disaggregated and aggregated base-case results

If a decision-tree model is used, present a detailed disaggregation of costs incurred at each branch by resource type for the intervention and comparator groups. For state transition models, present disaggregated discounted costs by resource type for each health state for the intervention and comparator groups. In all models, the proportions of patients predicted to experience alternative target clinical outcomes in the intervention and comparator groups should also be reported.

Examples of tables showing disaggregated costs are provided in Tables 3.9.2 and 3.9.3.

Table 3.9.2 Health care resource items: disaggregated summary of cost impacts in the economic evaluation

| Type of resource item | Subtype of resource item | Costs\* for proposed medicine | Costs\* for main comparator | Incremental cost\* | % of total incremental cost\* |
| --- | --- | --- | --- | --- | --- |
| Pharmaceutical products | PBS medicine | $x1 $x2 $xk | $y1 $y2 $yk | $x1 ­– $y1 $x2 – $y2 $xk – $yk | z1 % z2 % zk % |
| Health state 1 | ∑$x | ∑$y | ∑$x– ∑$y​ | ∑z% |
| Health state 2 | [add] | [add] | [add] | [add] |
| etc | [add] | [add] | [add] | [add] |
| Total | [add] | [add] | [add] | [add] |
| Non-PBS medicine | [add] | [add] | [add] | [add] |
| Health state 1 | [add] | [add] | [add] | [add] |
| Health state 2 | [add] | [add] | [add] | [add] |
| etc | [add] | [add] | [add] | [add] |
| Total | [add] | [add] | [add] | [add] |
| Medical services | Type of medical practitioner attendance | As above | As above | As above | As above |
| Health state 1 | [add] | [add] | [add] | [add] |
| etc | [add] | [add] | [add] | [add] |
| Total | [add] | [add] | [add] | [add] |
| Hospital services | Hospital admission | [add] | [add] | [add] | [add] |
| Health state 1 | [add] | [add] | [add] | [add] |
| etc | [add] | [add] | [add] | [add] |
| Total | [add] | [add] | [add] | [add] |
| Diagnostic and investigational services | Type of service | A$x | A$y | $x – $y | z% |
| Total | A$x | A$y | $x – $y | 100% |

PBS = Pharmaceutical Benefits Scheme  
\* Indicate clearly whether cost values are discounted costs (use of discounted costs is appropriate)

Table 3.9.3 List of health states and summary of cost impacts included in the economic evaluation

| Health state in model | Resource use by health state (modelled) | Proposed medicine costs | Main comparator costs | Incremental cost | % of total incremental cost |
| --- | --- | --- | --- | --- | --- |
| Health state 1 | Resource type 1 | $x1 | $y1 | $x1 ­– $y1 | z1% |
| Resource type 2 | $x2 | $y2 | $x2 – $y2 | z2% |
| etc | $xetc | $yetc | $xetc – $yetc | zetc% |
| **Total for health state 1** | **∑$x** | **∑$y** | **∑$x ­– ∑$y** | **∑z%** |
| Health state 2 | Resource type 1 | $xx1 | $yy1 | $xx1 – $yy1 | zz1% |
| Resource type k | $xxk | $yyk | $xxk – $yyk | zzk% |
| **Total for health state 2** | **∑$xx** | **∑$yy** | **∑$xx ­– ∑$yy** | **∑zz%** |
| etc | etc | etc | etc | etc | etc |
| **TOTAL** | **–** | **∑$x +∑$xx etc** | **∑$y +∑$yy etc** | **(∑$x +∑$xx etc) – (∑$y +∑$yy etc)** | **100%** |

Similarly, an example of a table showing outcomes disaggregated by health state is given in Table 3.9.4.

Table 3.9.4 List of health states and summary of health outcomes included in the economic evaluation

| Health state in model | Outcome for proposed medicine | Outcome for main comparator | Incremental outcome | % of total incremental outcome |
| --- | --- | --- | --- | --- |
| Health state 1 | x1 | y1 | x1 ­– y1 | z1% |
| Health state 2 | x2 | y2 | x2 – y2 | z2% |
| etc | xetc | yetc | xetc – yetc | zetc% |
| Total | x | y | x – y | 100% |

### Sensitivity and scenario analysis results

Present the results of the sensitivity and scenario analyses described in Subsection 3.8. Use a table to report the differences in costs and outcomes between the proposed medicine and its comparator, and the incremental cost-effectiveness for the base case and for all deterministic sensitivity analyses.

Tornado diagrams are a useful way of representing the relative effect of the uncertainty around alternative input parameters on the base-case incremental cost-effectiveness result.

Cost-effectiveness planes and acceptability curves should be used to present the results of a probabilistic sensitivity analysis, as well as the tabulated presentation of the interval estimates for incremental cost-effectiveness ratio or the incremental net benefits of the proposed medicine.

Identify the input parameters and model assumptions to which the incremental cost-effectiveness results are most sensitive.

Describe and justify a likely range of values within which the true estimate of the incremental cost-effectiveness of the proposed medicine is likely to lie. This range may be informed by a formal probabilistic sensitivity analysis, or by subjective interpretation of the presented deterministic sensitivity and scenario analyses.

Discuss the implications of the sensitivity and scenario analyses with respect to the certainty that the proposed medicine provides value for money.

## 3.10 Summary of model inputs, and key assumptions and associated impacts

**INFORMATION REQUESTS**

**Tabulate influential variables and assumptions**

Complete a table of all the variables and assumptions in the model, including the base-case parameter values, the ranges or scenarios tested in sensitivity analyses, and the direction and extent of the effect of the uncertainty around key input parameters on the ICER. Discuss limitations of the evidence base or the model, and the implications for the economic evaluation and the estimated ICER.

### Parameter values and assumptions

Tabulate all parameter values and assumptions included in the model in the format presented in Table 3.10.1.

Table 3.10.1 Summary of variables and their impacts on cost-effectiveness

| Variable or assumption | Base-case value | Plausible alternative(s) or range of values to test in scenario or sensitivity analyses | ICER |
| --- | --- | --- | --- |
| Discounting rate | Outcomes and costs: 5% | * Outcomes and costs: 3.5% * Outcomes and costs: 2.5% * Outcomes and costs: 0% * Costs: 5%; outcomes: 0% | ICER decreases with lower/zero discount rate on outcomes and costs |
| Time horizon | [add] | Trial based: 1, 5, 10, 15, 20 years, as appropriate | [add] |
| Model structure assumptions | [add] | [add] | [add] |
| Treatment effect, if modelled as a variable (eg hazard ratio or relative risk) | [add] | 95% confidence intervals around estimate | [add] |
| Patient characteristics, if relevant (eg age, sex, baseline risk) | [add] | [add] | [add] |
| Translation assumptions | [add] | [add] | [add] |
| Transition or event probabilities | [add] | [add] | [add] |
| Extrapolation variables or assumptions (*Recommended examples:*   * *extrapolation start point* * *choice of extrapolation model* * *assumption regarding ongoing treatment effect*) | (eg maximum follow-up of trial data) | Transition to extrapolated outcomes at median follow-up etc | [add] |
| Outcome-related assumptions or variables (eg surrogate-to-final outcome relationship, utility weights) | [add] | [add] | [add] |
| Cost-related assumptions or variables | [add] | [add] | [add] |
| Other variables or assumptions | [add] | [add] | [add] |

ICER = incremental cost-effectiveness ratio

Discuss the likely overall effect of deficiencies in the evidence base on the reported cost-effectiveness of the proposed medicine.

# Section 3B Cost minimisation

This section provides information requests for preparing Section 3 of a submission where the proposed medicine is therapeutically noninferior (or superior) to the main comparator in terms of both safety and effectiveness, and a cost-minimisation approach is appropriate (ie the difference between the proposed medicine and the main comparator is reduced to a comparison of costs). The extent of any health impact is not assessed other than to estimate the extent to which other health resources might be affected. This is a partial rather than a full economic evaluation – it does not quantitatively assess the ratio of comparative costs to comparative effectiveness.

The cost-minimisation approach is generally less preferred than a full economic evaluation, but may be acceptable under the following limited circumstances:

* The therapeutic claim is one of noninferiority (or superiority), and the safety profile is equivalent or superior in both nature and magnitude. In this case, a comparison of expected usage (through determination of equi-effective doses) may be sufficient to conservatively estimate the incremental health care resource use (savings) associated with use of the proposed medicine.

The therapeutic claim is one of noninferiority (or superiority), and the proposed medicine has a superior safety profile or simpler administration profile, such that there are expected cost offsets and an anticipated net reduction in overall use of health care resources (savings) associated with the proposed medicine.

Effectively, this means that the proposed medicine is unlikely to be granted a price advantage over the main comparator, and any restrictions applying to the main comparator and any other already listed medicines within the reference group of the main comparator would apply to the proposed medicine.

Such a submission need only present an abbreviated Section 3, except where there are differences in the costs of prescribing or administering the two alternatives. Take particular care to justify any decision to model a therapeutic difference due to a factor that is excluded in the trials. Only rarely has a model been accepted that contradicts a conclusion from the trial evidence whereby a statistically significant therapeutic advantage was not detected when designed to do so.

If the conclusion of noninferiority is not also supported by clinical data that enables a judgment regarding equi-effective doses, the submission will be difficult to evaluate. See Subsection 3.2 for the preferred approach to calculating equi-effective doses.

Irrespective of therapeutic superiority or noninferiority, if the adverse effect profiles of a proposed medicine and its main comparator are significantly different in nature, it is unlikely that the cost-minimisation approach will suffice. The implications of these differences, with respect to both health outcomes (ideally, utility) and resource use, should be explored in a full economic evaluation.

In all cases, assumptions of noninferiority or superiority, with respect to both effectiveness and safety, will need to be well justified for the cost-minimisation approach to be considered acceptable. However, assuming that the PBAC does accept such claims, a therapy providing acceptable outcomes in terms of both effectiveness and safety at a lower cost is preferable.

## Claim of noninferiority based on a surrogate outcome

A claim of noninferiority based on a surrogate outcome would only be considered when the PBAC has previously accepted the surrogate outcome as valid and **all** of the following are true:

* The proposed treatment effect is within the range of the comparative treatment effect previously identified in the accepted clinical evidence.
* The previously accepted surrogate outcome was accepted in the same population as the proposed listing.
* The medicines in the evidence used to previously validate the surrogate, the main comparator and the proposed medicine are all in the same class or have a similar mechanism of action.

Flowchart 3B shows an overview of the cost-minimisation approach.

**Flowchart 3B Overview of information requests for Section 3 of a submission to the PBAC based on a cost-minimisation approach**

Section 3B Cost minimisation (for a noninferior therapeutic conclusion)
3.1 Overview and rationale: What are the key features of the approach? Justify the assumption of noninferiority and summarise key components of the cost-minimisation approach.
3.2 Estimation of equi-effective doses: What doses of the proposed medicine and the comparator give the same effect? Calculate doses of the proposed medicine and the comparator that are equi-effective, present evidence to justify these doses.
3.3 Additional costs and/or cost offsets: What are the cost implications of using the proposed medicine? Compare the administration and safety profiles of the proposed medicine and the comparator; summarise additional costs and/or cost offsets associated with the proposed medicine.
3.4 Results: Will therapy with the proposed medicine minimise public costs? Present the economic findings in relation to cost minimisation (ie the cost may be the same as or less than the comparator).
Go to Section 4: Predicted use of the medicine in practice.

## 3.1 Overview and rationale of the cost-minimisation approach

**INFORMATION REQUESTS**

**Summarise the key components and assumptions of the approach**

Complete the summary table provided.

### Summary table of cost-minimisation approach

Complete Table 3.1.1 to summarise the key assumptions and components of the cost-minimisation approach.

Table 3.1.1 Key assumptions and components of the cost-minimisation approach

| Therapeutic claim: effectiveness | Based on evidence presented in Section 2, effectiveness is assumed to be [noninferior/superior] |
| --- | --- |
| Therapeutic claim: safety | Based on evidence presented in Section 2, safety is assumed to be [noninferior/superior] |
| Evidence base | [direct randomised trials/indirect comparison of randomised trials] |
| Equi-effective doses | Proposed medicine [describe dose/day/course] and comparator [describe dose/day/course] |
| Direct medicine costs | [lower/equivalent/higher]; [cost of proposed medicine] vs [cost of comparator] (costs are per patient per course for an acute or self-limited therapy, or per patient per year for a chronic or continuing therapy) |
| Cost offsets | [Yes/No] [if yes; brief description, eg adverse effect–related costs, monitoring costs, administration costs] |

## 3.2 Estimation of equi-effective doses

**INFORMATION REQUESTS**

**Calculate equi-effective doses**

Present the equi-effective doses using the best available evidence from the hierarchy of evidence shown in this section.

### Equi-effective doses

The first step in estimating the comparative costs in a cost-minimisation approach is to estimate the equi-effective doses.

Calculate equi-effective doses at ‘steady state’ (ie the average dose after dose titrations are complete and after excluding participants who discontinue the medicine). Assess the impact of extrapolating dose titration if there is evidence that the trial was of inadequate duration for the doses to have reached steady state.

If there is more than one trial or study, the weighted average dose is calculated using the number of participants still on the medicine at steady state as the weighting factor. There is no justification for weighting the doses between studies by the duration of therapy in the study as well as by the number of participants.

It is accepted that, in circumstances where a sponsor does not have access to the primary data from a study, the calculations would be limited to the way the doses are reported in the published report. For example, the average doses might have to be weighted by the number of participants enrolled rather than the number of participants at steady state.

Use one of the following formats as a guide to report the conclusion on the equi-effective dose calculations:

* for doses set by fixed protocols – ‘proposed medicine A mg for B frequency of dosing over C duration of therapy, and main comparator D mg for E frequency of dosing over F duration of therapy are equi-effective’

for doses established at steady state after full titration – ‘proposed medicine X mg and main comparator Y mg are equi-effective’.

#### Preferred sources of evidence

When estimating equi-effective doses, the following sources of evidence (presented in order of preference) may be appropriate:

* direct randomised trials where doses of both medicines are titrated against a response, or where doses of both medicines are fixed if the medicines are given in regular clinical practice according to a fixed protocol used in the trials
* direct randomised trials where doses of one or both medicines are arbitrarily fixed in a way that does not reflect regular clinical practice. Medicines might not have reached the same point on their respective dose-response curves if the doses are fixed. Therefore, present dose-response data for the two medicines to indicate whether the fixed doses are derived from a similar point on the respective dose-response curves and to confirm that the selected doses do not represent suboptimal doses, or doses on the plateau of the dose-response curve. Fixing the dose of just one medicine introduces a clearly unbalanced approach. Note also that calculating the average dose from a trial in which subjects are randomised to different doses of the same medicine does not form an acceptable basis for directly determining equi-effective doses. However, a randomised trial designed to compare many fixed doses of the proposed medicine and its main comparator, each in separate arms, might usefully demonstrate the existence and extent of dose-response effects, and thus directly generate comparative dose-response curves as an alternative basis for inferring equi-effective doses
* indirect comparisons of two or more sets of randomised trials involving one or more common references
* nonrandomised studies where both dose and effect are measured

nonrandomised studies (including market research data) where dose, but not effect, is measured. This source of evidence is the least preferred. It may be preferable to calculate doses directly from the Australian Government Department of Human Services Authorities Database, rather than using market research data.

Indicate whether these data are consistent with those recommended in each medicine’s TGA-approved product information in relation to:

* the doses (and fixed dose regimens, where relevant) used

the methods of titration (eg frequency of titration steps, any thresholds of outcomes used to guide a change in dose, extent of dose variation, duration of titration period).

The defined daily dose from the World Health Organization may provide supporting information.

## 3.3 Additional costs and/or cost offsets

**INFORMATION REQUESTS**

**Compare the administration profiles of the proposed medicine and the comparator**

Identify any differences in resource use associated with administration of either treatment, and note whether this will result in additional costs or cost offsets to be included in the approach.

**Compare the safety management profiles of the proposed medicine and the comparator**

Identify any differences in resource use associated with monitoring or managing adverse events between treatments, and note whether this will result in additional costs or cost offsets to be included in the approach.

### Comparison of administration profiles

If the proposed medicine and its main comparator are available in different forms (eg tablets, injections, implants and infusions), the different modes of administration might have cost consequences. In this case, identify the types of other health care resources affected, estimate the extent to which the quantity of each type of resource provided would change (in its natural units of measurement) were the proposed medicine to be listed, and multiply by the appropriate unit costs.

See also the *Manual of resource items and their associated costs* for further detail on costing administration-related resource use.

### Comparison of safety and toxicity management profiles

The cost-minimisation approach is only appropriate where the proposed medicine has a safety profile that is superior (preferably) or noninferior to the main comparator.

If the proposed medicine is demonstrated to be no worse in terms of effectiveness but to have a superior safety profile to the main comparator, a price advantage for the proposed medicine over its main comparator could be sought on the basis of cost offsets due to reduced costs of monitoring for, or managing of, adverse reactions. Practice in the clinical trials and the recommendations in the Australian product information may be used to support a claim that monitoring costs are reduced.

Where safety profiles are similar but the proposed medicine simply has a reduced magnitude of adverse effects (severity or incidence), a thorough description of the quantified differences in safety should be presented, with a justified estimate of any corresponding resource use implications.

Irrespective of therapeutic superiority or noninferiority, where the adverse effect profiles of a proposed medicine and its main comparator are different in nature, it is unlikely that the cost-minimisation approach will suffice. The preferred approach would be to incorporate the different adverse effect profile into the measurement of health outcomes with the associated incremental costs in a cost-effectiveness or cost-utility analysis.

However, cost analyses have sometimes been presented and found to be acceptable in these circumstances. A cost analysis could be presented to quantify a claim that the cost offsets from the reduction in health care resources required to treat the adverse events are sufficient to reduce the incremental cost to zero or a negative value.

See also the *Manual of resource items and their associated costs* for further detail on resource use and costing associated with monitoring and adverse effects.

## 3.4 Results

**INFORMATION REQUESTS**

**Present the results of the cost-minimisation approach**

Present detailed results of the cost-minimisation approach (based on equi-effective doses and incorporating cost offsets, if appropriate).

**Attach copies of relevant papers and original sources of data**

Provide copies of all sources of data in an attachment or a technical document (cross-referenced from the main body of the submission), and electronic copies of all computer-based analyses.

### Results of the cost-minimisation approach

If no other cost consequence is anticipated, consult the Pharmaceutical Benefits Pricing Authority Secretariat, as necessary, for the calculation of medicine prices from equi-effective doses.

List any costs associated with either the proposed medicine or the comparator, then aggregate these with the medicine cost (based on the equi-effective doses) to estimate the net cost impact.

The economic claim could be that, at the price requested, the overall cost of therapy with the proposed medicine is the same as, or less than, the overall cost of therapy with the main comparator.

### Sources of data

Separately provide copies of the original sources of all data (beyond those already presented in Section 2) or expert opinion used in the model in an attachment or technical document. Cross-reference the extraction of data from each source to the level of the page, table or figure number of the source document.

To enable independent verification of each analysis, provide an electronic copy of any computer-based calculations of the analysis.

# Section 4 Predicted use of the medicine in practice

## Introduction

Section 4 of a submission to the PBAC provides the most likely extent of use and financial estimates by presenting a set of budget impact analyses. These analyses are relevant to both the PBAC and the Australian Government. The results from Section 4 are important to estimate the likely uptake of the proposed medicine in clinical practice and the cost impact on the Australian Government budget, and, in some cases, to negotiate risk share arrangements.

There are two broad approaches for developing utilisation and financial estimates – epidemiological and market share – although their use is not mutually exclusive. An epidemiological approach is usually preferred for generating utilisation and financial estimates if the submission indicates a superior therapeutic conclusion in Subsection 2.8. However, a market-share approach might be preferred to generate the utilisation and financial estimates if the submission indicates a noninferior therapeutic conclusion in Subsection 2.8.

In some cases, both approaches may be informative – for example, where there is uncertainty in the therapeutic conclusion or the expected utilisation. Presenting both approaches and demonstrating a concordance of comparable results across the approaches might reduce uncertainty in the utilisation and financial estimates.

Where both epidemiological and market-share approaches are possible, the PBAC prefers that both are presented, with a comparison of the results and an interpretation of any discrepancies. Where only one approach is presented, the submission should clearly justify why this has been done.

Irrespective of the approach(es) taken to estimate the extent of use of the medicine (and other medicines or therapies) in the Australian setting, the submission should ensure that these estimates are consistent with evidence presented throughout the submission. Uptake of the medicine, change in the use of alternative medicines and offsets should all be consistent with the clinical place of the proposed medicine outlined in Section 1, the use of the medicine in the clinical trial setting (where applicable) (Section 2), and the circumstances presented in the economic evaluation (Section 3). Where there are discrepancies, these should be explained and adequately justified.

It is important that sufficient data are provided in the main body of the submission in Section 4 so that the steps taken are interpretable. Where the calculations performed to generate estimates are not transparent in the main body of the submission, additional data should be presented. Presentation of data in the standardised Excel workbook is discussed below.

The standardised Excel workbook for use with the epidemiological approach is available from the ‘Downloads’ section of the PBAC Guidelines website (in preparation, URL to be supplied)*.*

Flowchart 4 shows an overview of information requests in Section 4 for both the epidemiological and market-share approaches.

Flowchart 4 Overview of information requests for Section 4 of a submission to the PBAC

Section 4: Predicted use of the medicine in practice
4.1 Justification of data sources: What data sources are used in the analysis and why? Describe and justify all data sources.
4.2 Use and costs: How many patients will be treated and packs dispensed over 5 years? Epidemiological approach: use incidence or prevalence data to estimate the number of patients treated and packs dispensed. Market-share approach: use current market data to estimate market share, number of patients treated, number of packs dispensed and market growth.
4.3 Changes to other medicines: What other medicines will be affected and what will this cost? Identify PBS medicines that will be affected by the proposed listing; estimate the change in number of packs dispensed and costs over 5 years for these medicines.
4.4 Financial implications for the PBS: What is the overall public cost? Describe the net financial implications for the PBS (or RPBS or NIP) over 5 years.
4.5 Financial implications for the Australian Government: What is the overall cost to the Australian Government health budget? Estimate changes to prescription processing and MBS items, and net financial implications for the Australian Government health budget over 5 years.
4.6 Uncertainty: What are the sources of uncertainty, and how can uncertainty be reduced? Evaluate sources and impact of uncertainty in the budgetary estimates.
Go to Section 5: Other issues.

### Epidemiological approach

An epidemiological approach first estimates the number of people with the medical condition, and then uses several steps to estimate the use of the proposed medicine (see Subsection 4.2) and of other medicines in the context of the proposed patient indication (see Subsection 4.3). Subsections 4.2 to 4.4 request financial analyses of health care resources subsidised through the relevant funding program (eg PBS or National Immunisation Program [NIP] budgets). Subsection 4.5 requests that these analyses be broadened to include health care resources funded through the Australian Government health budget.

An epidemiological approach estimates the patients eligible for the proposed medicine; however, market-based data or market research may be required to establish estimates such as the rate of uptake of the medicine, the dose used in the community or the mix of beneficiary types.

In contrast to the economic evaluation presented in Section 3 of the submission, these financial analyses exclude health outcomes, do not use discounting, and exclude any resource item or co-payment from a source other than the identified budget (typically, this means that patient co-payments should be excluded; see Chapter 9 of the *Manual of resource items and their associated costs*).

The presentation of an epidemiological approach in Section 4 is aligned with the utilisation and cost worksheets supplied alongside these guidelines, based on a standardised Excel workbook. This workbook is **not** designed for presentation of utilisation and financial estimates for vaccines to be funded under the NIP or for the market-share approach, and may need adapting.

Where a submission seeks listing for more than one indication (see Subsection 1.4), present a separate standardised Excel workbook for each indication. As a final step in each of Subsections 4.4 and 4.5, these results can be aggregated across the indications.

### Market-share approach

The market-share approach first estimates the extent of the current market represented by the proposed patient indication and consequently the share likely to be taken by the proposed medicine.

Compared with the epidemiological approach, the market-share approach allows an abbreviated presentation of information, where justified, or provides an alternative way of generating estimates to compare with the epidemiological approach.

The key issue with estimates built on the market-share approach is whether the current market or market growth rate is expected to increase as a result of listing the proposed medicine on the PBS. If not, a medicine listed on a cost-minimisation basis would usually have a negligible effect on the net financial impact on the PBS, but may have financial impacts on other parts of the Australian Government health budget. Exceptions where medicines listed on a cost-minimisation basis may have net financial impact include:

* different MBS items required with the use of the new medicine – change in MBS costs

different restriction level from the currently listed medicine – change in Australian Government Department of Human Services (DHS) costs.

In each of these circumstances, or if the proposed medicine is likely to increase the market size or its growth rate, it is critical to estimate the extent of this likely increase.

### Standardised Excel workbook

An Excel workbook developed for submissions taking an epidemiological approach is available at <link to be inserted>, to provide guidance on how to present the utilisation implications and financial implications for the PBS/RPBS, the MBS and Medicare. This workbook enables the estimates presented in the submission to be validated by the PBAC. In some circumstances, additional spreadsheets may need to be created to handle complex analyses or to provide data to support assumptions.

It is important to ensure that calculations flow through the spreadsheets, so that changes to any variable flow appropriately to the results. To assist in understanding the spreadsheets, apply clear and unambiguous labels to spreadsheet values, together with cross-references to the source of the data (provided as an attachment). Formulas in the spreadsheets should be clear and consistent to facilitate the tracing and replication of the flow of calculations.

Throughout Section 4 of these guidelines, references to spreadsheet number (eg refer to the spreadsheets within the standardised Excel workbook for PBAC submissions. The submission should present a description of the approach taken, methods, assumptions and potential biases. Where possible, add comments to the Excel workbook to capture these descriptions, particularly if the approach is complex. Interpretation of calculations in the Excel workbook that cannot be reconciled with the relevant assumptions or approach reduces confidence in the estimates.

#### Adaptation of the Excel workbook for the market-share approach

The standardised Excel workbook is not designed for the market-share approach. However, the general approach could be adapted as follows:

* Spreadsheet 1 (Subsection 4.1). Summarise all the background information, primary (not calculated) variables and assumptions essential to the calculation of results presented.
* Spreadsheets 2 and 3 (Subsection 4.2). Calculate the results for the current market, the projected extent of uptake of the proposed medicine and the change in the numbers of patients treated, where appropriate.
* Spreadsheet 4 (Subsection 4.3). Calculate the results for the extent of substitution of current medicines.
* Spreadsheet 5 (Subsection 4.4). Calculate the net financial implications for the PBS and RPBS, and summarise any sensitivity analyses addressing uncertainty discussed in Subsection 4.6.

Subsequent spreadsheets (Subsection 4.5) can be used as necessary.

In some circumstances, a simpler approach might be appropriate, especially if the current market size or market growth rate is not expected to change because of listing the proposed medicine.

### Copies of the data

To allow independent assessment of the data, include copies of the data used (published, unpublished and commissioned) in an attachment to the submission. Ensure that the responses to Section 4 and the Excel workbook provide adequate cross-references of the extraction of all data used to generate the estimates in these analyses from each attached data source (to the level of the page, table or figure number of each source document). Where commissioned data have been used, include the correspondence that requested the data.

## 4.1 Justification of the selection of data sources

**INFORMATION REQUESTS**

**Present and assess available data sources**

For each data source, present the methods, assumptions, results and limitations of the data. For commissioned data, describe the information gap that required commissioned analysis.

**Summarise background information using Spreadsheet 1**

Summarise all the background information, primary (not calculated) variables and assumptions essential to the calculation of results presented in this section, using Spreadsheet 1 of the standardised Excel workbook.

### Available data sources

Data sources fall under the broad headings listed in Table 4.1.1; however, there might be other suitable data sources (see *Sources of epidemiological data for use in generating utilisation estimates*)*.*

The main sources of relevant data for the market-share approach are the PBS data, including those supplied by DHS and data for under-co-payment use of PBS-listed medicines by general beneficiaries, which can be estimated from several sources.

Table 4.1.1 Categories of data sources

| Data type | Examples |
| --- | --- |
| Disease epidemiological data (provide estimates of prevalence or incidence in the population) | * Australian case or mortality registers that estimate the incidence or prevalence of a disease * Large, well-designed Australian studies that estimate the incidence or prevalence of a disease * Australian national health surveys that estimate the prevalence of a disease |
| Pharmacoepidemiological data (provide estimates of treated prevalence) | * Surveys of the treated prevalence of the disease in Australia * Studies using utilisation databases, including PBS/RPBS data for therapeutically equivalent medicines |
| Market data | * Quantitative description of the existing market, including estimates of change in the size of the market over time * Estimates of relative market shares * Estimates of the impact of the requested PBS listing on current treatment paradigms, based on similar previous listings |
| Commissioned data | * Medicine usage evaluations * Data requests to registries, epidemiological studies or utilisation studies |

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Different sources of data may be required throughout Section 4. For each source of data, the submission should address the following in Subsection 4.1:

* Describe the data and data source.
* Explain the purpose of the data in the analysis.
* Describe how the data are relevant to the present Australian setting. Where data on overseas markets are provided, the submission should clearly state that Australian data were not available and discuss the applicability of these data to the Australian setting (with particular reference to the subsidy arrangements in the overseas jurisdiction).
* Where there are multiple sources of data, discuss the concordance across these sources and present sensitivity analyses for the different estimates across the sources.

For each estimate derived from source data, summarise the methods, and discuss any assumptions, limitations and biases in the approach taken.

#### Commissioned data

Where there is a gap in the available data, a commissioned study may be required. Commissioned studies may include medicine usage evaluations, data requests to disease registries, or epidemiological or utilisation studies. Whenever commissioned data are required, the submission should clearly state the purpose of the data and the information gap they fill. Where the commissioned data represent a survey of experts, see Appendix 1 for further guidance. When presenting commissioned data, provide the relevant correspondence requesting the data, including the precise questions asked of the experts, disease registry or study investigator.

### Summary of background information: Spreadsheet 1

Summarise the data sources, background information, primary (not calculated) variables and assumptions in Spreadsheet 1 (and additional supporting spreadsheets, where required).

## 4.2 Estimation of use and costs of the proposed medicine

**INFORMATION REQUESTS**

**Estimate the number of patients and packs dispensed – epidemiological approach**

For the epidemiological approach, estimate the number of patients with the medical condition targeted by the proposed medicine, the number of patients who would be eligible for the requested restriction, the number of patients likely to take the proposed medicine, and the number of packs dispensed each year over five years.

**Estimate the number of patients and packs dispensed – market-share approach**

For the market-share approach, describe the market and estimate the number of packs dispensed (and the number of patients this represents) for currently listed medicines. Estimate the rate of substitution of the proposed medicine and the number of packs dispensed each year over five years, and indicate whether the market or the market growth rate will increase because of listing.

**Provide estimates by beneficiary type**

Present estimates disaggregated into proportions for the PBS and RPBS, and for beneficiary type.

**Estimate the costs over five full calendar years**

For each form and strength of the proposed medicine, estimate the costs in each year over five full calendar years (January to December), and present the costs in aggregated and disaggregated forms.

**Identify risk-sharing arrangements or special pricing arrangements**

Identify and describe any proposed risk-sharing arrangements, and present costs both with and without any proposed risk-sharing arrangements or special pricing arrangements.

**Use Spreadsheets 2 and 3**

For the epidemiological approach, calculate the results for the estimated number of patients, using Spreadsheet 2 of the standardised Excel workbook, and calculate the results for the estimated number of packs and costs, using Spreadsheet 3.

For the market-share approach, present all calculations and results in an Excel workbook similar to the one provided for the epidemiological approach.

When estimating the incidence, prevalence or market growth over five years, the submission should justify the approach. Multiple factors may influence growth, and it may not be appropriate to assume linear growth in the data. It is important to base projections on the number of patients, and not dispensed packs, wherever possible. If the submission is using a market-share approach, the 10% PBS sample data provide both patients per year and scripts per patient per year.

### Epidemiological approach

#### Incidence or prevalence data

When taking an epidemiological approach, present the methods and assumptions for converting incidence or prevalence data to the number of patients likely to be taking the proposed medicine on a yearly basis.

The choice between using incidence or prevalence data depends on several factors, including the nature of the medical condition, its treatment and the data available. In general, treatments of short duration are best suited to using incidence data, and long-term treatments (eg for chronic diseases) may be better suited to using prevalence data. In some cases, a combination of prevalence and incidence data may be required (eg intermittent treatments for a chronic condition).

In some cases, the use of incidence data inappropriately disregards the prevalent population who may be eligible for treatment. An example might be a cancer therapy where there could be patients who receive best supportive care for one or several years before the proposed medicine becomes available. Only calculating the incident population would inaccurately estimate the likely number of patients to be treated in the first one or two years of listing.

The submission should also detail the impact of any grandfathered use of the proposed medicine when estimating patient numbers.

Expert epidemiological advice should be sought when estimating prevalence from incidence data or estimating incidence from prevalence data, particularly where there is doubt that the duration of disease has not remained constant over time, or where it is not expected to remain constant after the listing of the proposed medicine.

It is important to clearly describe and justify calculations when using incidence or prevalence data.

#### Estimate the number of patients with the medical condition

Estimate the likely number of patients in the current year and in the five years following listing, using one of the bases above (incidence or prevalence), and account for trends in disease incidence or prevalence. If appropriate, present more frequent periods (eg monthly or three-monthly) in supporting spreadsheets and summarise in annual aliquots for the required five years from listing. If estimating the number of patients using an incidence approach, estimate the prevalent population (from years before listing) that may add to the patient pool in year 1. Justify when a consideration of a prevalent population is not required.

For conditions that may have less clear parameters for diagnosis or a subjective element in their diagnosis, consider the impact of misdiagnosis of patients for the purposes of rendering them eligible for the proposed medicine.

#### Estimate the number of patients eligible for the requested restriction

Using the annual numbers of patients with the medical condition for five years, estimate the proportions who would be expected to be eligible for therapy according to each of the requested restrictions for PBS listing.

Where the requested restriction contains subjective elements, consider whether patients might be misclassified to be eligible for the proposed medicine.

#### Estimate the number of patients likely to take the proposed medicine

Using the annual numbers of eligible patients, estimate the proportions likely to take the proposed medicine in each of the five years. The resulting estimates should reflect the rate of uptake of the proposed medicine and include the impact of the use of alternative medicines. It is implausible that a medicine will achieve 100% uptake, particularly if it is not the only treatment for an indication and is associated with adverse events.

#### Estimate the number of packs dispensed

The estimate of the number of packs dispensed for each of five years should account for:

* the rate of uptake of the proposed medicine across the five years from listing (described above)
* the dose, frequency and duration of therapy involving the proposed medicine

different forms and strengths of the proposed medicine.

Each of the steps for estimating the number of packs dispensed should be presented separately. The order in which the steps are presented may not be important, provided that the progression from the number of patients to the number of packs is clear.

Ensure that the estimates reflect the quantities of medicine dispensed, rather than the quantities of medicine consumed, which may be affected by compliance, dose reductions, discontinuations and wastage. Estimates of medicine use are based on a number of assumptions that can be difficult to verify. Therefore, these assumptions should be clearly stated and, where there is substantial uncertainty, alternative estimates should be presented in sensitivity analyses.

The proposed listing may specify different forms, strengths and maximum quantities of the proposed medicine. When listed, such medicines will have separate PBS item numbers to distinguish between them. The estimated utilisation should be disaggregated for each of the forms, strengths and maximum quantities.

### Market-share approach

#### Describe the market

To generate estimates of expected utilisation and costs, the market-share approach should rely on medicine utilisation data or studies for currently available medicines that are likely to be substituted by the proposed medicine. This is the basis for predicting whether the market will change because of listing the proposed medicine.

#### Number of packs dispensed for currently listed medicines

Estimate the number of packs dispensed in the most recent 12 months of the relevant PBS market. This estimate should be based on:

* data from DHS for currently listed medicines

alternative sources of data to estimate usage when the co-payment equals the cost of the medicine (and PBS subsidy data will therefore not capture usage).

It is preferable that the submission presents both the number of packs dispensed and the number of patients this represents. This will be particularly important where a market-share approach is being compared, or used in conjunction, with an epidemiological approach. It may also be required where the submission is providing information on PBS-listed medicines that increase or decrease in usage, as this is often calculated from patient-level data rather than packs dispensed. The submission should consider the impact of wastage, discontinuations and noncompliance when back-calculating the number of patients from number of packs dispensed, or justify when these factors are unlikely to be important.

Estimate the rate of growth in this market over five years following listing. This should be based on historical trends in the market or other influences, but should be unrelated to the listing of the proposed medicine. Provide clear justification for the estimate of market growth in the absence of the listing of the proposed medicine.

Where more than one PBS item is likely to be substituted, the market share and rate of growth may need to be presented for each item. Disaggregating the estimated growth across different PBS items is important if they are likely to have different rates of growth, are likely to be substituted differentially by the proposed medicine, or have a different cost to the PBS. Where all substituted PBS-listed medicines come from a single group of medicines listed on a cost-minimisation basis and the cost differential of each against the proposed medicine is similar, disaggregation across different PBS items is less important.

#### Estimate the market share

Estimate the rate of substitution in the market by the proposed medicine for each year over five years. Provide evidence, such as market uptake rates from other markets and the applicability of these markets to the Australian setting, to justify the estimate of market share. An arbitrary or unjustified estimate of substitution in the market is difficult to interpret and markedly increases the uncertainty of the financial implications for the Australian Government. It is likely that there is a clear expectation, based on data, for the extent of market uptake following listing of the proposed medicine, and this should be clearly communicated.

The estimate of the rate of substitution may have to be presented for each of the following groups:

* different PBS-listed medicines that will be substituted where the rate of growth is different, the rate of substitution is different or the cost is different

different forms, doses and durations of treatment where multiple PBS item numbers are available for each PBS-listed medicine.

It may be appropriate to present an aggregated table in the submission; however, the disaggregated table should be presented in the Excel workbook, with the steps for aggregating the data clearly shown. The spreadsheet should make clear the proportions of each of the individual PBS items and PBS-listed medicines that are likely to be substituted by the proposed medicine.

#### Estimate the growth of the market after listing

Present an estimate of the number of packs dispensed for the proposed medicine for each year that is above the growth projected in the market using historical data. Report both the expected increase in patient numbers and the expected number of packs for each form, strength and duration for the proposed medicine.

The submission should justify when no additional growth in the market is predicted. When the proposed medicine may be used in clinical practice to treat people who are intolerant to an existing listed medicine, or following failure with that medicine, it is likely that entry of the proposed medicine into the market will increase the overall number of people treated.

As stated above, arbitrary or unjustified estimates of market growth (or absence of market growth) are difficult to interpret. In the absence of a clearly reasoned position, references to appropriate data of similar circumstances in similar markets and accounting for risks associated with market growth, the financial implications of listing the proposed medicine remain uncertain.

### Estimates by beneficiary type

For both the epidemiological and market-share approaches, present a breakdown of the estimates for the proposed medicine into proportions for the PBS and the RPBS, and by beneficiary type, as follows:

* PBS General
* PBS General Safety Net
* PBS Concessional
* PBS Concessional Safety Net
* RPBS

RPBS Safety Net.

One option, which would need to be assessed for its suitability in each case, would be to apply the breakdown for the closest therapy that is currently listed (specifically, the main comparator, if it is PBS listed). These breakdowns are available from the DHS website. If different weights can be demonstrated as being likely to apply, those should be presented instead.

These estimates may assist in determining the co-payment to be removed from the dispensed price for maximum quantity (DPMQ).

### Costs over five years

#### Disaggregated costs

Two sets of unit costs should usually be applied to the disaggregated estimates of numbers of dispensed packs of each of the forms and strengths of the proposed medicine:

* the DPMQ

the DPMQ with appropriate patient co-payments removed. A weighted co-payment can be used, but it should distinguish between PBS and RPBS patients. (Co-payments are stated in the Schedule of Pharmaceutical Benefits and are available on the [PBS website](http://www.pbs.gov.au/info/healthpro/explanatory-notes/front/fee).)

Where these prices do not apply (eg for products to be listed under section 100 arrangements or to be funded under the NIP), apply the following as unit costs:

* the price to the Australian Government

the price to the Australian Government less any amount charged as a patient co-payment.

For these calculations, use constant prices, make no allowance for inflation and use a zero discount rate. Further guidance is provided in Chapters 4 and 9 of the *Manual of resource items and their associated costs*.

#### Aggregated costs

Aggregate the estimated costs for each of the forms and strengths of the proposed medicine to the PBS and RPBS, for both the DPMQ and the DPMQ with appropriate patient co-payments subtracted.

Calculate the above sets of estimates of packs dispensed and costs in Spreadsheet 3 of the standardised Excel workbook.

### Risk-sharing arrangements

Risk-sharing arrangements may be proposed by the sponsor, the PBAC (usually in relation to cost-effectiveness and/or health outcomes) or the Department of Health (usually in relation to overall costs). If a sponsor is proposing a risk-sharing arrangement, it is preferable that this is indicated early in the process (ie in the submission to the PBAC).

Risk-sharing arrangements are negotiated with the sponsor by officers of the Department of Health on behalf of the Australian Government, and are finalised between the PBAC recommendation and PBS listing.

#### Identification of risks

Risk-sharing arrangements are designed to address the uncertainties that may result in an increased cost to the PBS or RPBS, and/or a reduction in the cost-effectiveness of the proposed medicine, in relation to the:

* number of patients likely to be treated
* average dose prescribed
* use beyond disease progression

introduction of an additional line of therapy.

Noting that these risks are not mutually exclusive, state which of the risks are intended to be addressed by the proposed risk-sharing arrangement.

#### Risk-sharing arrangement proposal

Describe the proposed risk-sharing arrangement and indicate how it manages each of the identified risks. Define all relevant variables, such as volume thresholds, dates of commencement, time horizons, price reductions and rebate arrangements.

Describe how data will be collected to monitor risks and state how the data are suitable for implementing the risk-sharing arrangement. Ensure that data collected can unambiguously identify any proposed thresholds at which price reductions or rebates are offered.

Thresholds applied in risk-sharing arrangements should correspond with the most likely usage estimates for the PBS or RPBS reported in Subsection 4.2.

Clearly state how the risk-sharing arrangement would function should an alternative medicine be subsequently listed for use in a similar population. A risk-sharing arrangement should not constitute a barrier to the listing of a subsequent medicine.

#### Confidentiality

Indicate any elements of the risk-sharing arrangement that are requested to be kept confidential. It is preferable that risk-sharing arrangements are transparent, and it would generally be required that the existence of such arrangements be made public so that the listing of future alternative medicines is not hindered.

#### Quantification of impacts

Where the risk relates to the overall cost to the PBS or RPBS, quantify the impact of the risk-sharing arrangement by presenting additional spreadsheets in the Excel workbook, both with and without the risk-sharing arrangement, where the utilisation, dose or duration of therapy exceeds that estimated in Subsection 4.2. Where the risk relates to the cost-effectiveness, quantify the impact of the risk-sharing arrangement on the economic evaluation.

### Special pricing arrangements

Where a special pricing arrangement has been offered, spreadsheets should be adapted in the standardised Excel workbook to show the costs over five years with and without the special pricing arrangement in place. The effect of the special pricing arrangement should be carried through the entire workbook. Where both a special pricing arrangement and a risk-sharing arrangement are proposed, present the impact of the risk-sharing arrangement with and without the special pricing arrangement in place.

## 4.3 Estimation of changes in use and cost of other medicines

**INFORMATION REQUESTS**

**Name the PBS medicines likely to be affected**

Identify the other PBS-listed medicines that are likely to be affected by listing the proposed medicine.

**Estimate the change in the number of packs dispensed over five years**

For each affected medicine, estimate the change in the number of packs (of each form and strength) in each year over five years (disaggregated into proportions for the PBS and the RPBS, and by beneficiary type).

**Estimate the costs over five years**

Estimate the costs of each form and strength of each affected medicine in each year over five years.

**Use Spreadsheet 4**

Calculate the change in number of packs dispensed and costs over five years using Spreadsheet 4 of the standardised Excel workbook.

### Identify PBS medicines likely to be affected

If the submission has taken a market-share approach, PBS-listed medicines that are likely to be substituted by the proposed medicine will have been identified in Subsection 4.2. However, identification of other PBS-listed medicines that will increase or decrease in usage may still be relevant.

PBS-listed medicines likely to be affected by the listing of the proposed medicine include:

* PBS-listed medicines substituted by the proposed medicine
* other PBS-listed medicines with decreased usage

other PBS-listed medicines with increased usage.

Identify and list all PBS-listed medicines that fall into each of these three categories. The list should include those PBS-listed medicines identified as comparators in Subsection 1.1 and as other relevant therapies in Subsection 1.2.

Where the proposed medicine is replacing a medical procedure or has no comparator medicine, there will be no substituted medicines. In general, where the proposed medicine will substitute for PBS-listed medicines, all listed medicines, disaggregated by form and strength, should be presented.

Where the submission has identified the potential for market growth or an increase in eligible patients because of listing the proposed medicine, nominate whether these patients are likely to have been taking another medicine. In some cases, patients will be receiving best supportive care in the absence of the proposed medicine, and therefore there will be no PBS-listed medicines substituted by the proposed medicine. Clearly state and justify any medicines that are to be replaced for the proportion of patients that represent market growth.

PBS-listed medicines with expected decreased usage after the listing of the proposed medicine include those that are co-administered with substituted medicines, those used to treat adverse reactions to substituted medicines, and those used to treat the clinical end points that might be reduced after therapy involving the proposed medicine.

PBS-listed medicines with expected increased usage after listing of the proposed medicine include those that are co-administered with the proposed medicine and those used to treat adverse reactions to the proposed medicine.

The impact of adverse reactions might have less weight if the evidence provided in the submission shows that they are of insufficient clinical importance to require management with PBS-listed medicines, or if they are similar for the proposed medicine and its major competitors. If there is insufficient information available from trial results or extended assessment of comparative harms to include the impact of adverse reactions on PBS expenditure, this should be noted.

### Change in the number of packs dispensed over five years

Where an epidemiological approach has been used, discuss the extent of change for each of the forms and strengths of PBS-listed medicines that will be substituted, and for those that are expected to increase or decrease in usage after listing of the proposed medicine. Present and justify the change in the number of packs for each of these medicines over five years. Clearly reference how the estimates were generated and the data on which the estimates are based. Present estimates by beneficiary type, as described in Subsection 4.2.

Section 3 may incorporate a change in PBS-listed medicines because of listing the proposed medicine. Justify any inconsistencies between Section 3 and Section 4 in terms of the identified medicines or the estimated extent of change of usage over the five years following listing of the proposed medicine.

Where a market-share approach has been used, the change in the number of packs for substituted PBS-listed medicines will represent the market share lost to the proposed medicine. The proportion of the market gained by the proposed medicine and lost by each substituted PBS-listed medicine should be clearly stated in Subsection 4.2, with justification for these projections. Where the submission has estimated a different rate of substitution across different PBS-listed medicines, this should be justified, particularly where there is differential pricing across the PBS-listed medicines.

#### Disaggregation of estimates

Disaggregation into proportions for the PBS and the RPBS, and by beneficiary type should be based on the most recent 12 months of usage data from DHS. An exception could be where the expected substitution is for a distinctive subgroup of current use of the substituted medicine(s), in which case the disaggregation should be based on the subgroup.

Calculate the results presented in this section using Spreadsheet 4 of the standardised Excel workbook.

### Costs over five years

On the basis of the estimated utilisation changes, estimate the costs in each year over five years for each of the forms and strengths of each of the medicines substituted, decreased and increased. Refer to Subsection 4.2 for the suggested approach. Present the disaggregated and aggregated costs, applying both the DPMQ and the DPMQ with appropriate patient co-payment subtracted, as per Subsection 4.2.

Calculate the results presented in this section using Spreadsheet 4 of the standardised Excel workbook.

## 4.4 Estimated financial implications for the PBS and RPBS (or NIP)

**INFORMATION REQUESTS**

**Calculate net financial implications for the PBS and RPBS (or NIP)**

Estimate the net financial implications for the PBS and the RPBS (or the NIP) in each year over five years.

**Use Spreadsheet 5**

Present the calculations for Subsection 4.4 in Spreadsheet 5 of the standardised Excel workbook.

### Net financial implications for the PBS and RPBS

Present the net financial implications for the PBS and RPBS (or the NIP) over five years, accounting for the estimated cost of the proposed medicine, the increased usage of other PBS-listed medicines and cost offsets for substituted medicines with a likely reduction in usage. Subtract the net cost offsets for both the aggregated estimates calculated in Subsection 4.3 from the corresponding estimates calculated in Subsection 4.2.

This financial estimate uses the DPMQ with appropriate patient co-payments removed, or the price to the Australian Government, as appropriate, for medicines to be listed under section 100 arrangements or vaccines to be funded under the NIP.

Calculate the two sets of net financial implications in Spreadsheet 5 of the standardised Excel workbook.

## 4.5 Estimated financial implications for the Australian Government health budget

**INFORMATION REQUESTS**

**Estimate prescription processing changes for DHS**

Estimate the extent of net change in the number of prescriptions processed by DHS for payment (and, where appropriate, the net change in the number of authorities by DHS) for five years.

**Estimate net changes to MBS items**

Estimate the extent of net change in the number of each type of affected MBS items provided for five years, and the net financial implications for the MBS in each year over five years.

**Estimate net financial implications for government**

Estimate the net financial implications for the Australian Government health budget for five years.

**Use Spreadsheets 6, 7 and 8**

Present the calculations for Subsection 4.5 in the standardised Excel workbook using Spreadsheets 6, 7 and 8, and create new spreadsheets if applicable.

Implementing a PBAC recommendation might have financial implications for other parts of the Australian Government’s health budget, including DHS and the MBS. This section extends the financial analyses presented in Subsection 4.4 to estimate those implications. If implications for other components of government health budgets are identified, the general approach outlined here should be applied.

### Net prescription processing changes for DHS

To estimate the numbers of prescriptions processed by DHS, use the estimates of the numbers of dispensed packs of the proposed medicine (from Subsection 4.2) and the net changes in the numbers of packs of other medicines dispensed (from Subsection 4.3). In some instances (usually when a market-share approach has been taken), the number of prescriptions estimated in Subsection 4.2 will be entirely offset by that estimated in Subsection 4.3. However, where there is likely to be a growth in the overall market due to listing of the proposed medicine, this section should be completed.

Where the proposed medicine or the medicines considered in Subsection 4.3 include medicines with a relevant restriction requiring authorisation by DHS, estimate the extent of net change in the number of authorisations in each year over five years, taking into account the number of repeat packs permitted per authorisation. Where applicable, distinguish between authorisations requiring a written application and those requiring a telephone application, and estimate each type separately.

The submission should seek to present the financial implications to DHS of:

* processing prescriptions for payment
* authorising prescriptions based on a telephone application, where applicable

authorising prescriptions based on a written application, where applicable.

Use Spreadsheet 6 of the standardised Excel workbook to calculate the sets of net financial implications to DHS.

### Net changes to MBS items

#### Identify affected MBS items

MBS items for which an increase in use might be expected include:

* MBS-funded procedures required to administer the proposed medicine (eg an implant or an infusion)
* MBS-funded consultations to manage adverse reactions to the proposed medicine
* MBS-funded consultations and tests to
* confirm diagnosis of the medical condition
* determine eligibility for the proposed medicine according to the requested restriction (see Subsection 1.4)

determine whether any continuation criteria in the requested restriction for the proposed medicine have been met (see Subsection 1.4).

MBS items for which a decrease in use might be expected include:

* substituted MBS-funded procedures
* MBS-funded items that would have been used to manage averted clinical events

MBS-funded consultations to manage adverse reactions to substituted medicines.

Generate the estimates of MBS usage by relating the number of patients estimated in response to Subsection 4.2 to the per-patient usage estimates generated in Section 3 of the submission.

When the submission is based on a cost-minimisation approach, this analysis may still be necessary if any expected increase in the rate of growth in the overall market due to listing the proposed medicine is expected to increase the frequency of accessing MBS services, or if there is a net impact on the costs of administration.

Identify and justify any inconsistency between Section 3 and Section 4 of the submission in the types of MBS items that would change because of listing the proposed medicine, and the extent of change per patient in the first five years of listing.

#### Apply the costs of MBS items

The appropriate benefit varies depending on the setting for the particular MBS service (see the Medical Benefits Schedule for more details).

Calculate the extent of net changes in the cost to the MBS for each item affected, using the schedule fee. Aggregate the MBS items to estimate the net financial implications for the MBS overall**.**

Use Spreadsheet 7 of the standardised Excel workbook to calculate the two sets of financial implications (schedule fee, and appropriate benefit with patient co-payment removed).

### Net implications for Australian Government health budget

Identify and justify any other financial implications for the Australian Government health budget. In presenting the calculations, follow the stepwise approach taken above to:

* estimate the numbers, in their natural units, of the disaggregated health care resources provided or freed
* apply the appropriate unit cost(s) to each type of health care resource to estimate the net financial implications for each type

aggregate the newly identified financial implications in each year over five years.

Create a new spreadsheet in the standardised Excel workbook to present details of these calculations.

Combine PBS and RPBS estimates, using the DPMQ, with the MBS estimates, using the schedule fee. Separately combine financial implications with appropriate co-payments removed. Then incorporate any other identified financial implications for the Australian Government health budget.

Calculate the aggregated sets of net financial implications in Spreadsheet 8 of the standardised Excel workbook.

## 4.6 Identification, estimation and reduction of uncertainty

**INFORMATION REQUESTS**

**Evaluate sources of uncertainty**

In each step of the calculations, assess the sources of uncertainty, and distinguish the type and degree of uncertainty in utilisation and financial estimates.

**Describe the impact of uncertainty**

Where possible, describe the direction and magnitude of the impact of uncertainty on the overall estimates.

**Suggest ways to reduce uncertainty**

Estimate the level of the uncertainly and propose ways to reduce it.

**Summarise results in Spreadsheet 5**

Provide a separate workbook to generate the results of any calculations (eg sensitivity analyses and scenario analyses) used to examine the impact of uncertainty. Summarise these in Spreadsheet 5 of the standardised Excel workbook. Where a risk-sharing arrangement has been proposed, present tables with and without the application of the risk-sharing arrangement.

### Sources of uncertainty

When estimating utilisation and financial implications, uncertainty arises as a result of the potential for usage that differs from expectations, and usage that extends beyond the restriction.

It is informative for the submission to address both of these sources of uncertainty and to clearly discriminate between the two. Where there is substantial uncertainty in the utilisation and financial estimates, particularly when this uncertainty is a result of usage beyond the restriction (‘leakage’), the submission may seek to minimise the impact of the uncertainty by proposing a risk-sharing arrangement.

#### Factors affecting uncertainty

The following lists summarise the factors that could be considered when assessing uncertainties in predicted utilisation patterns and financial implications resulting from listing of a proposed medicine as requested. The lists are not intended to be prescriptive, but generally reflect factors that have been considered previously by the Drug Utilisation Sub-Committee (DUSC) and the PBAC; they may arise from epidemiological data, pharmacoepidemiological data, expert opinion and assumptions used in generating the quantified predictions. Any of these factors might provide information that will increase understanding of the uncertainties present in utilisation estimates. It might be useful to consider these factors explicitly, but not all the factors will apply to all submissions. Thus, it might not be necessary to address any or all of these questions for each submission, as the uncertainties outlined might be very small or of little importance to the overall cost to the PBS. Therefore, consideration should be given to how relevant each of the factors might be for a particular submission.

##### Factors that could affect the extent of usage within the requested restriction

* Promotion might result in greater identification of the proposed medicine, resulting in more prescribers considering patients for treatment.
* Indirect media exposure to consumers might result in some consumers being more aware of the proposed medicine and seeking treatment with it. These patients might not be identified if a treated prevalence approach has been used.
* Outcomes of related research might have an impact on uptake of the proposed medicine. This could be positive or negative. They could emerge at the time the submission is lodged or might be expected to occur within five years of listing.
* More prescribers and patients might seek treatment if the proposed medicine treats a medical condition for which the alternatives are considered to be substantially inferior to the proposed medicine (eg in terms of effectiveness, tolerability, patient acceptability or convenience).
* Limited access to designated types of PBS prescribers or to designated diagnostic procedures in a requested restriction might limit uptake and utilisation.
* The duration of therapy might be longer than expected from the randomised trials, particularly when trials are truncated.
* Patients might be treated more or less often than expected, particularly in the case of medical conditions with episodic manifestations.
* There might be a likelihood of doses increasing over time.

Epidemiological or market-share trends may have been inaccurately forecast.

##### Factors that could affect the likelihood of usage beyond the requested restriction

Some of the factors listed above might also affect the likelihood of usage beyond the requested restriction. Many of these factors relating to the requested restriction could be considered to be more applicable to risk-sharing arrangements. More detailed guidance is given in Subsection 1.4 about ways of designing a restriction to minimise usage beyond its intention, but the following factors might be considered:

* The requested restriction is for a subset of the types of patients who are eligible according to the TGA-approved indication(s).
* The requested restriction is for a subset of the types of patients who were eligible for the randomised trial(s) published for the proposed medicine, or there are randomised trials demonstrating evidence in other medical conditions.
* The requested restriction is for a subset of the types of patients who have been subsidised by the sponsor before lodgment of the submission (eg on compassionate grounds or as part of clinical studies).
* The requested restriction is for a subset of the types of patients for whom the sponsor plans to promote use of the proposed medicine before or after PBS listing.
* The requested restriction is for a subset of the types of patients who have the underlying medical condition.
* Identify whether there are any likely difficulties for prescribers in determining eligibility for the proposed medicine (eg a difficult differential diagnosis, ambiguity in the wording of the restriction, poor precision or accuracy in a diagnostic test) that might result in misclassifications of eligible patients from the population with the underlying condition.

Identify whether patient advocacy groups are likely to have an influence on determination of eligibility by prescribers.

### Impact of uncertainty

The following aspects should be addressed in any consideration of uncertainty:

* the direction of impact on the estimate (underestimate or overestimate)

the impact on the magnitude of the estimate (small or large).

Although quantitative estimates of uncertainty are preferred, semiquantitative assessments may need to be given in many instances. Where the effects of some uncertainties are difficult to quantify, this should be noted. As a general principle, the more sensitive the overall financial implications are to a particular source of uncertainty, the more important it is to minimise that uncertainty.

### Reducing uncertainty

One way to reduce uncertainty is to use data from multiple sources, where available. This can be referred to as ‘triangulation’ (the use of multiple sources of data or multiple approaches to determine the consistency or otherwise of the conclusions from those sources or approaches). Where estimates derived from different sources are concordant, there might be more confidence and therefore less uncertainty in the resulting estimates. Where estimates are discordant, the disparity between the estimates might contribute to the estimate of uncertainty. A similar approach can be taken when more than one methodological approach has been applied (eg estimates based on a market-share base as well as an epidemiological base; or treated prevalence, where the prevalence of patients treated for a disease, determined from a pharmacoepidemiological database, is used as a surrogate for the true prevalence).

### Summary of calculations

Summarise the results of any calculations (eg sensitivity or scenario analyses) to quantitatively examine the impact of uncertainty in Spreadsheet 5 of the standardised Excel workbook. Do not include the supporting calculations in that spreadsheet. If additional calculations need to be explained, a separate workbook should be provided for any analysis other than the base-case (most likely) analysis. Spreadsheet 1 of the separate workbook should highlight the differences from the base-case workbook.

Where a risk-sharing arrangement has been proposed, provide calculations that examine the impact of uncertainty with and without the risk-sharing arrangement.

# Section 5 Options to present additional relevant information

## Introduction

Section 5 of a submission to the PBAC is intended to assist the consideration of issues that are important for some submissions but are not necessary for all submissions. These include quality use of medicines (QUM), risk-sharing arrangements, equity principles, ‘rule of rescue’ and other relevant factors that can affect the PBAC’s assessment of proposed medicines.

This guidance does not cover all possible issues. Ultimately, a sponsor may include in Section 5 any information that is relevant to the PBAC’s decision.

Flowchart 5 shows the main issues for consideration in Section 5.

Flowchart 5 Overview of information requests for Section 5 of a submission to the PBAC

Section 5: Other issues
5.1 Quality use of medicines: How will the sponsor support quality use of medicines or postmarketing surveillance? Details on QUM activities and postmarketing surveillance studies.
5.2 Other relevant factors: Are any other factors relevant to the submission? Equity, prudent use of antimicrobials, rule of rescue, etc.

## 5.1 Quality use of medicines

**INFORMATION REQUESTS**

**Describe any activities to support QUM**

Identify any activities (planned or under way) of the sponsor that are intended to support QUM and to achieve the desired health outcomes for the population identified by the requested restriction (including activities integrated with other QUM service providers).

### QUM activities

#### Relevance and definition of QUM

The cost-effectiveness of a medicine in regular clinical practice can be influenced by many factors that affect the achievement of the desired health outcome. Therefore, there is an extensive overlap between the concepts of QUM and of cost-effective subsidy arrangements for medicines delivered through the PBS. Many of the principles of QUM are embedded as design principles in earlier sections of these guidelines. These overlapping issues – such as a consideration of correct dose regimens, comparative benefits and comparative harms – should therefore be addressed in the relevant context earlier in the submission and need not be repeated in this section.

The National Strategy for Quality Use of Medicines has been developed to guide QUM in Australia. This strategy is not isolated, and recognises the interdependence of its aims and those of the PBS. Because of this interdependence, the integration of activities both within and across these aims is critical.

QUM involves the following three elements:

* Judicious selection of management options. This means consideration of the place of medicines in treating illness and maintaining health, recognising that nonmedicine therapies may be the best option for the management of many disorders.
* Appropriate choice of medicines, where a medicine is considered necessary. This means selecting (when medicines are required) the best option from the range available, taking into account the individual, the clinical condition, risks, benefits, dosage, length of treatment, comorbidities, other therapies and monitoring considerations. Appropriate choice also requires a consideration of costs, both human and economic. These costs should be considered for the individual, the community and the health system as a whole.

Safe and effective use. This means ensuring the best possible outcomes of therapy by monitoring outcomes, and minimising misuse, overuse and underuse. It also means improving the ability of all individuals to take appropriate actions to solve medication-related problems (eg managing adverse effects or multiple medications).

This definition of QUM applies equally to decisions about medicine use for individual patients (in primary and secondary care) and to decisions at the public health level (which affect the health of the population).

#### Supporting QUM

Matters that uniquely apply to QUM but could usefully be addressed in a submission for PBS subsidy should be provided in response to this section. Current or future sponsor activities to support QUM and thus to achieve the desired population health outcomes may include activities integrated with other QUM service providers, because these can help build partnerships that promote QUM. The range of activities may include:

* assisting in judicious management and appropriate selection of the proposed medicine within the requested restriction (eg if the restriction is narrower than the TGA-approved indication and/or if the therapeutic conclusion in the submission is of noninferiority rather than superiority, and it is planned that the promotional activities for the proposed medicine will be aligned with these aspects of the submission, describe how this will be achieved)
* promoting the applicability of trial results to the population and circumstances of use identified for the requested listing
* minimising sources of uncertainty identified in estimating uptake and overall utilisation patterns of the proposed medicine

maximising safe and effective use once therapy has begun, such as development and distribution of consumer medicine information, appropriate packaging (eg vial strengths, blister pack quantities) and appropriate labelling; this includes reducing unintentional adverse events.

These activities could reassure both the PBAC and government that uncertainty about cost‑effectiveness and usage within the requested restriction will be minimised.

## 5.2 Other relevant factors

**INFORMATION REQUESTS**

**Describe equity issues**

If the submission raises any issue relating to equity principles, discuss it in descriptive terms.

**Incorporate prudent use principles for antimicrobials**

If the submission is for a new antimicrobial agent, take account of relevant prudent use principles for such agents.

**Establish a basis for any claim for the ‘rule of rescue’**

If the submission makes any claim that the ‘rule of rescue’ is applicable, set out the basis for that claim.

**Discuss any other relevant factor**

If the submission identifies any other relevant factor not requested elsewhere, discuss it in response to this section.

### Equity issues

From a general policy viewpoint, the PBS promotes fairness in its subsidy arrangements by promoting affordable access to cost-effective medicines. Discuss how the proposed medicine might promote (or hinder) patient equity or access. For example, if the requested listing of the proposed medicine would raise particular patient affordability considerations, their implications should be discussed.

### Prudent use principles for antimicrobial agents

The submission for a new antimicrobial agent should be aware of the government-endorsed prudent use principles proposed by the 1999 report of the [Joint Expert Advisory Committee on Antibiotic Resistance](http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pubs-jetacar-cnt.htm/$FILE/jetacar.pdf) (JETACAR) when considering target populations, and should provide relevant data on the development of resistance as appropriate (with cross-referencing to the responses to Section 2 if the development of resistance has been demonstrated to affect health outcomes). Any issues arising should be addressed, and submissions should indicate whether any aspect of any restriction requested in response to Subsection 1.4 is designed to minimise the development of resistance.

### Basis for any claim for the ‘rule of rescue’

Four factors, which apply in exceptional circumstances, are particularly influential in favour of listing. When all four factors apply concurrently, this is called the ‘rule of rescue’. The four factors are as follows:

* No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no nonpharmacological or pharmacological interventions for these patients.
* The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the PBAC’s consideration.
* The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the PBAC’s consideration. However, the PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.

The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the PBAC’s consideration.

As with other relevant factors, the rule of rescue supplements, rather than substitutes for, the evidence-based consideration of comparative cost-effectiveness. A decision on whether the rule of rescue is relevant is only necessary if the PBAC would be inclined to reject a submission because of its consideration of comparative cost-effectiveness (and any other relevant factors). In such a circumstance, if the PBAC concludes that the rule of rescue is relevant, it would then consider whether this is sufficiently influential in favour of a recommendation to list that the PBAC would reverse a decision not to recommend listing if the rule of rescue were not relevant.

This guidance on the rule of rescue is kept deliberately narrow. Although there are relevant arguments for broadening the guidance, the PBAC is concerned that doing this would reduce the relative influence of the rule of rescue when it is applied to a broader set of eligible submissions. In other words, the greater the proportion of submissions that the rule of rescue is applied to, the smaller its average impact in favour of listing across the identified submissions.

One issue that has arisen concerning the rule of rescue is that a second medicine to treat the medical condition that is considered to meet the requirements of the rule is not suitable for this consideration. This is because, by definition, the second medicine does not meet the essential first factor (ie that there is currently no alternative intervention). This causes a difficulty if listing of the second medicine is sought on a cost-minimisation basis.

Another difficulty is that indiscriminate application of arguments such as the rule of rescue can lead to overall inefficiencies, unless the PBAC compensates when considering medicines that clearly fall outside the rule.

### Any other relevant factor

If any other relevant factor is thought to be worth emphasising and is not already requested elsewhere for inclusion in the submission, discuss it in the response to this section.

# Part B – Information requests for specific product types

# Product type 1 – Fixed dose combination products

This subsection applies to a submission for a fixed combination of active component medicines seeking subsidisation under the Pharmaceutical Benefits Scheme (PBS) or the National Immunisation Program (NIP). It applies both to a combination of medicines in a single dosage form and to individual dosage forms in a composite packaging.

In general, submissions seeking consideration of fixed dose combination products should address all of the information requests in this section. Where an information request is not addressed, this should be clearly explained and justified. Submissions should also explain, and present evidence for, the value of the fixed dose combination product over and above the use of the individual components.

This subsection does not apply to medicines that – for specific indications – are almost invariably used together in fixed dose combinations for clinical reasons, such as oral contraceptives, hormone replacement therapy and *Helicobacter pylori* eradication regimens.

The labelling of the combination product should clearly identify the component generic medicines.

## P1.1 Listing fixed dose combination products

**ADDITIONAL INFORMATION REQUESTS**

**Complete all information requests**

Comply with all information requests in Part A of these guidelines, where applicable.

**Provide additional information for Section 1**

Provide information in Section 1 to show:

* the main comparator products (Subsection 1.1)
* the Therapeutic Goods Administration (TGA) status of the combination product and its components (Subsection 1.3)
* that listing the combination product would not result in inappropriate dosing or unnecessary proliferation of products or dosage forms (Subsection 1.4).

**Show additive effectiveness**

Provide data in Section 2 to show additive (not necessarily synergistic) beneficial effectiveness of the components.

**Substantiate other claims**

In particular, justify any claims of:

* improved patient convenience or compliance in terms of their impact on improving health outcomes (in Sections 2 or 3)
* reduced provision of other health care resources (in Sections 2 or 3)
* reduced expenditure in the Australian Government health budget (in Section 4).

**Show that inappropriate usage (misuse or increased usage) would not occur**

Provide an analysis of any potential for inappropriate (including increased) use as part of Section 4.

**The requests for information in this section are in addition to the requests in the main body of the submission, which should be completed for the combination product.**

### Additional information for Section 1

#### Main comparators (Subsection 1.1)

The submission should seek to nominate the following main comparators identified in following comparisons:

* the combination product against its component products given concomitantly, as the basis for a cost-minimisation approach (this need not apply where the combination product consists of the individual dosage forms in a composite packaging)
* the combination product (or its components given concomitantly) against each of the component products given alone, as the basis for establishing at least an additive beneficial effectiveness
* the combination product against the therapy that prescribers would most replace in practice, should this be expected to vary from the current concomitant use of the individual components.

#### TGA status (Subsection 1.3)

Confirm that all components in the combination product are approved by the TGA. Confirm that any requested indication is consistent with the approved indication for each component of the combination product.

#### Listing status (Subsection 1.4)

For each component of the combination product:

* provide information on reimbursement through the PBS or NIP
* confirm that any restriction for each component is consistent with any proposed restriction for the combination product
* present the doses available for each component and compare them with the doses available for the combination product
* confirm that current dosing with individual components would remain unchanged upon patients transitioning to the combination product, or describe the expected change
* confirm that the combination product does not risk unnecessary proliferation of products or dose forms.

### Additive effectiveness (Section 2)

An additive effect of the combination product could be demonstrated with reference to any of the following:

* the outcome upon which the components were listed
* if it is not feasible to measure this outcome, a validated surrogate outcome (such as blood pressure or forced expiratory volume)
* in the case of fixed combination vaccine products, no loss of beneficial effectiveness of the components across different diseases or strains of pathogens (see product type 3).

### Substantiate other claims (Sections 2 and 3)

In general, for the purposes of informing a cost-minimisation approach, submissions will seek to demonstrate equivalence (or noninferiority) of the combination product to its component medicines. Where a cost-minimisation approach is taken, the pricing of a combination product would normally be no greater than the sum of its individual components (at the current price to pharmacist level for PBS products or at the price to the Australian Government for NIP products), usually calculated on a per-milligram basis.

Where the combination product(s) is expected to substitute for two or more strengths of the component products, the price to pharmacist should reflect the sum of the individual components as a function of the expected proportions of substitution.

The submission may claim a price advantage where evidence of acceptable cost-effectiveness through improved health outcomes or acceptable cost offsets is demonstrated. Where all of the components of the combination medicine are currently available on the PBS or routinely used in clinical practice, evidence of improved health outcomes may be difficult to establish over the individual components.

The submission may claim improved compliance, improved health outcomes or a reduction in toxicity. Subsection 101(4AC) of the *National Health Act 1953* requires the Pharmaceutical Benefits Advisory Committee (PBAC) to advise the Minister for Health when the committee is satisfied that therapy involving a combination item, compared with alternative therapies, provides, for some patients:

* a significant improvement in patient compliance with the therapy; or
* a significant improvement in efficacy or reduction in toxicity.

Any advice provided by the PBAC under subsection 101(4AC) will be relevant to both existing combination items and new combination items when they are recommended for listing.

These claims must be adequately justified in the submission. Unsupported or inadequately substantiated claims of improved compliance, improved health outcomes or a reduction in toxicity will render these claims uncertain.

#### Supporting a claim of improved compliance (Section 2)

The PBS subsidises medicines that improve health outcomes and provide value for money. Compliance with medication regimens is one factor that can influence the achievement of health outcomes and affect the cost-effectiveness of a medicine. Therefore, evaluating evidence on the extent of compliance with medicines and the effect on health outcomes is of concern to the PBAC when considering therapies to be recommended for subsidy.

The purpose of this section is to provide guidance on the approach required for supporting a claim of a significant improvement in compliance for a combination product over its comparator. The general steps the submission should take to support this claim are, first, provide evidence of improved compliance and, second, provide evidence to support why this improvement is significant, most often by establishing that the improvement in compliance would result in a meaningful change to patient health.

Compliance is a broad term that encompasses consumers' acceptance of, adherence to and persistence with a prescribed medicine. These terms are defined below:

* Acceptance – the consumer’s informed decision to undertake behaviours that are expected to lead to improved health outcome (such as taking a medicine that has been prescribed).[*reference to be inserted, WHO 2003*]
* Adherence – the extent to which the consumer conforms to the agreed behaviours, with respect to timing, dosage and frequency of medication taking.[*reference to be inserted, Cramer 2007*]
* Persistence – The duration of time from initiation to discontinuation of therapy.[*reference to be inserted, Cramer 2007*]

Evaluation of compliance for combination items has become increasingly important to the PBAC following the amendment of the National Health Act associated with the PBS Reforms in 2007. These statutory changes now include a provision in subsection 101(4AC) that requires the PBAC to evaluate claims of improved compliance for combination items and advise the minister when a combination item significantly improves compliance.

##### Approach to support a claim of improved compliance

The submission should address the following to support a claim of improved compliance for the combination product over the main comparator. The information provided should be for the combination product and for its alternative therapies. In general, the alternative therapy of interest is the use of the individual components of the combination product. Where some of the individual components are already available as a fixed dose combination product, the comparison would be against that product used in combination with additional components. Where the main comparator is not the components of the combination product, this should have been clearly established in Subsection 1.1.

###### Current level of compliance

Describe the current level of compliance for the components of the combination product and for the combination product. Provide detail on the acceptance, adherence and persistence of each of the medicines. Relevant sources of information may include:

* a structured literature review or a systematic review
* current persistence in PBS administrative data and prescription claims data
* other studies of compliance, including validated self-report, direct observation, pill counts, prescription refills and electronic medicine monitoring.

Present estimates of compliance and the source of information used to establish the estimates. State any assumptions used to generate estimates of compliance and provide evidence to support the assumptions. Where possible, present evidence from multiple sources and discuss differences between the sources. Provide an estimate of the uncertainty for the data provided.

The submission should discuss where there is evidence of poor compliance, and reasons commonly given by consumers for poor compliance. State whether there are subgroups of the population with different levels of compliance and present reasons why.

State whether the estimates of compliance are relevant to the target Australian population and setting.

###### Factors likely to affect compliance

Describe the factors that affect compliance for these medicines. Examples of the types of factors that may affect compliance are:

* patient or care giver characteristics or behaviours
* disease characteristics
* prescriber or practitioner characteristics
* health system or setting factors
* characteristics of the medicine such as cost, adverse effects, formulation and regimen.

Where a factor that may influence compliance is identified, discuss whether this is relevant to the Australian setting. Where the factor predicting compliance is not relevant to the proposed population, proposed use of the medicine or Australian health care system, this should be stated.

Although factors that affect compliance should be relevant to the use of the proposed medicine, the submission should provide some supporting evidence that the factors identified are relevant across other medicines or settings. Given the difficulty in establishing the impact of certain factors on compliance, where there is not a consistent relationship across alternative scenarios, this should be explained.

Relevant sources of information for addressing this may include:

* qualitative and quantitative studies of factors affecting compliance
* cross-sectional surveys of reasons for noncompliance
* self-report surveys in randomised trials that include reasons for noncompliance.

###### Effect of the combination product on factors affecting compliance

Describe how use of the combination product, compared with its alternative(s), affects the factors contributing to noncompliance in the population of interest. The description should include a plausible explanation of the link between the use of the combination product and the factors affecting compliance. This explanation should be supported by published studies and/or surveys of prescribers and/or surveys of consumers.

###### Evidence of improvements in compliance

Provide evidence of a measurable difference in compliance associated with use of the combination product compared with its alternative therapies. Estimate the extent of the difference in compliance and the uncertainty in this estimate.

Evidence of improved compliance may be sourced from comparative studies of compliance for the combination item compared with alternative therapies. Study designs may be observational or pragmatic trials. It is important to establish that study patients who are taking the combination product and their settings are similar, in terms of factors that may predict compliance, to those taking the alternative therapy. Present a comparison of the patients, in terms of the factors identified above, who are receiving the two therapies in the study purporting to show differences in compliance. Comment on the similarity of the overall study population and setting to the Australian population and setting.

###### Evidence of compliance affecting health outcomes

Discuss how important compliance is to achieving the desired health outcomes for the medicine.

Present evidence of an impact on health outcomes of a difference in compliance of a magnitude identified above. State whether the difference in health outcomes that is likely to occur from the extent of improved compliance is clinically significant.

Possible sources of evidence to establish a link between compliance and health outcomes include:

* studies of the effect of compliance on health outcomes (preferably from studies designed to measure compliance that also include measures of health outcomes)
* pharmacokinetic studies
* dose-response studies, including data on duration of medicine usage
* outcomes data from randomised trials.

###### Financial implications

PBS expenditure for combination products changes when there is an accepted claim of improved compliance. Generally, a combination product will have the same cost as its components, and, when one component undergoes a statutory price reduction, this will affect the price of the combination product. Therefore, for combination products claiming improved compliance, it is important to present the effect on PBS expenditure.

Present the estimate of PBS expenditure at the currently listed price. Present the estimate of PBS expenditure following price reductions applied from component medicines.

#### Supporting a claim of improved efficacy or reduced toxicity (Section 2)

To enable PBAC consideration of whether the relevant combination item provides, for some patients, a significant improvement in efficacy or a significant reduction in toxicity over alternative therapies, supply information concerning the impact of the efficacy improvement or toxicity reduction on clinical importance and patient relevance. Such improvements in health outcomes for patients need not necessarily arise from significant improvements in compliance.

### Inappropriate usage (Section 4)

Provide an analysis in Section 4 to show that listing the combination product would not encourage or result in an inappropriate increase in overall use of its individual components, nor in inappropriate use of one or more of the components in specific patient groups.

### Quality use of medicines (Section 5)

Explore potential QUM issues associated with the proposed listing of the fixed dose combination product, as outlined in Part A, Subsection 5.1.

# Product type 2 – Nutritional products

This section applies to a submission for a nutritional product seeking subsidisation under the PBS. It includes requests for general additional information relating to nutritional products, and additional information for specific medical conditions. This section also provides additional guidance for identifying the main comparator in relation to nutritional products.

These additional requests for information are not exhaustive, but seek to clarify the particular needs of the PBAC and its Nutritional Products Working Party (NPWP), which advises the PBAC on submissions for nutritional products.

## P2.1 Details of proposed product and its comparators (Section 1)

**ADDITIONAL INFORMATION REQUESTS**

**Complete all information requests**

Comply with all information requests in Part A of these guidelines, where applicable.

**Describe the main comparator(s) (Subsection 1.1)**

In Subsection 1.1, include a description of the main comparator product(s).

**Provide additional information for specific medical conditions (Subsection 1.1)**

Supply additional information in Subsection 1.1 if the submission includes a product for use in the management of one of the following conditions:

* multifood allergy
* monosaccharide intolerance
* weaning from total parenteral nutrition (TPN) to formula
* patients requiring ketogenic diets
* infant formula products, such as a formula used in infants younger than 12 months.

**Confirm regulatory compliance (Subsection 1.3)**

Include evidence of compliance with the Australia New Zealand Food Standards Code *–* [Standard 2.9.5: Food for Special Medical Purposes](http://www.comlaw.gov.au/Details/F2016C00081).

**Provide additional information about the proposed product and its use (Subsection 1.4)**

In Subsection 1.4, provide:

* a list of all ingredients
* justification for the requested maximum quantity allowed and repeats
* a table of nutrient contents in relation to recommended dietary intakes (RDIs) and the nutritional needs of patients
* instructions for preparation and use of the proposed product
* a comparison of the proposed product against the nutritional needs of patients, whether given in conjunction with other foods or not.

### Main comparator(s) (Subsection 1.1)

In theory, and consistent with other types of products proposed for subsidy under the PBS, the main comparator for a nutritional product is the therapy that prescribers would most replace in practice. In some cases, comparisons with more than one comparator will be necessary, or will provide the NPWP and the PBAC with sufficient information on which to base their recommendations.

The description of the main comparator product(s) in Subsection 1.1 should be based on a relevant amount of nutrient in relation to the RDI, rather than to the total product volume. As an example, for an amino acid formula, this description for comparative purposes should be based on a stated protein equivalent, not 100 g of the comparator products.

The information in the following sections will help sponsors of nutritional products to select the appropriate main comparator product(s).

#### Existing products with similar mechanisms of action

If the proposed product is in a class that contains other, already listed dietary supplements with the same or similar mechanism of action, the main comparator would usually be the product in the class that is prescribed on the PBS for the largest number of patients in the appropriate age group. A comparison with a more appropriate form (similar in mechanism of action), not necessarily subsidised on the PBS but available internationally, might provide the NPWP and the PBAC with the necessary nutritional comparison and the necessary scientific data to support an assessment of the proposed product’s clinical effectiveness and safety. However, this comparison would not necessarily inform the economic factors involved in considering the proposed product.

#### New therapeutic classes

If the proposed product is in a new therapeutic class (eg has a new or additional mechanism of action), the main comparator would usually be the product that is prescribed on the PBS to treat that indication for the largest number of patients in the appropriate age group. If there is no similarly listed PBS product, a comparison with any other alternative product for which data exist might help the NPWP and the PBAC in making an assessment of the proposed product’s clinical effectiveness and safety. However, such a comparison would not necessarily inform the economic factors involved in considering the proposed product.

#### No currently listed products

If no currently listed product is available, the main comparator would usually be standard medical management (this could include special dietary restrictions). This should be clearly and consistently defined in both the submission and the comparative randomised trials.

### Specific medical conditions, if applicable (Subsection 1.1)

#### Multifood allergy

Confirm that the formula of the proposed product will supply the protein, vitamin and mineral requirements for a child younger than two years of age, noting that such a child might have a limited range and amount of food, and so greater volumes of formula might be necessary than for a child on a normal diet.

#### Monosaccharide intolerance

Confirm that the formula of the proposed product will supply the initial protein, energy, fatty acid, vitamin and mineral requirements for the patient, noting that such a child, at least initially, may need to obtain 100% of the RDI of the identified nutrients, which may be elevated to permit catch-up growth, via the product. These needs will change as recovery occurs.

#### Weaning from total parenteral nutrition (TPN) to formula

Confirm that the formula of the proposed product will supply incremental increases in protein, energy, fatty acid, vitamin and mineral requirements until full 100% RDI nutrient intake is achieved enterically. Formula can be gradually reduced as foods are introduced.

#### Patients requiring ketogenic diets

Confirm that the formula of the proposed product will supply the patient’s protein, vitamin and mineral requirements. For this to occur, the formula should be multi-ingredient and individually calculated, and a fat source will need to be added (such as Calogen or Liquigen oil emulsions), together with a small prescribed amount of carbohydrates. Patients who can eat foods would need less or no formula after about four years of age.

#### Infant formula products, such as a formula used in infants younger than 12 months

Present a table comparing the proposed product with the requirements of the Australia New Zealand Food Standards Code – [Standard 2.9.1: Infant Formula Products](http://www.comlaw.gov.au/Series/F2008B00658), using the terminology of the code. Confirm that the proposed product complies with this code or justify any deviations from particular parts of the code.

### Regulatory compliance (Subsection 1.3)

The Australia New Zealand Food Standards Code – [Standard 2.9.5: Food for Special Medical Purposes](http://www.comlaw.gov.au/Series/F2012L01347) sets out the requirements under these standards for foods that have medical purposes. Subsection 1.3 of the submission should confirm that these requirements have been met.

### Product and use (Subsection 1.4)

#### List of ingredients

For nutritional products, information should be provided about all the ingredients. In the case of products that will be used to overcome allergies or food intolerances, this should include information on the origin of the ingredients.

#### Maximum quantity and repeats

The requested maximum quantity and repeats for the proposed product should be justified, based on the understanding that these are usually calculated as a one-month supply with five repeats for an infant or child on an appropriate dose to meet the nutritional need for the age range for one of the following:

* total nutrition
* when the proposed product is used in conjunction with solid foods (eg in severe multiprotein food allergy), the amount of product that would be needed to supply total nutrition to children younger than two years of age, and thereafter the expected decreased amount as other foods are introduced into the diet
* when the proposed product is an amino acid supplement used in disorders of protein metabolism, the amount of product that is expected to increase with age and weight and to be in inverse proportion to the amount of regular foods tolerated.

#### Tables of RDIs and nutritional needs of patients

Australian RDIs are listed in [Nutrient Reference Values for Australia and New Zealand](http://www.nhmrc.gov.au/publications/synopses/n35syn.htm).

The nutrient contents should be presented in tables to allow an assessment of whether the proposed product and its main comparator product(s) provide the required amount of key nutrient for patients for whom the proposed product is intended. This assessment should include (as applicable) the following age ranges:

* infants younger than one year
* children 1–2 years
* children 2–5 years
* children 5–10 years
* older children 10–15 years
* adolescents 15–20 years
* adults (older than 20 years).

The age used should be the midpoint of the age range. For the nonadult age ranges, the nutrient calculations should be compared for a child whose weight is on the 50th percentile for weight, using accepted growth charts (eg from the [World Health Organization](http://www.who.int/childgrowth/standards/en/) or the [Centers for Disease Control and Prevention](http://www.cdc.gov/growthcharts/)). For the adult age range, pregnancy and lactation tables should also be included for the product, unless the product is unsuitable for pregnant or lactating women.

#### Comparison of proposed product with nutritional needs of patients

For the comparison of the composition of the proposed product with the nutritional needs of the patients who would be eligible to receive it, the key nutrient will vary according to the product. For example:

* for amino acid–type products, the comparison should be based on amino acid or protein equivalents
* for a protein-free supplement, the comparison should be based on an energy index
* for an infant formula, the comparison should be based on the volume that meets the Australia New Zealand Food Standards Code – [Standard 2.9.1: Infant Formula Products](http://www.comlaw.gov.au/Details/F2011C00547).

Identify where the proposed product is used in conjunction with other foods. Where this is the case, give the percentage of nutrients provided by the proposed product as proportions of a strict dietary regimen.

#### Instructions for use

Provide the instructions for preparation and use of the proposed product, including per cent solution (weight per volume), scoop volumetric size and weight of product it holds, and scoops to water volume for a ‘normal’ dilution.

## P2.2 Clinical evaluation (Section 2)

**INFORMATION REQUEST**

**Present trial or study data for use of the proposed product in patients (Section 2)**

Provide comparative randomised trial or other clinical study data in a format consistent with the information requests in Section 2.

### Trial or study data

As a minimum, provide any available data arising from use of the proposed product in patients. This extends the assessment beyond a comparative review of nutritional content to inform a comparative clinical assessment of effectiveness and safety. Data on use of the proposed product in regular clinical practice may also supplement the trial or study data included in Section 2 of the submission.

Provide comparative randomised trial or other study data in a format consistent with the guidance provided in Section 2.

# Product type 3 – Vaccine products

This section applies to a submission for a vaccine seeking listing under the PBS or seeking funding under the NIP.

These additional requests for information are not exhaustive but are to clarify the needs of the PBAC when applying the general approach of these guidelines to the specific circumstances of vaccines. They are not an alternative set of requests; comply with all information requests in Part A of these guidelines, where applicable.

The order of this section follows the order of the main submission sections of these guidelines.

## P3.1 Details of the proposed vaccine and its comparator (Section 1)

**ADDITIONAL INFORMATION REQUESTS**

**Provide information about the proposed vaccine and disease (Subsection 1.1)**

In Subsection 1.1, provide information about the proposed vaccine and the disease to be prevented.

**Define treatment details (Subsection 1.1)**

Specify the proposed schedule of administration of the vaccine and any consequential programmatic requirements for administration (eg within and/or beyond current NIP arrangements).

**Define the main comparator(s) (Subsection 1.1)**

In Subsection 1.1, define the main comparator in terms of the current approach to preventing the disease that is likely to be most replaced in practice. Where the defined main comparator is an alternative vaccine, identify differences between the vaccines (use a table, if appropriate).

**Provide information about funding, restrictions and catch-up programs (Subsection 1.4)**

In Subsection 1.4, provide information about a preference for PBS listing or NIP funding, restrictions and any catch-up programs, and relationships between the proposed and currently available vaccines.

### Proposed vaccine and disease (Subsection 1.1)

Include the following information about the proposed vaccine:

* number, identification and amounts of antigens (components)
* formulation
* any expectation of a limited initial supply, where relevant.

Present information on other relevant defining characteristics of the vaccine, including:

* whether the immunising agent is live, attenuated or killed; absorbed or non-absorbed; and viral or bacterial
* any cold storage requirements for distribution
* the external dimensions of the vaccine packed for storage.

See product type 1 for details of the additional information requests for submissions containing fixed combination vaccine products. As mentioned in Subsection P1.1, the component products that prevent different diseases should preferably be listed on the PBS or funded under the NIP at the time the submission is lodged.

Describe the relevant characteristics of the disease to be prevented by the vaccine.

### Treatment details (Subsection 1.1)

Specify the proposed schedule of administration of the vaccine, including details of doses, and whether primary immunisation and/or booster vaccinations are requested. Also specify any consequential programmatic requirements for administration (eg within and/or beyond current NIP arrangements). Indicate when such programmatic requirements are expected to extend to include other particular delivery systems (which might vary across states and territories), such as through clinics, community centres and schools.

Where appropriate, discuss whether a vaccination course that begins with the proposed vaccine can be completed with a competing vaccine (or vice versa).

Identify and justify any differences from treatment recommendations in the TGA-approved product information or the [*Australian* *immunisation handbook*](http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home) (or the latest draft version of either document, where these are not finalised). The *Australian immunisation handbook* is published every two or three years by the National Health and Medical Research Council following its preparation by the Australian Technical Advisory Group on Immunisation (ATAGI). Where relevant, chapters in the handbook contain a section describing any conflicts between advice in the handbook and the text of the TGA-approved product information.

Specify any new or additional requirements that are likely to have an impact on the financial implications of listing the proposed vaccine. Specify whether the proposed vaccine is to be available as a substitute for existing products, or added to current arrangements for either the NIP or the PBS.

### Main comparator (Subsection 1.1)

If an alternative vaccine is available on the NIP or PBS, this will usually be the main comparator. If an alternative vaccine is not currently funded, the advice of the department may be sought. If there is currently no vaccine available, the main comparator would usually be standard medical management.

Where the main comparator is an alternative vaccine, present a table if this would assist in comparing the content and characteristics of the vaccines (eg the antigens included in the vaccines, the strength of the vaccines, the scheduling of doses, the routes of administration and the fit with the current vaccine schedule). If the trials presented in Section 2 use other vaccines, consider including these other vaccines in the comparative table, if one is presented.

### Funding, requested restrictions and catch-up programs (Subsection 1.4)

#### PBS listing/NIP funding

Indicate whether the submission is for listing on the PBS or funding under the NIP, with a rationale.

Several factors affect whether vaccines will be listed on the PBS or funded under the NIP. A vaccine should generally be proposed for funding under the NIP where there is expected to be an additional health benefit to the community beyond the individuals vaccinated, which would be improved by maximising coverage rates of the proposed vaccine in the identified individuals. More specific considerations favouring a submission for NIP funding include the following:

* The target for the proposed vaccine is a broader population in which there is either no need to assess risk factors for the disease in each individual, or the assessment of risk factors at an individual level is straightforward (eg age, sex, ethnicity, geography).
* There is a reason to maximise population coverage of the proposed vaccine because the proposed vaccine reduces one or more of
  + the proportion of susceptible individuals
  + carriage of the pathogen(s) affected by the vaccine
  + transmission of the infection (including nosocomial infections, or infections in other institutional settings, such as childcare centres, schools or nursing homes).

Integral to these specific considerations are the following:

* The proposed vaccine protects against a new infection or reactivation of an existing infection.
* The efficacy of the proposed vaccine is sufficient to reduce the proportion of susceptible individuals, carriage of the pathogen affected by the vaccine, or transmission of the infection.
* The disease is sufficiently severe or prevalent in an unimmunised population to justify maximising the use of the proposed vaccine to achieve its full community health benefit.
* The proposed vaccine needs to be delivered as only a single dose or a few doses.

An additional factor that might be considered in supporting a request for funding under the NIP is the existence of claimed advantages of increasing herd immunity, particularly where these advantages are supported by clinical evidence (see additional requests in Subsection P3.3 for the presentation of such advantages and evidence).

PBS listing might be favoured when the proposed vaccine is ‘discretionary’ for the majority of the population (eg to vaccinate an individual against a disease that is not sufficiently prevalent in Australia to justify maximising the use of the proposed vaccine), or the assessment of risk factors is less straightforward (eg an assessment of immune system status is required).

A vaccine may be simultaneously listed on the PBS and funded under the NIP for different indications.

#### Restrictions

Explain and justify any restrictions on subsidised use of the proposed vaccine to certain populations, seasons, geographical distributions and ethnic groups.

Given that the target for the proposed vaccine is a broad population, a restriction under the NIP should involve a straightforward assessment of risk factors at an individual level (eg age, sex, ethnicity, geography). The usual aim is to vaccinate all eligible individuals once they reach the age range specified for the eligible population, which results in an ongoing primary program. Where a more complex assessment of risk factors for the disease in each individual is required, a restriction under the PBS would be more appropriate.

Describe any requested PBS restriction or NIP scheduling in relation to the TGA-approved indication and the *Australian immunisation handbook* (or the latest draft version of either document, where these are not finalised), with an explanation and justification for any discrepancies.

#### Catch-up program

If a catch-up program is also requested, define and justify its duration from commencement of the overall funding arrangement, and its extent in terms of extra targeted population groups.

A catch-up program provides coverage of individuals who could benefit from vaccination at the introduction of a new program, but who are older than the age range specified for efficient delivery of the ongoing primary vaccination program. A catch-up program might also provide a faster onset of any herd immunity generated by the vaccine (see Subsection P3.4, below). A catch-up program may be considered appropriate by ATAGI.

Describe the arrangements for any requested catch-up program(s) and compare them with those of the requested ongoing primary vaccination program. Justify the selection of the requested age range(s) of eligible individuals within these programs (and any other characteristics of the eligible individuals) and the requested duration(s) of the programs (and any other features of the programs). See also Subsection P3.4, below.

#### Relationship with other listed vaccines

Explain the relationship between the proposed vaccine and vaccines currently available on the NIP (or the PBS, as relevant) in terms of both their antigen content and their dosage schedules. A new vaccine program funded under the NIP should integrate with current programs as much as possible, to maximise coverage and efficient delivery of the overall vaccination schedule.

See also additional requests in relation to Subsection 1.4.

## P3.2 Clinical evaluation (Section 2)

**ADDITIONAL INFORMATION REQUESTS**

**Assess noninferiority between a vaccine combination product and its components (Section 2)**

For a proposed combination vaccine, assess whether there is any clinically important loss of beneficial effectiveness when antigens are combined, compared with when they are given individually.

**Assess comparative harms (Subsections 2.5 and 2.7)**

Because vaccines are generally given to a ‘well’ population, describe potential harms adequately. In Subsection 2.5, explain how adverse events were ascertained in the trials. In Subsection 2.7, provide any information on adverse reactions that might have arisen following launch of the proposed vaccine in other markets.

**Apply the clinical evaluation to different populations** **(Subsection 2.7)**

As appropriate, apply the clinical evaluation to any different population identified in the request for listing, including for a catch-up program.

### Noninferiority assessment (Section 2)

As discussed in Subsection P1.1, the components of a vaccine combination product should have an additive (not necessarily synergistic) beneficial effectiveness. For a vaccine that combines antigens, this means that there should be no loss of beneficial effectiveness of each of the components. For example, if there is any reduction in titres for any components of a fixed combination vaccine product compared with its individual component products, the noninferiority assessment would be whether this would be expected to reduce the overall vaccine effectiveness to a clinically important extent. Appropriate evidence comparing the proposed combination vaccine product with each of its individual components would usually be required as part of Section 2. Further guidance on assessing noninferiority is given in Appendix 4 (Assessment of noninferiority).

### Comparative harms and adverse reactions (Subsections 2.5 and 2.7)

The assessment of comparative harms should extend beyond those temporally associated with the administration of the vaccine to those that might emerge some time after the vaccine course is completed. This might include the consequences of possibly delaying rather than preventing the disease, in addition to adverse reactions to the vaccine.

### Applicability of clinical evaluation to different populations (Subsection 2.7)

This may be necessary if the trials recruited participants who were older or younger than the requested target populations. For example, justify any claims that the extent of vaccine effectiveness is similar for individuals in the primary and catch-up populations.

## P3.3 Economic evaluation (Section 3)

**ADDITIONAL INFORMATION REQUESTS**

**Submit a cost-utility (preferred) or other cost-effectiveness analysis, where appropriate (Section 3)**

In the context of a conclusion of therapeutic superiority, provide a cost-utility or other cost-effectiveness analysis. Provide a cost-benefit analysis as a supplementary analysis only.

**Estimate the epidemiology in the Australian population (Subsection 3.1)**

Present, and assess the appropriateness of, available evidence to estimate the epidemiology of the disease in the Australian population and any subgroup as identified by the restrictions requested in response to Subsection 1.4.

**Describe and justify the model structure (Subsection 3.2)**

Provide details about the type of model used, including whether a static or a dynamic model is used to estimate the epidemiological impact of the program involving the proposed vaccine, and whether a joint analysis has been considered (and included, where appropriate).

Justify the duration of the model, and explain and justify the approach taken in the mathematical modelling of consequences, such as any waning or limited duration of vaccine effectiveness or herd immunity implications.

**Transform immunogenicity outcomes** **(Subsection 3.4)**

Establish and describe the basis to transform immunogenicity outcomes reported in the clinical evaluation to patient-relevant outcomes, where such outcomes are the primary outcomes of the trials or are otherwise important to the submission.

**Describe any regulatory standards for immunogenicity outcomes** **(Subsection 3.5)**

Provide any regulatory standards for immunogenicity outcomes that would inform the transformation of these surrogate outcomes.

**Include additional program costs (Subsection 3.6)**

Include additional program costs where these are expected to change with the introduction of the proposed vaccine.

**Present a sensitivity analysis (Subsection 3.8)**

Because of the likely number of uncertain parameters, present multivariate sensitivity analyses in addition to univariate sensitivity analyses. Where catch-up programs are requested, present additional sensitivity analyses to examine the consequences of the request, including for different definitions of the catch-up programs.

**Present a systematic review to support variables (Subsection 3.10)**

Present a systematic basis to support the evidence or assumptions used for all variables that are expected to affect overall vaccine effectiveness.

### Type of economic analysis (Section 3)

Consistent with Section 3 and Appendix 6 (Preference for utility valuation over monetary valuation of health outcomes), a cost-utility or other cost-effectiveness analysis is preferred to a cost-benefit analysis for the economic evaluation in the context of a conclusion of therapeutic superiority. A cost-benefit analysis might be useful as a supplement to a cost-utility analysis to estimate the value of the consequences of the proposed vaccine that might not be captured by other means (eg changes to injection frequency or adverse reactions).

Refer to Appendix 8 (Including nonhealth outcomes in a supplementary analysis) if productivity changes (nonhealth outcomes) are claimed in a supplementary analysis.

A cost-minimisation approach is relevant for the economic evaluation in the context of a conclusion of therapeutic noninferiority.

### Epidemiology in the Australian population (Subsection 3.1)

The base case of the modelled evaluation should be for the primary population. When assessing the appropriateness of available evidence for estimating the prevalence of the disease in Australia, possible sources of epidemiological evidence include routine surveillance data, seroprevalence studies and surveys.

### Model structure (Subsection 3.2)

#### Type of model

The type of model used (static or dynamic) should be stated. Static models are those in which the force of infection (probability per unit of time that a susceptible person acquires infection) is constant over time. These are usually structured as decision analysis models or Markov models. Static models ignore herd immunity effects (see below).

Dynamic models are those in which the force of infection depends on the number of infectious individuals in the population at each time point, and this number would be expected to decline following immunisation. Dynamic models allow herd immunity and age shift to be assessed, and should be considered when the force of infection is likely to change following immunisation (ie if the proposed vaccine blocks transmission of infection, and coverage is extensive), and when the risk or severity of the disease depends on age.

In situations where a small proportion of the population is to be immunised, either through low coverage or targeted immunisation, or the proposed vaccine does not prevent circulation of the pathogen, herd immunity effects would be expected to be negligible, and so a static model would be more appropriate.

#### Joint analysis

In an analysis of all affected vaccinations, a joint analysis refers to whether the cost of delivery or the coverage rate across multiple vaccinations is likely to be affected by a new proposed strategy. For example, this might apply when the proposed vaccine contains multiple components and could change the number of injections at one or more steps in the vaccination schedule.

#### Duration of model

The duration of a model should be justified because the cost-effectiveness ratio for vaccination programs generally reaches a plateau after a length of time, and the time span of a model should not be limited to a time before a plateau is reached. Presenting model traces over time of key variables, such as the incremental cost-effectiveness ratio, would assist in assessing the impact of varying the time horizon of the model, and also assessing the consequences of any waning or limited duration of vaccine effectiveness or herd immunity implications.

#### Modelling of consequences

Two sources of uncertainty that usually have an important impact on the results of an economic evaluation of a vaccine in a new disease area are the extent of duration of effectiveness before any waning of effect, and the extent of any herd immunity.

### Transformation of immunogenicity outcomes (Subsection 3.4)

For the proposed vaccine, transforming an immunogenicity outcome from a vaccine trial usually requires two separate analyses that:

* show that a threshold level of antibody response predicts a particular extent of protection and thus a subsequent magnitude of reduction in cases of the disease presenting in each of one or more manifestations
* assess whether there is any limit to the duration of this predicted effect or waning of the effect over time.

### Regulatory standards for outcomes (Subsection 3.5)

Although any relevant regulatory standards for immunogenicity outcomes should be provided, they might not always satisfy the requirements needed to map the direction and magnitude of a change in the surrogate immunogenicity outcome to the duration, magnitude and severity of one or more changes in subsequent clinical outcomes, for inclusion in an economic evaluation.

### Additional program costs (Subsection 3.6)

The description of the additional program costs that may change should include the costs of additional Australian Childhood Immunisation Register payments if additional encounters are required to give the proposed vaccine. There might also be changes to the delivery of the proposed vaccine through clinics, community centres and schools. If initiation of one or more specific enhancements of a surveillance program is requested, or advised by ATAGI, as being an essential component of funding the proposed vaccine under the NIP, also include the costs of the resources for such a program. The advice of the department, particularly the Immunisation Policy Section, should be sought.

### Sensitivity analyses (Subsection 3.8)

As models of vaccines might be sensitive to the discount rate used for calculating the net present value of health outcomes, sensitivity analyses varying this rate should be presented, together with any arguments seeking to justify a rate other than those specified in the guidelines.

Where catch-up programs are requested, present sensitivity analyses in Subsection 3.9 to examine the sensitivity of the model’s base case to the marginal costs and benefits of different options of adding a catch-up program, and then:

* extending the catch-up population
* lengthening the duration of the catch-up program.

### Support for variables (Subsection 3.10)

The systematic basis to support variables should include any waning or limited duration of vaccine effectiveness (such as surveillance studies on the need for booster doses) and/or herd immunity implications (such as observational studies). The quality of these nonrandomised studies for extrapolation purposes should be presented and assessed separately.

## P3.4 Budgetary implications (Section 4)

**ADDITIONAL INFORMATION REQUESTS**

**Estimate financial implications**

Estimate costs using the basis for pricing that applies to the NIP or PBS, as relevant to the application.

**Estimate extent of use and costs for primary vaccination program (Subsection 4.2)**

Where the proposed vaccine is to replace an existing product, present estimates of extent of use based on data from current estimates of vaccinated cohorts.

Where the proposed vaccine is indicated for a new disease, present estimates of extent of use based on standard population estimates, with modification as necessary if restricted to specific target populations.

**Estimate extent of use and costs for any catch-up cohorts (Subsection 4.2)**

Where a program for a catch-up cohort is requested, explain and justify the approach used to estimate the extent of use and cost of the proposed vaccine in the program.

**Estimate administration costs (Subsection 4.4)**

Include costs of administration through the NIP or PBS, as appropriate, including delivery through general practice.

### Financial implications for the NIP

Where NIP funding is sought, the costs presented in Section 4 of the submission should estimate costs using the price to the Australian Government that applies to vaccines funded under the NIP. Where PBS listing is sought, these costs should use the dispensed price for maximum quantity, with appropriate patient co-payments removed, that applies to vaccines listed on the PBS.

### Extent of use and costs for primary vaccination program (Subsection 4.2)

Estimates of use as a result of NIP funding should also include allowance for estimates of wastage and usage beyond the target population. The advice of the department, particularly the Immunisation Policy Section, should be sought. Where an epidemiological approach is needed to modify the estimates of extent of use based on standard population estimates to estimate use in a specific target population, see also additional requests above for information in response to Subsection 3.1 for possible sources of epidemiological evidence.

### Extent of use and costs for any catch-up cohorts (Subsection 3.2)

Consistent with the additional requests for information (above) in response to Subsection 3.2, present these estimates for a catch-up cohort as a series of marginal analyses examining the impacts of various options for the size and duration of the catch‑up program.

### Administration costs (Subsection 4.4)

In addition to the costs of administration, cost consequences to government budgets beyond the health sector (such as clinics, community centres and schools) could also be identified and estimated for separate presentation in response to this section. These cost consequences might vary across states and territories.

# Product type 4 – Codependent technologies

Note: this section on codependent technologies will be provided as part of a staggered public consultation process. It is anticipated to be available for public consultation in mid-March. Stakeholders will be notified of its release.

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