
Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee

Version 5.0

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(Version 5.0)

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Foreword

This revision of the *Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee* is the first full revision of the guidelines since 2006, and has involved substantial changes in many areas of the document. These changes have built on experience gained since 2006. This version 5.0 is shorter, while also addressing emerging new technical issues. The revision process was driven by an external consultancy incorporating Australian and international experts reporting to a Guidelines Revision Steering Committee. It has benefited from extensive discussions among members of the Pharmaceutical Benefits Advisory Committee and its subcommittees, as well as a wide range of contributors from industry, government, academia and the community.

This revision acknowledges the increasing international trend towards reliance on information about the costs and effectiveness of medicines by large third-party payers, including governments managing medicine subsidy programs. It reflects changes in the medicine development process internationally. Awareness of these trends has influenced the development of this revision.

These guidelines are carefully structured. They cover a wide range of requests for information. Not all requests will be relevant to all submissions. However, by responding to the requests where appropriate, the key matters for the specific circumstances of each submission will be presented transparently so that they can be understood clearly.

These guidelines reflect best practice as far as possible. The requests for information are designed to promote comparability across submissions and to improve confidence in decision making where possible. However, while they represent the currently preferred approach, reflecting the experience of nearly 2000 decisions, they are not prescriptive and there is flexibility in their interpretation. Given that it is rare for there to be an ideal evidence base for a submission, the guidelines take a pragmatic approach to preparing submissions. This means that PBAC decision making requires judgment, and preparing submissions cannot be likened to simply following a formula to guarantee success.

The guidelines changes are intended to help clarify the information that will best support PBAC decision making, taking into account developments in health technology assessment and PBAC experience of submissions. There is no substantive change in the key factors influencing decision making by the PBAC.

These guidelines will remain subject to regular review. They explicitly provide for the introduction of new methods. As these new methods become established and accepted, they will influence future updates.

I commend this revision to you. It distils the influence of many methodological disciplines, many contributions in a wide consultation process and, perhaps most importantly, many difficult decisions relating to many important submissions.

Andrew Wilson
Chair
Pharmaceutical Benefits Advisory Committee

Record of updates

| Date | Version | Summary of changes |
|----------------|---------|---|
| August 1990 | 1.0 | Draft guidelines issued for comment |
| August 1992 | 2.0 | Minor rearrangement, extension and clarification |
| November 1995 | 3.0 | Clarification of technical aspects of measuring changes in costs and outcomes |
| November 2002 | 3.1 | Update to include minor changes endorsed since November 1995 |
| November 2006 | 4.0 | Major revision and reorganisation of text |
| December 2006 | 4.1 | Version for co-publishing in HTML format, with excerpts in RTF format, plus minor editorial corrections |
| December 2007 | 4.2 | Version to provide clarification in Subsections A.1, A.5, B.7, C, D.5, F.3, PT1 based on initial feedback on the major revision and to update URLs |
| December 2008 | 4.3 | Version to enable primary publication in pbs.gov.au website, update URLs and correct a small number of typographical errors |
| July 2013 | 4.4 | Version to make minor corrections and updates, and enable improved information design and navigation, including development of a designated website and online |
| July 2015 | 4.5 | Version to make minor updates to the requirements for lodging submissions, including the requirement for submissions to be lodged electronically on USB storage devices |
| September 2016 | 5.0 | Major revision and reorganisation of text |

Contents

| | |
|--|-------------|
| Foreword | iii |
| Record of updates | iv |
| Contents | v |
| Abbreviations and acronyms | viii |
| | |
| About the guidelines | 1 |
| Who uses the guidelines? | 1 |
| Structure of a submission to the PBAC | 1 |
| Structure of the PBAC Guidelines | 2 |
| Key factors influencing decision making by the PBAC..... | 4 |
| Key points for preparing a PBAC submission | 5 |
| Associated documents | 5 |
| Contact details | 6 |
| Document table | 7 |
| | |
| Part A – Guidelines for preparing the main body of a submission | 8 |
| Submission executive summary | 9 |
| Section 1 Context | 10 |
| Introduction | 10 |
| 1.1 Clinical issue addressed by the submission | 12 |
| 1.2 Clinical management..... | 15 |
| 1.3 Regulatory process..... | 17 |
| 1.4 Proposed PBS listing..... | 18 |
| Section 2 Clinical evaluation | 23 |
| Introduction | 23 |
| 2.1 Literature search methods..... | 25 |
| 2.2 Identify relevant trials | 27 |
| 2.3 Trial design and execution | 29 |
| 2.4 Trial characteristics | 33 |
| 2.5 Trial results: whole trial population | 40 |
| 2.6 Trial results: additional analyses | 45 |
| 2.7 Assessment of differences between the trial setting and the Australian setting after listing | 55 |
| 2.8 Interpretation of the clinical evidence | 58 |
| Section 3 Economic evaluation | 60 |
| Introduction | 60 |

| | |
|--|------------|
| Section 3A Cost-effectiveness analysis | 61 |
| 3A.1 Overview and rationale of the economic evaluation | 63 |
| 3A.2 Computational methods and structure of the economic evaluation | 67 |
| 3A.3 Population and setting | 71 |
| 3A.4 Model transition probabilities or variables, transformation and extrapolation | 73 |
| 3A.5 Health outcomes | 76 |
| 3A.6 Health care resource use and costs..... | 81 |
| 3A.7 Model validation | 85 |
| 3A.8 Results of the base-case economic evaluation..... | 86 |
| 3A.9 Uncertainty analysis: model inputs and assumptions | 91 |
| Section 3B Cost minimisation | 95 |
| 3B.1 Overview and rationale for the cost-minimisation approach..... | 97 |
| 3B.2 Estimation of equi-effective doses | 97 |
| 3B.3 Additional costs and/or cost offsets..... | 99 |
| 3B.4 Results..... | 100 |
| Section 4 Use of the medicine in practice | 101 |
| Introduction | 101 |
| 4.1 Justification of the selection of data sources | 105 |
| 4.2 Estimation of use and financial impact of the proposed medicine | 107 |
| 4.3 Estimation of changes in use and financial impact of other medicines..... | 111 |
| 4.4 Estimated financial impact for the PBS/RPBS or the NIP | 113 |
| 4.5 Estimated financial implications for the health budget | 114 |
| 4.6 Identification, estimation and reduction of uncertainty | 116 |
| 4.7 Quality use of medicines..... | 119 |
| Section 5 Options to present additional relevant information | 121 |
| Introduction | 121 |
| 5.1 Issues influencing decision making | 122 |
| 5.2 Supplementary analyses | 122 |
| 5.3 Prudent-use principles for antimicrobial agents | 123 |
| 5.4 Basis for any claim for the ‘rule of rescue’ | 123 |
| Part B – Information requests for specific product types | 124 |
| Product type 1 – Fixed-dose combination products | 125 |
| P1.1 Listing fixed-dose combination products | 125 |
| Product type 2 – Nutritional products | 131 |
| P2.1 Details of proposed product and its comparators (Section 1)..... | 131 |
| P2.2 Clinical evaluation (Section 2) | 135 |
| Product type 3 – Vaccine products | 136 |

| | | |
|--|--|------------|
| P3.1 | Details of the proposed vaccine and its comparator (Section 1) | 136 |
| P3.2 | Clinical evaluation (Section 2) | 139 |
| P3.3 | Economic evaluation (Section 3) | 140 |
| P3.4 | Budgetary implications (Section 4) | 143 |
| Product type 4 – Codependent technologies | | 144 |
| | Introduction | 144 |
| P4.1 | Overview of information requested in codependent submissions | 147 |
| P4.2 | Specific codependent technology information requests | 153 |
| | Section 1 – Context | 153 |
| | Section 2 – Clinical evaluation | 161 |
| | Section 3 – Economic evaluation | 171 |
| | Section 4 – Use of the medicine in practice | 178 |
| Appendixes | | 180 |
| Appendix 1 Expert opinion | | 181 |
| | Uses of expert opinion | 181 |
| | Presenting expert opinion | 181 |
| | Describing the collection and collation of expert opinion | 181 |
| Appendix 2 Literature search methods | | 184 |
| | Search criteria and terms | 184 |
| Appendix 3 Identify relevant trials | | 186 |
| | Search results | 186 |
| | Master list of relevant trials | 188 |
| | Selecting trials for an indirect comparison | 189 |
| Appendix 4 Heterogeneity of treatment effect across studies | | 192 |
| Appendix 5 Translating comparative treatment effects of proposed surrogate measures to target clinical outcomes | | 194 |
| | Introduction | 194 |
| A5.1 | Definition, selection and measurement | 195 |
| A5.2 | Biological reasoning and epidemiological evidence | 196 |
| A5.3 | Randomised trial data for all medicines | 197 |
| A5.4 | Applying the relationship between comparative treatment effects to the proposed medicine | 201 |
| Appendix 6 Including nonhealth outcomes in a supplementary analysis | | 203 |
| | Presenting nonhealth outcomes | 203 |
| | Production changes | 203 |
| References | | 205 |

Abbreviations and acronyms

| Term | Definition |
|-------------|--|
| CEA | cost-effectiveness analysis |
| CI | confidence interval |
| CUA | cost-utility analysis |
| DHS | Australian Government Department of Human Services |
| DPMA | dispensed price for maximum amount |
| DPMQ | dispensed price for maximum quantity |
| ICER | incremental cost-effectiveness ratio |
| MAUI | multi-attribute utility instrument |
| MBS | Medicare Benefits Schedule |
| MCID | minimal clinically important difference |
| MSAC | Medical Services Advisory Committee |
| NIP | National Immunisation Program |
| PBAC | Pharmaceutical Benefits Advisory Committee |
| PBS | Pharmaceutical Benefits Scheme |
| PEB | Pharmaceutical Evaluation Branch |
| PSA | probabilistic sensitivity analysis |
| PSM | proposed surrogate measure |
| QALY | quality-adjusted life year |
| QUM | quality use of medicines |
| RPBS | Repatriation Pharmaceutical Benefits Scheme |
| TCO | target clinical outcome |
| TGA | Therapeutic Goods Administration |

About the guidelines

These *Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee* (PBAC Guidelines), version 5.0, assist applicants to prepare a submission to the PBAC for the public funding of a new medicine or medicinal product as part of the Pharmaceutical Benefits Scheme (PBS).

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 for 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. However, although the guidelines present the currently preferred approach to the preparation of submissions to the PBAC, the approach is not prescriptive. Alternative approaches are permitted when adequately justified and supported by data.

These guidelines are available as an online resource at the [PBAC Guidelines website](#).^a The site also includes additional information about the:

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

A submission template, Excel workbook, and other forms and checklists to help prepare a submission are all provided on the 'Downloads' section of this 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.

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(ies) likely to be most replaced by prescribers in practice (the 'main comparator').

^a <https://pbac.pbs.gov.au>

- 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, or, 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 – 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 – Options to present additional relevant information (optional). Includes any 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.

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 is appropriate for a submission (Sections 1–5; see above).

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 submissions concerning the following product types:

- Product type 1 – fixed-dose combination products
- Product type 2 – nutritional products
- Product type 3 – vaccine products
- Product type 4 – 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.
- Cross-references to other sections and subsections within the same part are given as ‘see Section 3’ or ‘Subsection 3A.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.
- 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.
- Appendixes are labelled Appendix 1, Appendix 2 etc, with subsections as A1.1, A1.2 etc (but only as required for cross-referencing) and appendix tables are labelled consecutively within each appendix – for example, Table A2.1 in Appendix 2.

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 are highlighted as a checklist of information requests in boxes. Further explanation for each request and any subsidiary requests are provided under the numbered subheadings following these boxes. These text headings therefore provide a template for the submission. Following these requests and heading template will improve the comparability of submissions considered by the PBAC and, hence, the consistency of decision making.

Resubmissions to the PBAC should address the concerns raised by the PBAC in response to the previous submission, as well as the information requests that are relevant to the inclusion of new information or revised analyses. Information presented in the submission that is not in dispute does not need to be repeated; however, the resubmission should stand alone and contain all the relevant supporting documentation required for PBAC to reach a decision. The aim of a resubmission should be to highlight and integrate new information into the body of the resubmission, and to discuss how new information addresses the main matters of concern to the PBAC.

Notes: If the submission is requesting listings for multiple patient indications, present separate Sections 1–4 in separate submissions or seek advice from the Pharmaceutical Evaluation Branch – see ‘Contact details’ below.

Key factors influencing decision making by the PBAC

The PBAC is established under the *National Health Act 1953*. Its primary role is to recommend to the Minister for Health which medicines should be subsidised under the PBS. The PBAC is required, under the Act, to consider the effectiveness and cost of the proposed medicine compared with existing therapies. The functions of the PBAC are outlined in s101 of the Act.

In particular, the PBAC is required to consider the effectiveness and cost of the proposed medicine compared with alternative therapies. It cannot make a positive recommendation for a medicine that is substantially more costly than an alternative medicine unless it is satisfied that the proposed medicine also provides a significant improvement in health.

PBAC decision making is influenced by five quantitative factors:

- Comparative health gain. Assessed in terms of both the 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).
- 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 health care resources (discussed in Section 3).
- 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 or the National Immunisation Program (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 (discussed in Subsection 4.5).

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

- Overall confidence in the evidence and assumptions relied on in the submission.
- Equity. Implicit equity and ethical assumptions, such as age, or socioeconomic and geographical status, may vary for different submissions and need to be re-evaluated case by case.
- Presence of effective therapeutic alternatives. This helps to determine the clinical need for the proposed medicine.
- Severity of the medical condition treated. Relates to any restrictions requested in Subsection 1.4. The emphasis is on the nature and extent of disease as it is currently managed (see Subsection 1.2).
- Ability to target therapy with the proposed medicine precisely and effectively to patients likely to benefit most. 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.

- Public health issues; for example, development of resistance (for antimicrobial agents; see Subsection 5.3).
- Any other relevant factor that may affect the suitability of the medicine for listing on the PBS.

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.
- The order of information requests in these guidelines forms a template for a submission. Presenting information in any other order will reduce the PBAC's ability to evaluate the submission.
- 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.
- The guidelines may state a preference for certain approaches or information to be presented as supplementary analyses. This preference enables the approach to the base case to be consistent across submissions. Ensure that supplementary analyses are well justified and clearly presented.
- Ensure that information presented in the submission is fit for purpose. When considering a more complex analysis, weigh the additional information requirements and evaluation burden against the additional confidence that such an analysis provides. Where complex methods reduce the confidence in estimates compared with simpler methods, they are unlikely to be preferred.

Attempt to address all of the relevant information requests in the PBAC Guidelines. Where an information request cannot be addressed, provide a clear explanation. The PBAC will find a submission difficult to assess when information requests are not addressed and no justification has been provided for the omission. Submissions should clearly explain when an information request is not relevant or the resulting evidence would not alter the certainty of the key factors influencing decision making by the PBAC.

Associated documents

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

- [Manual of resource items and their associated costs](#)^b for use in submissions to the PBAC involving economic evaluation (Department of Health). This manual is revised periodically in the same way as the PBAC Guidelines.
- [Glossary of terms](#):^c 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).

^b www.pbs.gov.au/info/industry/useful-resources/manual

- [Sources of data for use in generating utilisation estimates](#)^d (Department of Health)
- Information on Section 100 – [Highly Specialised Drugs Program criteria](#)^e
- Standardised utilisation and cost model Excel workbook for PBAC submissions, which is available on the ‘Downloads’ section of the [PBAC Guidelines website](#).^f

Procedures to support submissions are also available on the [PBAC Guidelines website](#).^g

Contact details

Enquiries about PBAC submissions can be mailed or emailed to the Pharmaceutical Evaluation Branch at the following address:

Pharmaceutical Evaluation Branch
MDP 910
Department of Health
GPO Box 9848
Canberra ACT 2601
PBAC@health.gov.au

^c www.pbs.gov.au/info/industry/useful-resources/glossary

^d www.pbs.gov.au/info/industry/useful-resources/sources

^e www.pbs.gov.au/info/browse/section-100/s100-highly-specialised-drugs

^f <https://pbac.pbs.gov.au>

^g <https://pbac.pbs.gov.au>

Document table

Include the following document table at the beginning of each submission. The document table may act as a checklist for sponsors, and will enable the PBAC, subcommittees and evaluators to quickly identify unavailable documents.

| Document requested ^a | 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] |
| If the medicine is NOT TGA registered (see Subsection 1.3): | [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 (eg an Endnote library), including reasons for exclusion of studies that meet the criteria in Subsection 2.2 | [add] |
| Periodic safety update report and development of the safety update report | [add] |
| If an economic model is presented, provide the search strategy and literature yield related to the model structure or variables (eg an Endnote library), 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] |

^a 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 Checklist 1

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; therefore, it is important to lay out clearly the key aspects and issues presented in the submission. The summary also 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 submission.

Checklist 1 Checklist for the executive summary of a 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, from an indirect comparison 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, if applicable | [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 six years | [Yes/No] |

Section 1 Context

Introduction

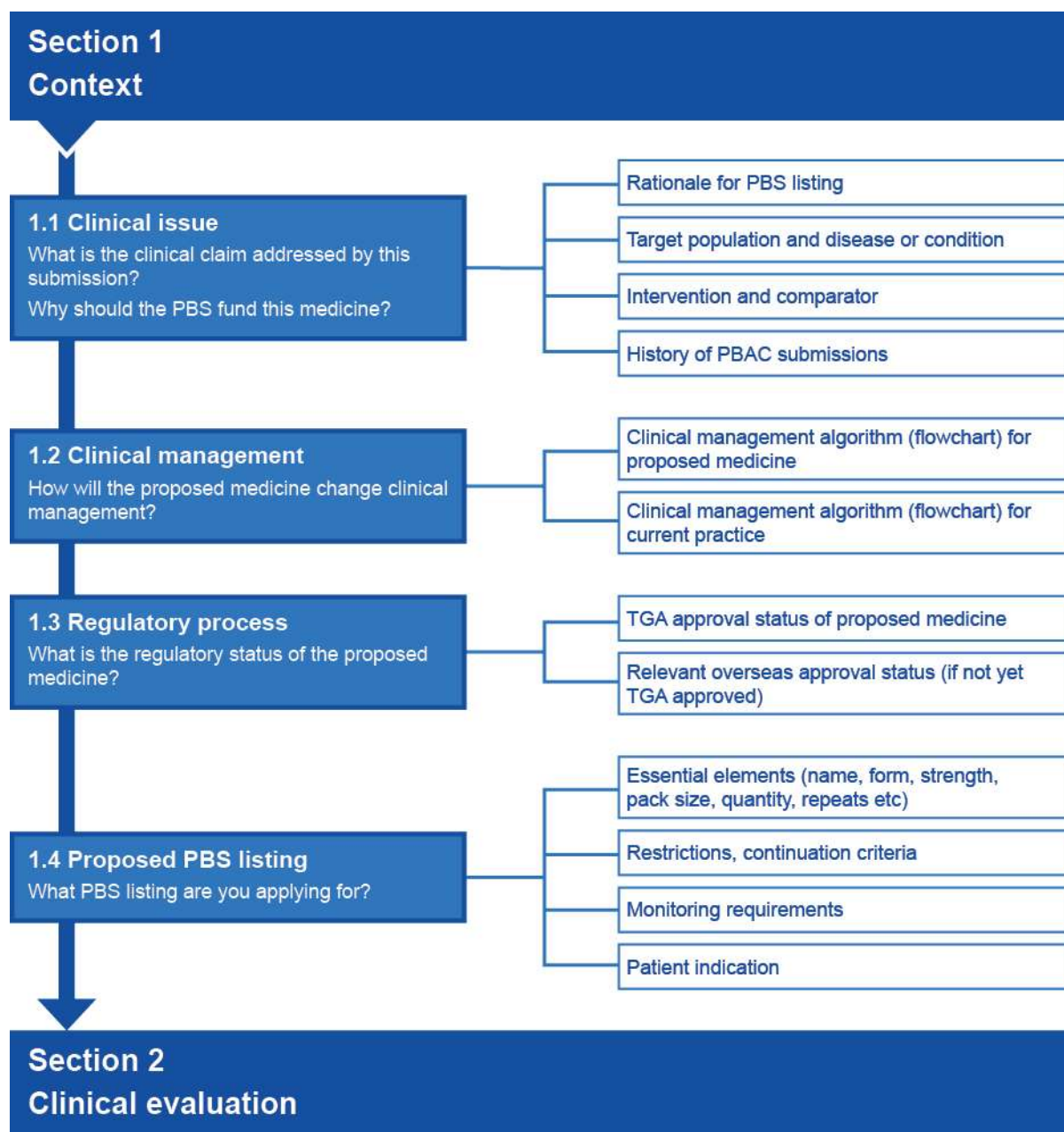
In Section 1, establish the context for the submission by providing the following essential details of the medicine and its proposed use:

- the rationale for listing key components of the clinical claim (Subsection 1.1)
- the way the proposed 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.

Note: The singular term 'comparator' is used to denote one or more comparators. Provide all the requested information for each comparator, if there is more than one main comparator.

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



1.1 Clinical issue addressed by the submission

INFORMATION REQUESTS

- Summarise the rationale for listing the medicine and tabulate the key components of the clinical claim (Subsection 1.1.1)
- Describe the target population and disease or condition in the Australian setting (Subsection 1.1.2)
- Describe the proposed intervention, justify the main comparator and identify key differences between them (Subsection 1.1.3)
- Provide the dates of previous PBAC submissions for the medicine; for resubmissions, describe how the current resubmission addresses the main PBAC concerns (Subsection 1.1.4)

1.1.1 Rationale for listing

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.

Under the *National Health Act 1953*, the primary objective of the PBS is to improve health, so the PBAC primarily focuses on health outcomes. The details of nonhealth-related impacts of the proposed medicine should be presented as supplementary analyses in Section 2 and/or Section 3, or discussed in Section 5 as other relevant factors.

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

Table 1.1.1 Key components of the clinical issue addressed by the submission

| Component | Description |
|----------------|---|
| Population | Briefly state the target disease or condition and population to be treated |
| Intervention | Briefly describe the intervention |
| Comparator | Briefly describe the comparator |
| Outcomes | Briefly state the patient-relevant clinical effectiveness and safety outcomes ^a |
| Clinical claim | State the clinical claim that the submission presents as follows: 'In [population and health issue], [proposed medicine] is no worse than/as effective as/more effective than [main comparator] at improving/reducing [outcome(s)]' |

^a Outcomes should be directly related to the quality and/or length of a patient's life.

1.1.2 Target population and disease or condition

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

If the medicine is proposed for use in a subgroup(s) of the Australian population with the disease or condition, indicate whether the usual course of the disease or condition – or the available treatment options for that subgroup(s) – differs from that of the whole population.

Describe the Australian population who would be treated with the proposed medicine, such as their age, sex, important comorbidities, and disease- or condition-related characteristics. Provide data (preferably include Australian datasets or studies involving Australian participants). Summarise the

incidence and prevalence of the disease or condition in Australia using data from a reputable source, such as those listed in '[Sources of data for use in generating utilisation estimates](#)'^h (see also Section 4).

Where data sources involving Australian participants are not available, discuss whether population characteristics presented here are likely to be representative of the Australian setting. Include percentages and means with estimates of uncertainty (eg interquartile range, standard deviation and ranges) for these data, where possible.

1.1.3 Intervention and comparator

Pharmacological action and therapeutic class of the proposed medicine

Present the therapeutic class, [Anatomical Therapeutic Chemical classification](#)ⁱ and a description of the pharmacological action of the proposed medicine. Provide enough detail to support the proposed target Australian population described in Subsection 1.1.2 and the proposed listing. Tabulate this information to allow an easy comparison of the proposed medicine with the comparator(s).

Selection of the comparator(s)

Select the comparator(s) in the context of the targeted Australian population, the current alternative therapies in Australia, and the therapies most likely to be replaced in clinical practice. A single comparator will be appropriate in most circumstances.

Most comparators will be one of the following:

- A current PBS listed medicine. If the proposed medicine is likely to replace listed PBS medicines, the relevant comparator would be a medicine prescribed on the PBS to treat that target population.
- Standard medical management. If the proposed medicine is for a target population 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 comparator would usually be standard medical management. Standard medical management would need to be clearly defined and could include a non-listed medicine, a surgical procedure, best supportive care or conservative management. In the absence of a PBS-listed medicine, standard medical management may be to use a medicine that is not PBS listed. In this circumstance, this medicine may be the appropriate comparator.

Choosing the medicine most likely to be replaced

Where there is more than one comparator, the main comparator should be the therapy that prescribers would most replace with the proposed medicine. The PBAC bases its judgment about the main comparator on what would be likely to happen, rather than what should happen, in keeping with the above approach to the main comparator.

The following general hierarchy is intended to assist in selecting the appropriate main comparator:

- (a) An existing pharmacological analogue. If the proposed medicine is in a therapeutic class for which pharmacological analogues are already listed, the main comparator would usually be the analogue that is prescribed on the PBS for the largest number of patients in the target

^h www.pbs.gov.au/info/industry/useful-resources/sources

ⁱ www.whocc.no/atc_ddd_index

population. Reference to the TGA-approved indications, to trial evidence, or to any other authority, would not usually constitute reasonable grounds to exclude an unrestricted pharmacological analogue as a main comparator.

- (b) New therapeutic class. If the proposed medicine is in a new therapeutic class but would be used for a target population for which there are other, widely used, listed medicines, the main comparator would usually be the medicine that is prescribed on the PBS for the largest number of patients in the target population.
- (c) Manner of administration. A particular manner of administration of the proposed medicine (for example, injected or instilled as an eye drop rather than taken orally) is also a significant consideration.

Near market comparator

If there is a reasonable expectation that another medicine will enter the Australian market for the targeted Australian population, and that it might be considered at the same or an adjacent PBAC meeting, then it would be prudent to regard this other medicine as an additional contingency comparator to inform a PBAC consideration across the new competing medicines.

Different comparators for different subpopulations or different target populations

It may be appropriate to use different comparators for different subpopulations where the overall target population for the proposed medicine includes one or more sub-populations and:

- the proposed medicine is claimed to be significantly more effective or significantly less toxic than the main alternative comparator therapy in the subpopulation(s) (but not in the remainder of the target population), or,
- where the main comparator therapy used to treat the overall target population cannot be used. That therapy is, therefore, not an alternative therapy for that subpopulation.

In these circumstances, it may be useful also to provide information permitting a comparison with other alternative therapies for the subpopulation(s). The PBAC will usually assess the overall cost and effectiveness of the proposed medicine, considering:

- the evidence justifying the claim for the difference in responses for different populations and therefore for the alternative comparator
- whether the price of the proposed medicine reflects the comparisons for the particular subpopulations
- the size of the subpopulations as a proportion of the overall target population.

Similar considerations are likely to apply where listing of the proposed medicine is sought for more than one target population, and the alternative therapies are different for some of the populations.

1.1.4 History of PBAC submissions for the medicine

Tabulate the dates of previous PBAC considerations (and the listing dates, where applicable) for all indications for which the proposed medicine sought listing in Table 1.1.2.

Table 1.1.2 PBAC submission history

| Indication | PBAC meeting date(s) | Listing date (if applicable) |
|------------|----------------------|------------------------------|
| [add] | [add] | [add] |
| [add] | [add] | [add] |

For resubmissions, present a table with a summary of the issues raised by the PBAC (cross-reference to the PBAC minutes), and show how the current resubmission addresses the issues, with cross-referencing to the relevant sections of the current resubmission.

1.2 Clinical management

INFORMATION REQUESTS

- Present clinical management algorithms for current practice and the use of the proposed medicine (Subsection 1.2.1)
- Compare the two algorithms (Subsection 1.2.2)
- Identify changes to the use of other therapies (Subsection 1.2.3)

1.2.1 Clinical management algorithms

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. Present a second flowchart that depicts 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.

Ensure that the population and the use of the proposed medicine and main comparator(s) in the clinical management algorithm are consistent with those described in Subsection 1.1.

Use the following sources to inform the flowchart(s):

- a literature review of relevant published clinical management guidelines (preferred). The PBAC prefers 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 or condition) and circumstances of use of the medicine
- who is managing clinical care, who will be prescribing the medicine and whether any special training or specialised facilities are required for prescribing or administration; 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.

Use the clinical management algorithm to 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 (eg changes to the use of other medicines). Extend the clinical algorithm to the expected end of the disease or condition process, capturing all the treatment options. If the clinical algorithms for the proposed medicine and the comparator are clearly indicated to be the same after a particular time point in the algorithm, the algorithms may be truncated.

If it is not appropriate to capture all relevant details within the flowchart(s), provide a text description of the details excluded from the clinical management algorithm.

Justify the positioning of the proposed medicine in the clinical management algorithm, and explain why alternative positions for the proposed medicine in the clinical management algorithm are inappropriate.

Variation of a current PBS restriction

If seeking a variation of the current PBS listing of a proposed medicine, restrict the clinical management algorithm to patients whose management will change. Exclude patients from the algorithm who receive the same treatment, regardless of the proposed change to the listing.

Treat a request for a new clinical indication the same way as a request for listing of a new medicine but represent only patients with the new indication in the clinical management algorithm.

For other variations to the PBS restriction, use the proposed clinical management algorithm to reflect the change in practice that would occur if the restriction were to change – for example:

- 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 a last line to an earlier line of therapy).

1.2.2 Comparison of the two algorithms

Summarise the differences between the current and proposed clinical management, as depicted in the algorithm(s).

1.2.3 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 (Subsection 1.3.1)
- List the TGA-approved indications (Subsection 1.3.2)
- Indicate whether overseas regulatory approval has been obtained and, where TGA approval has not yet been granted, provide Food and Drug Administration (FDA) or European Medicines Agency (EMA) registration reports (Subsection 1.3.3)

1.3.1 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 requested in Table 1.3.1 to the Pharmaceutical Evaluation Branch (PEB) 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

1.3.2 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. If the TGA evaluator's report, delegate's overview or Advisory Committee on Prescription Medicines advice affects the proposed indication or product information, clearly state this.

1.3.3 Overseas approval status

Provide information on the overseas registration status of the medicine, including registration conditions or boxed warnings that may apply. Provide the registration reports (or most recent interim reports) from the FDA and/or the EMA, if the proposed medicine is not yet TGA registered.

1.4 Proposed PBS listing

INFORMATION REQUESTS

- List the essential elements of the requested PBS listing with and without proposed special pricing arrangements, and justify the choice of the maximum quantity (Subsection 1.4.1)
- 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 (Subsection 1.4.2)
- Justify any continuation criteria (Subsection 1.4.3)
- Describe any assessment or monitoring requirements (Subsection 1.4.4)
- Identify the proposed patient indication(s) for unrestricted listings (Subsection 1.4.5)

1.4.1 Essential elements of the requested listing

Complete Table 1.4.1 for the requested listing.

If a sponsor is unwilling to publish the effective price in the PBS schedule, they may request that the Australian Government approve a higher price to be published.

If the government approves the inclusion of a 'published' price in the Schedule of Pharmaceutical Benefits, the sponsor will be required to enter into a Deed of Agreement, to define a special pricing arrangement with the government. Special pricing arrangements allow for a rebate to be paid to the government every three months by the sponsor for the difference in government expenditure between the published and the effective price of the medicine. The medicine will be identified as having a special pricing arrangement, but the details of this may be confidential.

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

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, strength(s), form(s)] | [n] | [n] | [n] | [\$] [\$ SPA] | [Brand name, manufacturer] |

\$ SPA = price related to proposed special price arrangement

Where an injectable or infusible chemotherapy medicine is involved, the requested quantities and price should reflect a maximum amount and a dispensed price for maximum amount (DPMA) as in Table 1.4.2.

Table 1.4.2 Essential elements of the requested listing for chemotherapy medicines

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

\$ SPA = price related to proposed special price arrangement

Maximum quantities/amounts and number of repeats

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

- For an acute-use therapy, demonstrate that the requested maximum quantity/amount 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/amount 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.

Justify proposed deviations from this general approach – for example, to minimise wastage or to facilitate intermittent therapy, as described in Subsection 3A.6.1.

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

Interchangeability and brand substitution

Discuss whether the proposed medicine is likely to be interchangeable on an individual patient basis with another medicine listed on the PBS. This is likely to be the case for medicines that belong to a therapeutic class in which already-listed medicines have been regarded as interchangeable. Cross-reference to evidence in the submission that may support or refute a determination of interchangeability.

State whether the proposed medicine may be eligible for brand substitution (also known as ‘a’ flagging). Cross-reference to evidence in the submission that may be relevant for the PBAC when deciding on brand substitution.

Multiple listing scenarios

Where clinical practice or evidence do not clearly inform restriction criteria (eg population characteristics or line of therapy), more than one listing scenario may be presented to the PBAC for consideration. Present alternative listing scenarios and support these with evidence in Sections 2, 3 and 4. For economic evaluations, the preferred approach would be to present a single model that is capable of presenting multiple scenarios rather than separate models with different structures.

1.4.2 Requested restriction(s)

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

- ‘Restricted’ benefits can only be prescribed for specific therapeutic use.
- ‘Authority Required’ and ‘Authority Required (Streamlined)’ benefits seek to limit eligibility for subsidised treatment to specific patient groups in whom treatment is cost-effective. For Authority Required listings, prescribers may need to seek prior approval to prescribe by providing documentation to or telephoning the Australian Government Department of Human Services (Medicare). For ‘Authority Required (Streamlined)’ listings, prior approval is not required and prescribers declare the use is consistent with the restriction criteria by endorsing the prescription with the appropriate ‘streamlined code’.

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

Complete the [restriction template](#)^j from the Australian Government Department of Health. This document provides guidance on how to formulate the restriction wording and justify restriction criteria.

State whether the requested restriction(s) is consistent with the (proposed) TGA-approved indication(s), and the details provided in Subsections 1.1.2 and 1.1.3. Discuss the implications of a requested restriction that are likely to have an effect on the restriction of another PBS-listed medicine (eg its initiation or continuation criteria).

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 PBAC considers the appropriateness of a request for an Authority Required benefit on initial listing against 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.

Other important factors are quality use of the medicine, safety and administrative burden.

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

- The intention of the requested restriction.
- Alternative options that would be acceptable to the sponsor. Consideration of these options help the PBAC to determine the simplest but most effective restriction to administer.
- 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.

^j <https://pbac.pbs.gov.au/information/checklists.html>

- The justification for the requested restriction level, method of applying the restriction and criteria proposed in the restriction.

Word the restriction to identify the use that should eventuate, and be consistent with TGA-approved indications (and other sections of the product information). Restrictions may increase the administrative burden associated with prescribing and the PBAC would prefer that the complexity of the criteria be weighed against the risk and consequences of use outside the target population.

Grandfathering

An Authority Required restriction might need to include grandfathering provisions for eligible individuals who start therapy before the requested PBS listing is implemented. If so, include the following information in the submission:

- Details of the patients (such as estimated numbers, disease or condition 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. Ensure that you also identify and count the estimated number of patients currently receiving the proposed medicine in Section 4.
- An explanation of why patients currently receiving the proposed medicine would not be able to access the proposed medicine under the requested restriction (where patients would be eligible, no grandfathering clause is required).
- Justification of a grandfathering provision that would enable patients currently receiving the proposed medicine to access it through the PBS. This might 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.

1.4.3 Justification for continuation criteria

Continuation criteria should only be applied when use of a medicine may cease to be cost-effective in specified future circumstances. These circumstances include evidence of response to specified tests, progressive disease or a limited number of doses per patient. The PBAC may specify that the prescriber provides documentation to support continuing therapy (referred to as continuation rules). 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^k](#)). Unambiguously justify each element in the continuation criteria on clinical grounds, using objective rather than subjective measures. 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 where recommencement is likely but breaks in therapy are likely to cause rebound, where there is an increased risk of toxicity associated with subsequent recommencement, or where there is reduced likelihood of benefit from subsequent recommencement. Continuation criteria may not be acceptable where the criteria involve subjective

^k <https://pbac.pbs.gov.au/information/checklists.html>

assessments or are likely to result in prescribers seeking to maintain subsidy despite the continuation rules.

1.4.4 Assessment and monitoring requirements

Describe any tests or investigations that are required to determine initial patient eligibility or continuing eligibility for the proposed medicine. Where a required test is not currently listed on the MBS, or the MBS item descriptor needs amending to permit use with the proposed medicine, a material codependency may exist (refer to Part B, Product type 4).

Present required tests or investigations in Subsection 1.2. Where the use of tests or investigations differ from those required by the nominated comparator, include the following information:

- In Section 3, the costs associated with testing, the costs and health outcomes associated with adverse events that arise from testing, and an analysis of the applicability of the tests used in the clinical evidence to the Australian setting.
- In Section 4, the costs of testing and of treating any adverse events that arise from testing.

1.4.5 Patient indication(s)

When requesting an unrestricted listing, state the main patient indication. This should be within the (proposed) TGA-approved indications listed in Subsection 1.3, be consistent with the population and treatment details described in Subsection 1.1, and account for the largest proportion of patients treated in Section 4. The patient indication is defined as what would eventuate following listing in the absence of a Restricted benefit.

If there is no clear 'main' indication, present Sections 1–4 for each indication (preferably in separate submissions; seek advice from the PEB).

Section 2 Clinical evaluation

Introduction

In Section 2, present the best available clinical evidence to support the effectiveness and safety of the proposed medicine and patient indication (see Subsection 1.4).

Section 2 has four components:

- a systematic search of the literature to identify relevant clinical trials or studies (Subsections 2.1–2.2)
- 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 (Subsections 2.3–2.5)
- additional analyses that are used to estimate the comparative treatment effect of the new medicine (or new use of the medicine) when these cannot be derived from the whole trial population of trials presented in Section 2.5 (Subsection 2.6).
- an assessment of the applicability of the presented evidence to the Australian setting (Subsection 2.7).

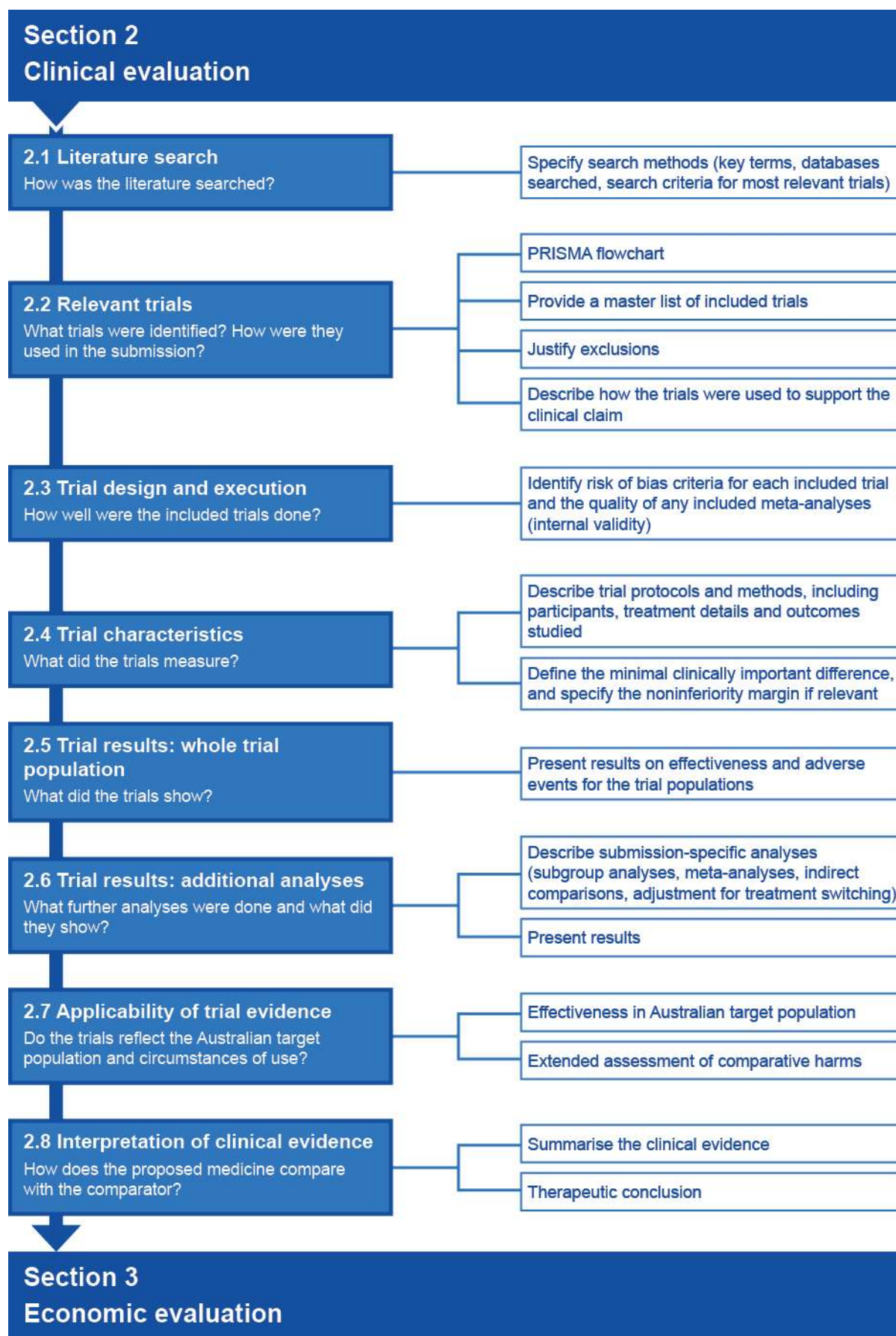
A final subsection (Subsection 2.8) provides a therapeutic conclusion for the effectiveness and safety of the proposed medicine relative to the comparator. This conclusion forms the basis for the economic evaluation in Section 3.

The PBAC strongly prefers clinical and economic evaluations that are based on direct randomised trials. However, direct randomised trials are not always available, and these guidelines provide a framework for considering indirect comparisons of randomised trials and nonrandomised studies.

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



2.1 Literature search methods

INFORMATION REQUESTS

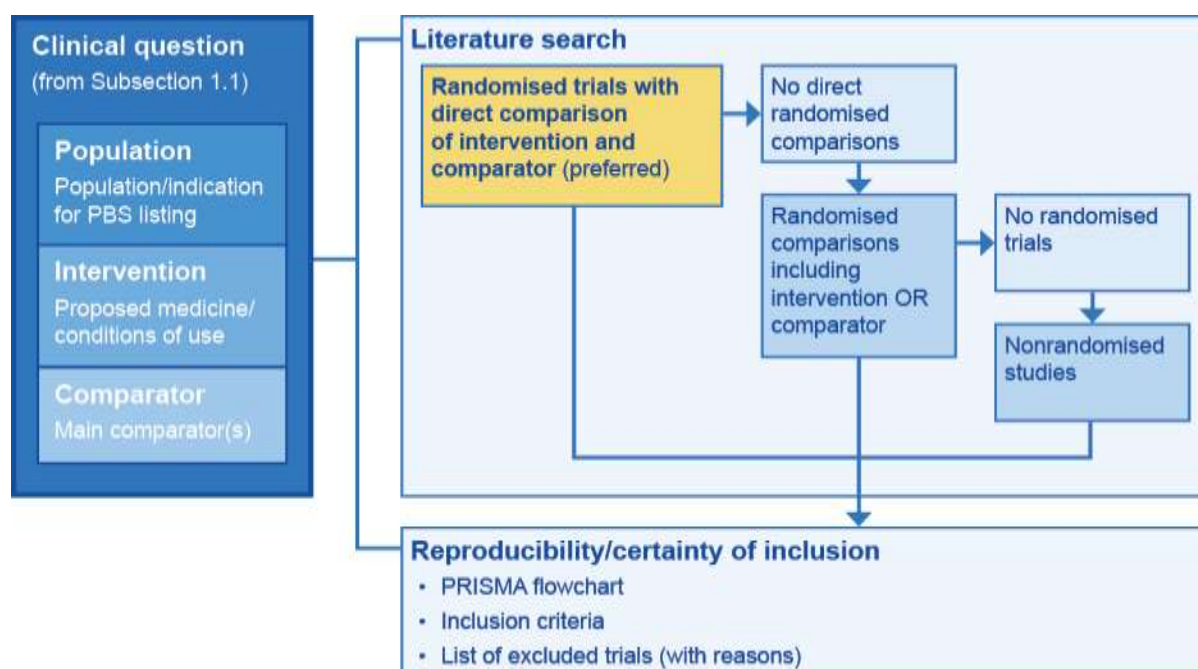
- Define the criteria used to search for the most relevant evidence (Subsection 2.1.1)
- Tabulate the search terms (Subsection 2.1.1)
- Document the search strategy (Subsection 2.1.1)

Subsection 2.1 details the search methods that ensure that all relevant randomised trials (or nonrandomised studies) have been included in the clinical evaluation. The primary objective is to identify all randomised trials that compare the proposed medicine with the main comparator. If no direct randomised comparisons are located, search for randomised trials that would enable an indirect comparison. If no indirect comparison is possible, search for nonrandomised studies.

This approach is based on an assumed hierarchy of evidence from randomised trials compared with nonrandomised studies. However, although 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. If you wish to present a well-conducted nonrandomised study alongside an indirect comparison of randomised trials, justify this approach.

An overview of this approach is shown in Flowchart 2.2.

Flowchart 2.2 Selection of trials for inclusion in the clinical evaluation



2.1.1 Search strategy

Present the search terms for the systematic literature search. Ensure that the search terms are consistent with the search criteria described in Appendix 2 and present them according to Table A2.1.

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.

If direct randomised trials comparing the proposed medicine with the main comparator are not identified, search again separately for randomised trials of either the proposed medicine or the main comparator. Present both search strategies (for the proposed medicine and for the main comparator). Use these trials to generate an indirect comparison.

If neither direct randomised trials nor other randomised trials suitable for an indirect comparison are retrieved, broaden the original search for the proposed medicine 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. Relevant study types include cohort studies, case-control studies and quasi-experimental studies.

In general, nonrandomised studies may 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 or 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).

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 A2.1 in Appendix 2 (provide detail in attachments).

Search the following sources:

- the published literature using the databases listed in Table A2.2 of Appendix 2
- registers of randomised trials
- 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)
- reference lists of all relevant articles that are obtained.

Present the full search strategy for PubMed in an attachment. Summarise the search strategy for other data sources according to Table A2.2 (Appendix 2).

2.2 Identify relevant trials

INFORMATION REQUESTS

- Present search results using a PRISMA flowchart (Subsection 2.2.1)
- Present a list of the trials or studies identified during the search, and indicate those that are included or excluded, and the reason for exclusion (Subsection 2.2.2)
- Create a master list of included trials (Subsection 2.2.3)
- Identify trials used in an indirect comparison (if applicable) and justify the exclusion of any trials (Subsection 2.2.4)
- Describe how the included trials were used to support the clinical claim (Subsection 2.2.5)
- Attach copies of included trials (Subsection 2.2.6)

2.2.1 Search results

Use a PRISMA flowchart (Figure A3.1, Appendix 3) to present the study selection process for each search.^{1,2}

Exclude studies on the following bases:

- A not a randomised trial (not relevant when the search is repeated to find nonrandomised studies)
- B incorrect intervention (such as when the intervention is used in combination with another medicine that is outside the use described in the requested restriction)
- C does not include the PBS population (not enough patients are enrolled who would be eligible for the proposed medicine according to the requested restriction or relevant to the proposed patient indication)
- D not compared with the main comparator (or other relevant 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).

Adapt the selection process as indicated for submissions relying on an indirect comparison of randomised trials or nonrandomised evidence.

2.2.2 Annotated search results

List identified trials (eg in a spreadsheet), and indicate which trials were excluded and the basis for their exclusion (use categories A–D from Subsection 2.2.1).

2.2.3 Master list of relevant trials

Present a master list of all included trials and relevant systematic reviews or meta-analyses that meet the inclusion criteria from Subsection 2.2.1 according to Table A3.1 of Appendix 3.

2.2.4 Further selection of trials for an indirect comparison

Where the submission includes an indirect comparison, justify the exclusion of trials that are unsuitable for use in the indirect comparison. Appendix 3 provides an acceptable approach for selecting appropriate trials to include in an indirect comparison. A general approach is summarised here:

1. Follow the approach outlined in Subsection 2.2.1 to identify all trials involving the proposed medicine (irrespective of comparator arm) and all trials involving the main comparator (irrespective of comparator arm).
2. Draw a network diagram to show all the possible links.
3. Where pairwise comparisons are possible, the submission may seek to exclude linkages requiring multiple steps, or include these as a supplementary analysis.
4. Examine heterogeneity within trial sets and across trial sets, and justify the exclusion of trials with differences in factors that may affect the transitivity of the trials in the indirect comparison.
5. Examine the event rates in the common reference arms and justify the exclusion of trials.
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 all analyses.

2.2.5 Approach taken to support the clinical claim

Describe how the included studies are combined or compared to support the clinical claim.

Example:

The submission is based on a meta-analysis of three 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 subgroups were used to support the clinical claim, justify this in Subsection 2.6.1.

2.2.6 Copies of included trials

Include sufficient details of the relevant trials (key publications, supplementary data, clinical study reports) as attachments to the submission. Indicate the location of the trial reports in the document table at the beginning of the submission.

Where there is more than one report of a randomised trial (eg one or more published papers, one or more trial reports internal to the sponsor), provide the published paper(s) and the complete internal trial (clinical study) report(s). If the results vary between reports of the same randomised trial, discuss the differences, justify the results used in the base case and cross-reference the source of the extracted results. Provide a copy of each publication that reports 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) using an approach relevant to the design of the studies included in the submission (Subsections 2.3.1–2.3.3)

2.3.1 Internal validity

Assess the risk of bias to provide the PBAC with a clear idea of which trials are of greater scientific rigour. Information needed to inform an assessment of the risk of bias differs for randomised trials and nonrandomised studies, and the two approaches are described in Subsections 2.3.2 and 2.3.3, respectively.

Where the rarity of the disease or condition prohibits the use of a traditional parallel-group randomised controlled trial, alternative trial designs may be acceptable (eg 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 as for randomised trials.

The best approach to assessing the validity of single-arm studies will depend on the design of the study. Justify the approach (or modifications to the approaches below) taken to capture the key limitations of the study design.

2.3.2 Risk of bias assessment for randomised trials

The preferred approach for randomised trials is described in Chapter 8 of the [Cochrane handbook for systematic reviews of interventions](#)¹ (version 5.1.0).³ Complete Table 2.3.1 for each included trial.

Present factual information about the design and conduct of the trial – such as how the participants were allocated to groups, or whether or not participants or assessors were blinded. After the table, provide additional information about 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 has 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) for decisions such as either stopping treatment or starting a new or concomitant treatment in response to adverse events, treatment failure 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 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.

¹ <http://handbook.cochrane.org>

- **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 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.

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 2.3.1 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 knowing 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 knowing 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] |

Note: Adapted from the Cochrane Collaboration's tool for assessing risk of bias ([Chapter 8 of the Cochrane handbook for systematic reviews of interventions](#), version 5.1.0^m)³

^m http://handbook.cochrane.org/chapter_8/table_8_5_a_the_cochrane_collaborations_tool_for_assessing.htm

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 | <i>N</i> | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | Reference the source of this information |
| | Main comparator | <i>N</i> | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | Reference the source of this information |
| Trial 2 | Proposed medicine (high dose) | <i>N</i> | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | Reference the source of this information |
| | Proposed medicine (low dose) | <i>N</i> | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | Reference the source of this information |
| | Main comparator | <i>N</i> | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | Reference the source of this information |
| Trial 3 | [etc] | [etc] | [etc] | [etc] | [etc] | [etc] | [etc] |

Systematic reviews and meta-analyses

Assess the risk of bias for included individual trials within an identified systematic review or meta-analysis. 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, clearly report the risk of bias assessment undertaken by the authors of the systematic review; also assess the quality of the systematic review using a validated tool (eg AMSTAR⁴ or ROBIS⁵).

2.3.3 Risk of bias assessment for nonrandomised studies

Nonrandomised studies are at high risk of bias. Methods for mitigating the risks associated with the differential distribution of known confounders because of nonrandom treatment allocation (such as matching and controlling for confounders in the analysis) cannot adjust for the differential distribution of unknown confounders.

Present an assessment of risk of bias appropriate for the study design and conduct of the included nonrandomised studies. The internal validity of a nonrandomised study can be elicited by reference to how the study design or conduct differs from that of a well-designed, double-blind randomised controlled trial. Discuss whether there is a risk of bias as a result of the study design or the conduct of the study, and describe any measures taken to mitigate the risk of bias. Potential sources of bias include:

- imbalances in baseline or post-baseline characteristics that are potential confounders (see Appendix 4)
- treatment switching or imbalances in the use of later-line or concomitant therapies
- patients who are selected into the study and are already receiving the intervention (or comparator), where these patients are different to those who are not, or who have started then stopped, the intervention, and where these two groups may have different expected outcomes

- a definition of the intervention or comparator (doses, duration, setting) that is too broad or ambiguous, and where allocation of intervention status may be influenced by the knowledge of outcomes
- missing data that are not missing at random, not balanced across groups and of sufficient magnitude to affect the estimate of the outcome or the method of accounting for missing data affects the estimate of the outcome irrespective of whether data are missing at random
- outcome measures that are subjective, or outcome assessors who are not blinded to treatment allocation
- timing of measurement of outcomes, or the method of determining outcomes, that differs between study arms
- reporting of only some of the results that were pre-defined in the protocol
- reporting of outcomes, time points or subgroups that were not pre-defined in the protocol.

The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool⁶ provides guidance on how to identify and report study characteristics that may impact on the comparative treatment effect in nonrandomised studies. Use the domains identified in the ROBINS-I tool to organise a discussion of the risk of bias. It is not necessary to complete the ROBINS-I tool. If another tool is used, or an alternative approach is taken, describe the approach.

Present factual information on the design and conduct of the study. Provide references to support the information.

2.4 Trial characteristics

INFORMATION REQUESTS

- Present the trial eligibility criteria, the demographic and clinical characteristics of participants in each trial and for relevant subgroups (Subsection 2.4.1)
- Provide details of the treatments in each trial and for relevant subgroups (Subsection 2.4.2)
- Describe the primary outcome and important patient-relevant outcomes in each trial (Subsection 2.4.3)
- Define the minimal clinically important difference (Subsection 2.4.4)
- Specify the noninferiority margin, if appropriate (Subsection 2.4.5)
- Cross-reference the source documents (Subsection 2.4.6)

Note: Where the submission has included a systematic review containing multiple studies, present the trial characteristics for the individual studies, as detailed in the individual publications or, where these are unavailable, as detailed in the systematic review.

2.4.1 Participants

Provide the following details about the trial participants for each trial in an attachment:

- eligibility criteria for participants considered for recruitment into the trial
- baseline demographic and clinical characteristics for each randomised group or study arm
- 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 (or trials) in terms of the extent or timing of patients lost to follow-up, patient withdrawals, or missed or refused assessments, present (in an attachment) the baseline demographic and clinical characteristics for the following groups (or state where these data are unavailable):

- 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 condition, or the medicine).

In the main body of the submission, present differences in the baseline demographic or clinical characteristics across arms in the trials or across trials. Report whether differences are statistically significant, but note that statistical significance may not always correlate with important differences, 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.

It is important that the information requested in this section is provided for the whole trial population as well as any subgroups (and their complements) presented in Section 2.6. The PBAC is concerned when there are imbalances in important prognostic factors across arms, or between a subgroup and its complement. Where baseline characteristics are unavailable for a subgroup(s), state why and provide any relevant details to reduce the uncertainty related to an imbalance of patient characteristics within the subgroup analysis.

2.4.2 Treatment details

For each trial, provide the intended treatment regimen (for both arms) as outlined in the trial 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. State whether the dose or treatment regimen, including the use of concomitant treatments, is supported by high-quality clinical practice guidelines and by the product information for each of the medicines. Justify where the protocol's specified dose (or the actual dose in the trial) differs from recommended dosing.

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.

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.

Discuss differences of treatment duration across arms and across trials. Explain 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.

2.4.3 Outcomes

Present the following outcomes from each trial:

- the primary outcome specified in the trial protocol
- secondary outcomes that are patient-relevant.

Present a surrogate outcome (that is not the primary outcome) only when it is critical to the therapeutic conclusion or economic evaluation. State the target clinical (patient-relevant) outcome for which it is a surrogate and present a transformation of the surrogate outcome to a patient-relevant outcome as described in Subsection 3A.4.2 (or cross-reference to Subsection 3A.4.2 if the transformation is presented there).

For each outcome:

- state whether it was the primary outcome
- state the units of measurement and the method of statistical analysis
- describe and justify the population in which the analysis is performed (ie intention to treat, per protocol)
- 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.

When describing the method of statistical analysis, include the name of the statistical test and sufficient details to allow the PBAC to ascertain how the analysis was performed. For analyses that are not included in the clinical study report, provide a statistical appendix – including the statistical code and statistical output – with notation explaining the variables used in the analysis. Describe the analysis set (eg total randomised population or described as per protocol subset), and 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. Where missing data has been discussed elsewhere, cross-reference the appropriate subsection.

Where there are multiple trials, clearly present any differences in the definition of outcomes or the method of statistical analysis. 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 |
|------------------------------------|---------|--|--------------------------------|-------------------|
| Example: progression-free 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] |
| Example: 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] |

Describe how each outcome was measured, including:

- the instrument used to measure the outcome (eg questionnaire, criteria such as RECIST,⁷ blood test)
- threshold for categorisation as an outcome (if applicable)
- timing of the measurement of the outcome
- personnel who administered the instrument (eg investigator, study nurse, patient)
- 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 reference its validation.

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 in Subsection 2.5 or 2.6.

Composite outcomes

A composite outcome is one in which multiple endpoints are combined. It is usually defined as having been experienced when the first of any of the component endpoints is experienced, even though subsequent component endpoints may occur.

If one or more of the reported outcomes is a composite, discuss and compare the clinical importance of each of the components of the 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.

Composite outcomes need to be appropriately handled when disaggregating the component outcomes so that the true estimate for each component outcome is appropriately captured.

Patient-reported outcome measures

Patient-reported outcome measures include generic ('global') or condition-specific (eg for respiratory conditions, depression, arthritis) measures of quality of life, symptoms or function.

Patient-reported outcome measures may also include multiattribute utility instruments (MAUIs), in which the scoring method for the instrument is anchored on a quality-adjusted life year scale of 0 (death) to 1 (full health). Several commonly used MAUIs for which a detailed discussion of the validity or reliability is not required are the Health Utilities Index (HUI2 or HUI3), the EQ5D-3L or -5L ('EuroQol'), the SF-6D (a subset of the Short Form 36, or SF-36), the Assessment of Quality of Life (AQoL) instruments, and the Child Health Utility 9D (CHU9D) index for children and adolescents.

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

Where a patient-reported outcome measure is used, or a MAUI that is not listed above, provide, in an attachment, a discussion of (or reference supporting) the:

- domains of quality of life, symptoms or function that are covered by the instrument
- scoring method of the instrument
- validity of the instrument
- reliability of the instrument
- responsiveness of the instrument to differences in health states between individuals and to changes in health states over time experienced by an individual
- clinical importance of any differences detected by the instrument (see Subsection 2.4.4 for guidance on minimal clinically important differences [MCIDs]).

To explain how the patient-reported outcome measure is used within the study, describe:

- the timing of assessments, including how often and at what points in the study the instruments were administered
- who administered the questionnaire and in what setting
- why assessments were missed and how missed assessments were dealt with.

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 this has been presented in Subsection 2.3, cross-reference it. If an investigator assessment of patient wellbeing (or performance score) is captured for all patients at all time points, 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.

2.4.4 Minimal clinically important difference

An MCID is the smallest difference in a particular outcome that patients perceive as beneficial (or detrimental). This is usually determined by patients, although an MCID may be determined by a consensus of experts. An MCID should be specified for the primary outcome and the main patient-relevant outcome (where this is not the primary outcome). For submissions relying on a claim of

noninferiority for which a noninferiority margin is specified, present an MCID only if it informs the noninferiority margin.

Likely sources for an MCID may be:

- the protocol (often for the purposes of powering the study)
- a previously accepted MCID by the PBAC, as indicated in a public summary document, that is relevant to both the trial population and the proposed indication
- a commonly accepted MCID in the literature, relevant to the trial population and the proposed indication
- an internal study 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.

Present the details for selected MCIDs in Table 2.4.2. Regardless of the method of derivation, describe the influence of consumer or patient input, where possible.

Where data are time to event (eg overall survival) or dichotomous (eg haemorrhage or no haemorrhage), the determination of an MCID is not straightforward. The most common approach for determining a meaningful benefit to patients involves a consensus of clinical experts in the relevant fields, and should account for the values of patients and families. An example of an expert process for determining a meaningful benefit in terms of overall survival to patients with selected cancers was published in 2014.⁸ Where the primary outcome is a surrogate for another endpoint (eg cholesterol for cardiovascular events), the justification of an MCID should be the change in the surrogate required to result in a meaningful change in the target outcome.

Patient-reported outcomes or patient-relevant continuous/ordinal outcomes

For patient-relevant outcomes that are measured on a scale (eg a patient-reported outcome measure, a quality-of-life instrument, the Visual Analogue Scale, the LogMAR vision acuity test, the 6-Minute Walk Distance test), the MCID may be established using an anchor approach.^{9,10} Although alternative approaches (statistical or consensus) are available, they are less preferred. For these types of outcomes, the MCID can be used as a threshold, beyond which an individual patient would be regarded as a ‘responder’.¹¹

Table 2.4.2 Details of proposed minimal clinically important differences (MCIDs) for outcomes in the included trials

| Item | Response |
|---|---|
| Proposed MCID (value) | [Present this as an absolute change in units] |
| Source of MCID | [Provide source] |
| Method of derivation of the MCID ^a | [Outline (eg anchor, consensus, statistical)] |
| Comparison of the derivation of the MCID and the studies included in the submission | [Describe] |
| Population | [Describe any differences in the population or indication] |
| Outcome definition | [Describe any differences in the outcome definition] |
| Baseline value for measurement | [Describe any differences in the baseline value from which change was measured] |

^a Methods for deriving an MCID commonly fall within three categories.¹²⁻¹⁵

2.4.5 Noninferiority margin

A claim of noninferiority means that, in terms of safety and effectiveness, the proposed medicine is no worse than the main comparator. However, a lack of a statistically significant difference between the proposed medicine and the comparator does not adequately establish noninferiority. It is common practice to require that the confidence limits of the difference in treatment effect do not include an *a priori* stated clinically meaningful difference favouring the comparator.

Choice of patient-relevant outcome(s)

Establish a noninferiority margin for the primary outcome and the most important patient-relevant outcome (where this is not the primary outcome). Where the proposed medicine impacts on two distinct indications, or contains two active components (see Product type 1) that affect two distinct indications, establish noninferiority for the primary and most patient-relevant outcomes for both indications.

Justification of the noninferiority margin

Select a noninferiority margin to assure that the proposed medicine is not inferior to the main comparator by an important difference.

Propose a magnitude of difference in outcome that would be regarded as unimportant and can be used as the noninferiority margin. Justify the approach taken to establish the noninferiority margin, noting that a statistical approach by itself is inadequate,¹⁶ and indicate whether there is agreement across multiple sources. It is common to estimate an unimportant difference as less than a minimal clinically important difference (Section 2.4.4).

Prespecified noninferiority margin

Where the included trial has prespecified a noninferiority margin, present and justify the choice of the margin. Explain how the noninferiority margin meets the assurance previously described. Reference the justification presented in the trial protocol. Where the justification provided in the protocol does not adequately address the assurance previously described, provide supporting evidence. Some noninferiority trials are designed to ensure that the proposed medicine retains superiority over placebo. However, a noninferiority margin designed to achieve this may still allow an important reduction in treatment effect compared with the main comparator. In this case, redefine the margin and retest noninferiority.

Non-prespecified noninferiority margin

Where there is no prospectively defined noninferiority margin, justification of such a margin after trial completion (ie post hoc) is difficult¹⁶ and not preferred by the PBAC. Therefore, choose a conservative margin for the submission. This may happen where there are, for example:

- failed superiority trials of the proposed medicine versus comparator¹⁷
- indirect comparisons of the proposed medicine versus comparator via a common reference
- outcomes in noninferiority trials that did not have a prespecified noninferiority margin.

When selecting post hoc noninferiority margins, where possible, present multiple sources of evidence for selecting a margin that represents an unimportant loss of treatment effect, and that converge on a similar estimate. Present and discuss the list of estimates, their sources and the methods used to derive the estimates. Justify the selection of one particular estimate as the proposed noninferiority margin.

2.4.6 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, cross-reference to the page, table or figure numbers of the relevant trial report(s) (in a separate technical document or attachment, if necessary).

2.5 Trial results: whole trial population

INFORMATION REQUESTS

- Present the results on effectiveness for each trial for relevant outcomes (Subsection 2.5.1)
- Present adverse event data (Subsection 2.5.2)
- Cross-reference the source documents (Subsection 2.5.3)

Report the results from the studies for the whole trial population in this subsection. Additional analyses – such as subgroup analyses, meta-analyses, indirect comparisons or adjustments for treatment switching – are presented in Subsection 2.6.

In some cases, the results for the whole trial population will be presented in Subsection 2.6 as part of the additional analysis. If this is the case, cross-reference to the relevant tables in Subsection 2.6 but interpret the results (in the context of the nominated MCID, where applicable) for the whole trial population for each trial in Subsection 2.5.

2.5.1 Effectiveness

For each trial 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.

In general, 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 (standard deviation) or medians (interquartile range) within groups as appropriate
- CIs of the outcomes within groups
- relative and absolute differences between groups, and CIs
- an interpretation of the results
- a discussion of the results in the context of the nominated MCID
- a statement of whether the results are used in an economic evaluation in Section 3.

Tables 2.5.1–2.5.3 show examples of how to present the different types of data.

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) 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, present these differences below each results table. Justify and discuss any early stopping of a trial or reliance on interim analysis in the interpretation of the results.

Dichotomous data

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

| Trial ID | Proposed medicine | Main comparator | Relative risk (95% CI) | Risk difference (95% CI) |
|----------|------------------------------------|------------------------------------|------------------------|--------------------------|
| Trial 1 | <i>n</i> / <i>N</i> with event (%) | <i>n</i> / <i>N</i> with event (%) | [add] | [add] |
| Trial 2 | <i>n</i> / <i>N</i> with event (%) | <i>n</i> / <i>N</i> 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

Many trials measure a continuous variable at baseline and again at a prespecified time point. The treatment effect from such trials can be reported in several ways. Analysis of covariance (ANCOVA) is the most commonly used general approach, but other approaches might also be acceptable. The usual output from ANCOVA is the difference in mean change scores, adjusted for baseline scores. Report these in Table 2.5.2. Where statistical control has been applied (eg ANCOVA), report and justify the covariates used and the assumptions required for the approach (and how they were tested), and discuss the effect of controlling for covariates on the estimated comparative treatment effect.

If the outcome was measured at more than one time point, justify why that end point was selected. Discuss whether the treatment effect differs across other time points, and present these results in an attachment, or provide a clear reference to where they are presented in the sponsor's study report.

Table 2.5.2 Results of [outcome] across the studies: continuous data (with outcome presented as change from baseline)

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

ANCOVA = analysis of covariance; CI = confidence interval; SD = standard deviation

a For each trial, state the number of participants in the group and the number reporting data for each time point.

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. If the threshold is not well supported by the literature, present sensitivity analyses using different thresholds, or present a cumulative distribution function of the continuous outcome separated by treatment arm. Clearly show the effect of the choice of threshold to determine the dichotomous outcome on the comparative treatment effect.

Time-to-event data

Table 2.5.3 Results of [outcome] across the studies: time-to-event data

| Trial ID | Proposed medicine | Proposed medicine | Main comparator | Main comparator | Difference in median | P value (log rank test) | Hazard ratio (95% CI) |
|----------|------------------------------------|-------------------------------|------------------------------------|-------------------------------|----------------------|-------------------------|-----------------------|
| Trial 1 | <i>n</i> / <i>N</i> with event (%) | Median time to event (95% CI) | <i>n</i> / <i>N</i> 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.

Describe the method for analysing the time-to-event data. State any assumptions and how they have been tested. For example, where the analysis is based on a Cox proportional hazards model, present the hazard ratios and their 95% CIs. 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

Attempt a similar approach as the method described for continuous data 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 the data.

Multiattribute utility instrument data

Report MAUI results (with 95% CI) for each time point and each arm within the trial. Report the number of patients eligible for the questionnaire and the number of patients who responded for each time point. Where this cannot be done, explain why and present the results as specified in the trial protocol. Report the difference between the arms (with 95% CI) as the integrals between the mean utility weights obtained over time up to the median (or other relevant time point) follow-up in the trial. If an alternative approach for comparing MAUIs was used, explain how this was done.

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

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

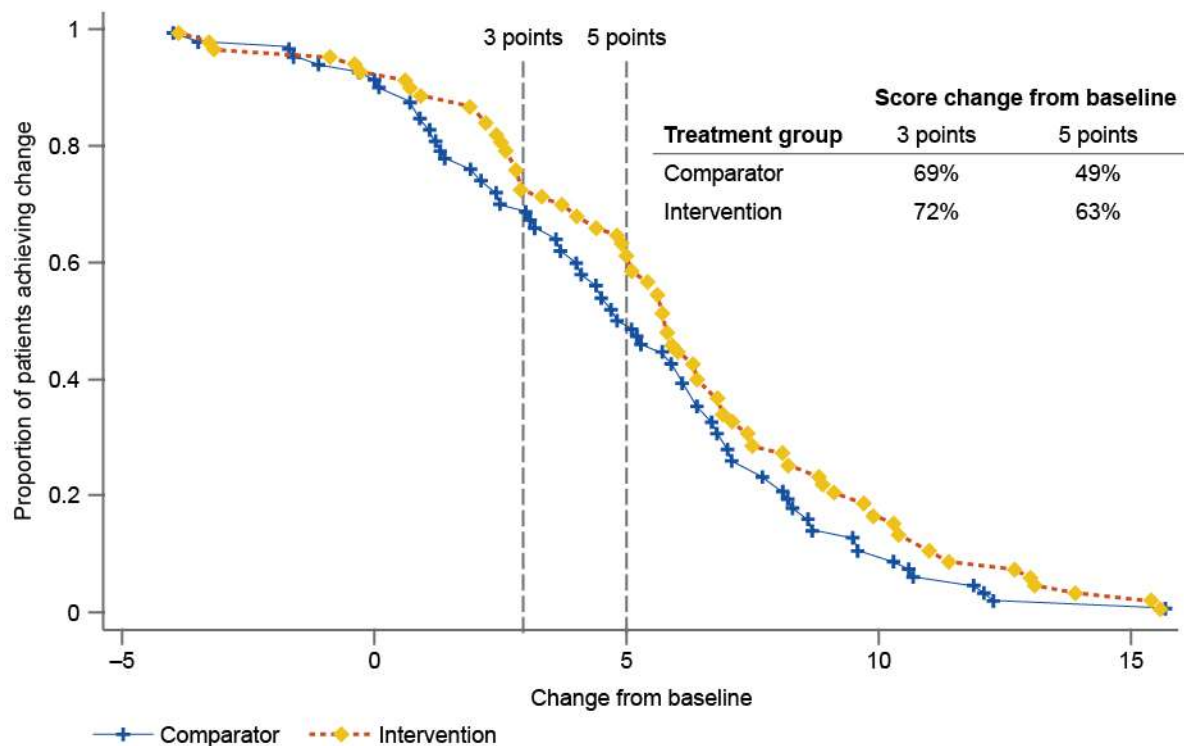
Effectiveness in the context of minimal clinically important difference

Discuss the results of the primary outcome and main patient-relevant outcome with reference to the MCID. Also follow this guidance for analyses presented in Subsection 2.6.

State whether the intervention group has achieved a difference as large as or larger than the proposed MCID when compared with the comparator group. Comment on the extent to which the CI for the comparison includes differences smaller than the proposed MCID.

In addition to the analysis above, where continuous or ordinal outcomes (eg patient-reported outcome measures) can be presented as a responder analysis, present such an analysis. Present a cumulative distribution function (see example in Figure 2.5.1). Compare the number of patients in each arm that achieved a response greater than the proposed MCID (derived in Section 2.4.4) using a relevant statistical test and for alternative values of the MCID, where possible.

Figure 2.5.1 Cumulative distribution function



Applying a noninferiority margin

Compare the least favourable tail of a 95% CI with the noninferiority margin and determine whether the 'worse' result would be regarded as noninferior. Assess this using both intention-to-treat and per-protocol approaches. Discuss discrepancies between the approaches. Where one approach is not available, discuss whether the approach may have resulted in a different conclusion.

Important differences are usually presented as absolute differences, whereas trial comparisons are usually done using relative measures. Explain how the noninferiority margin is converted from one outcome measure to another, if necessary.

Discuss possible reasons if noninferiority cannot be concluded. Discuss other considerations that may support the conclusion of noninferiority (eg whether the medicines are of the same class, the point estimate favours the proposed medicine, whether there are safety or tolerability advantages of the proposed medicine).

Explain and justify any alternative approach to establish noninferiority to that described above and ensure it clearly tests that the proposed medicine is superior to placebo and is not inferior to the proposed comparator by an important extent.

2.5.2 Adverse events

At 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 event¹⁸
- 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.

Where additional adverse events are to be reported (eg treatment-emergent adverse events, adverse events of special interest), explain the importance of the adverse event and interpret the result.

Report adverse event data 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 in Subsection 2.5.1, and include relative risks and risk differences with their 95% CIs across the groups for each study, separately. Interpret the results, where appropriate.

Analyse the relative adverse event rates (events per period at risk), if the average period at risk per participant varies substantially between treatment groups (eg using a straight Poisson regression or a negative binomial approach). Present the assumptions associated with statistical analyses and how they were tested.

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

2.5.3 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 for this subsection, cross-reference the page, table or figure numbers of the relevant trial report(s) (in a separate technical document or attachment, if necessary).

For statistical approaches that are not presented in a clinical study report and cannot be replicated using the data provided in this subsection, 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 additional relevant:

- subgroup analyses (Subsection 2.6.1)
- meta-analyses (Subsection 2.6.2)
- indirect comparisons (Subsection 2.6.3)
- adjustments for treatment switching (Subsection 2.6.4)

2.6.1 Subgroup analyses

If only some of the participants from the whole trial population would be eligible for treatment according to the proposed listing, present a subgroup analysis to show the relative effectiveness of the proposed medicine in eligible participants.

Ensure that the participant characteristics and treatment details have been presented in Subsection 2.4 for the whole trial population, each relevant subgroup and its complement (ie all the participants who are not included in the subgroup).

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, clarify 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:

- The plausibility of a variation in treatment effect for the subgroup, as it relates to the pharmacological, biological or clinical rationale for using the medicine. An unexplained variation is difficult to interpret in the absence of such plausibility (cross-reference Subsection 1.1, if appropriate).
- 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.
- The number of subgroup analyses originally conducted and any statistical adjustment for multiple comparisons.

Results of subgroup analyses

For each outcome relevant to the submission, present the relative and absolute treatment effect measures for the whole trial population, the subgroup and the complement. The data to present will differ according to the type of outcome (see example tables in Subsection 2.5.1, which may be adapted to report subgroups). An example using dichotomous outcomes is shown in Table 2.6.1.

Include relative and absolute treatment effect measures for the subgroup, the complement of the subgroup and the total trial population. Test for interaction between the subgroup and its complement to support and quantify the association between the treatment effect and the covariate defining the subgroup. If the subgroup is defined by a continuous variable, particularly if

the subgroup was not prespecified, present a sensitivity analysis on the threshold value chosen to define the subgroup for different thresholds.

Use a random effects meta-analysis for pooling data, if feasible (see Subsection 2.6.2 for further guidance on meta-analyses). See Subsection 2.6.3 for subgroup analysis in an indirect comparison of randomised trials.

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 (%)] | RR or OR (95% CI) | RD (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 =) |
| | I-squared 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 =) |
| | I-squared 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 =) |
| | I-squared statistic with 95% uncertainty interval | – | – | [add] | [add] |
| Test for treatment effect variation | – | – | – | P = | P = |

– = not required; 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; OR = odds ratio; P = probability; RD = risk difference; RR = relative risk

Present adverse event data as for dichotomous data (refer to Subsection 2.5.2 for guidance). Take care when testing for interaction where the average period at risk per participant varies substantially between the relevant subgroup and its complement.

2.6.2 Meta-analyses

Where more than one trial reports a particular outcome, present a meta-analysis of the aggregated results of each trial that reported the relevant outcome, if this is feasible.

State the software used for the analysis. The Cochrane Collaboration’s RevMan¹⁹ succinctly conveys the requested array of meta-analysed information in a suitable format. Stata software²⁰ is an acceptable alternative.

Use a DerSimonian-Laird random effects model to pool group-level trial data. Explain and justify any other method used. Provide adequate detail of all sources of information relied on for these analyses, and document and reference the methods used to make them independently reproducible and verifiable.

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.

Justify any decision to not present a pooled result (eg because there is significant clinical heterogeneity between studies).

Publication bias

Assess the risk of publication bias.²¹ Where there are sufficient trials, present a funnel plot, and a statistical test such as the Begg test²² or Egger test,²³ if possible.

Results of meta-analyses

Adapt Tables 2.5.1–2.5.3 to present the pooled estimates with their 95% CIs. For example, Table 2.5.1 would be presented with Table 2.6.2. For dichotomous outcomes, separately present analyses for the relative risk, odds ratio and risk difference.

Report results for the extent of statistical heterogeneity observed using a Cochran *Q* statistic, degrees of freedom, chi-square test for heterogeneity, and the I-squared statistic with its 95% uncertainty interval.

For each outcome, 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. Discuss the implications of substantial differences in duration of follow-up or time at which patients are at risk of an event.

Table 2.6.2 Example of adapted results tables to include relevant information on pooled results

| Measurement | Outcome | Chi-square (Q) for heterogeneity, df and P value | I-squared statistic with 95% uncertainty interval |
|---|---------|--|---|
| Pooled result from random effects model (RR, 95% CI, <i>k</i>) | [add] | [add] | [add] |
| Pooled result from random effects model (OR, 95% CI, <i>k</i>) | [add] | [add] | [add] |
| Pooled result from random effects model (RD, 95% CI, <i>k</i>) | [add] | [add] | [add] |

CI = confidence interval; df = degrees of freedom; *k* = number of studies contributing to the pooled estimate of effect; OR = odds ratio; *P* = probability; RD = risk difference; RR = relative risk

Comment on the consistency of treatment effects across the trials. Include a forest plot of relative and absolute treatment effects where it is important to interpret the data or if subgroups are presented. Discuss the results for each outcome. If the forest plot is not important to interpret the data, include it as an attachment.

Assess the clinical and statistical heterogeneity in the meta-analyses

Discuss and explain any heterogeneity of treatment effect across trials and the I-squared statistic. 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.

Consider the factors in Appendix 4 when assessing heterogeneity. If appropriate, present Table A4.1 from Appendix 4, and outline where trials are similar and where they differ. Cross-reference the table if it is elsewhere and discuss the differences in the context of the meta-analysis.

Present the pooled incidence rate differences, if there is a risk of heterogeneity because the trials have different periods of follow-up.

Pooled time-to-event outcome data

Where multiple trials report on a time-to-event outcome, present the pooled results across the trials, the number of trials contributing to the forest plot and the proportion of 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. The preferred method is to pool individual patient data from a Cox proportional hazards model. Justify and reference the method(s) used. Describe the methods and provide sufficient data as an attachment to allow the results to be reproduced and verified independently.

Ensure 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% CI. If hazard ratios with their standard errors are not all available, pool dichotomised data based on a common duration of follow-up. A biostatistician can provide expert advice about pooling the integral between Kaplan–Meier curves.

Adverse event data

Present the meta-analysis of adverse event data as for dichotomous data (see Tables 2.5.1 and 2.6.2). Report the duration over which adverse events were recorded for each trial. If events per period at risk have been analysed (eg using straight Poisson regression or negative binomial approach, as appropriate), pool these results across trials.

Meta-analyses of subgroups

When the submission relies on a subgroup analysis, present this meta-analysis in Subsection 2.6.1 with the subgroup analysis. Justify the omission if a meta-analysis of the whole trial population or of the complement to the subgroup has not been presented

2.6.3 Indirect comparisons

Baseline characteristics, treatment details, outcomes and outcome definitions for the included trials that are relevant to the assessment of an indirect comparison are presented in Subsection 2.4. Results for the individual included trials are presented in Section 2.5. Cross-reference to these subsections where relevant.

Indirect comparison methodology

Describe the method(s) used for the indirect comparison, such as the Bucher single pairwise method,²⁴ matching-adjusted indirect comparison,²⁵ simulated treatment comparison,²⁶ network meta-analysis or mixed treatment comparison. Where there are multiple common comparators in the network, perform pairwise comparisons for each possible pathway in the network. The Bucher method²⁴ is widely used; it 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.²⁷

More complex methods, such as network meta-analyses, may be presented as supplementary analyses. For network meta-analyses, present the results of pairwise comparisons for each link in the network. Although some methods consider nonrandomised studies in a network, avoid including nonrandomised studies. Where nonrandomised studies must be included, present the results of the network meta-analysis both with and without the nonrandomised studies.

Unadjusted indirect comparisons (such as a naive comparison between single arms), or indirect comparisons where differences in trial characteristics may affect the transitivity of the trials in the comparison, are difficult to interpret and reduce the confidence of the PBAC in decision making. Where patient-level data are available for at least one study in the comparison, use matching-adjusted indirect comparisons or simulated treatment comparisons to correct for trial differences to improve the transitivity of the comparison.

When considering complex approaches (eg matching-adjusted indirect comparisons, simulated treatment comparisons, network meta-analyses, mixed treatment comparisons), balance the additional information requests and challenges these approaches may present with any reduction in uncertainty they may deliver. Provide sufficient detail to repeat the analysis, including programming code for statistical software such as Stata, R, SAS or WinBUGS. For methods that require individual patient data (matching-adjusted indirect comparison or simulated treatment comparison), attach the individual patient dataset in a spreadsheet. Justify where this is not possible.

Transitivity assumption

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

Table 2.6.3 Steps to assess the transitivity assumption

| Comparison | Issues to consider |
|---------------------------------|--|
| A vs C direct randomised trials | <ol style="list-style-type: none"> 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 | <ol style="list-style-type: none"> 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 | <ol style="list-style-type: none"> 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 (see Appendix 4). If Table A4.1 of Appendix 4 was completed during an assessment of heterogeneity for the inclusion of studies in Subsection 2.2, cross-reference the table; otherwise, present the table as an attachment, to compare factors within and across trial sets. Cross-reference Subsection 2.4 (baseline characteristics, treatment details and outcome definitions presented for the individual trials) 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 an indirect comparison includes confounders, adjustment using a meta-regression may be appropriate. However, meta-regression usually requires at least 10 trials per adjustment variable to achieve stability in the meta-regression results.²⁸ An alternative approach is to present a matching-adjusted indirect comparison or a simulated treatment comparison, in addition to the pairwise comparisons (ie Bucher method).

Assessing event rates in the common reference groups

Compare the event rates across the common reference arms of the pairwise comparisons. Cross-reference if this has been presented elsewhere (eg Subsection 2.2). Report and discuss the implications of any differences in the event rates. Where event rates differ, and this is likely to be because of differences in patient baseline risk, 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

Where the indirect comparison is based on multiple A versus C and/or B versus C trials, present the statistical heterogeneity within the meta-analyses of each trial set using both an absolute and relative outcome measure. Specify which outcome measure (odds ratio, relative risk, absolute risk difference) results in the smallest amount of statistical heterogeneity and apply this outcome measure in the indirect comparison, or describe and justify an alternative outcome measure. The choice of outcome measure should minimise the variation in the comparative treatment effect within each and all sets of included randomised trials – that is, be least affected by differences between trials in terms of baseline risk or other factors. Discuss the evidence to support a constant treatment effect using the nominated outcome measure across the indirect comparison.

Particularly where the desired final outcome is an absolute risk difference yet a relative outcome measure is more consistent across trials, perform the indirect comparison using an odds ratio and convert this to an estimate of relative risk or absolute risk difference.²⁹

Results of the indirect comparison

Present the results of the indirect comparison:

- For dichotomous outcomes, present the results of each individual randomised trial as the odds ratio, relative risk and absolute risk difference with 95% CIs 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% CI between the common reference, and the proposed medicine and the main comparator. Also report the median event-free survival in each arm 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% CIs using the random effects model (Subsection 2.6.2 discusses how to present 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% CI or, if previously justified, the absolute risk difference.
- 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. Present a supplementary network meta-analysis to synthesise the available data, if appropriate.
- Where trials or trial sets have been excluded in Subsection 2.2, include sensitivity analyses in which these trials are included, if possible. Similarly, if trials or trial sets have been included that may be increasing heterogeneity, include sensitivity analyses in which these trials are excluded, if possible.

An example summary table for dichotomous outcomes is shown in Table 2.6.4. Adapt Tables 2.5.1–2.5.3 for other types of outcomes.

Table 2.6.4 Summary of results of the indirect comparison (for a dichotomous outcome)

| Trial type or estimate | Trial ID | <i>n</i> with event/ <i>N</i> (%) | Common reference <i>n</i> with event/ <i>N</i> (%) | Treatment effect (OR) | Treatment effect (RR) |
|---|----------|------------------------------------|--|-----------------------|-----------------------|
| Proposed medicine vs common reference trials | Trial 1 | <i>n</i> / <i>N</i> (%) | <i>n</i> / <i>N</i> (%) | OR (95% CI) | RR (95% CI) |
| | Trial 2 | <i>n</i> / <i>N</i> (%) | <i>n</i> / <i>N</i> (%) | OR (95% CI) | RR (95% CI) |
| | Pooled | total <i>n</i> /total <i>N</i> (%) | total <i>n</i> /total <i>N</i> (%) | Pooled OR (95% CI) | Pooled RR (95% CI) |
| Comparator vs common reference trials | Pooled | total <i>n</i> /total <i>N</i> (%) | total <i>n</i> /total <i>N</i> (%) | Pooled OR (95% CI) | Pooled RR (95% CI) |
| | Trial 3 | <i>n</i> / <i>N</i> (%) | <i>n</i> / <i>N</i> (%) | OR (95% CI) | RR (95% CI) |
| | Trial 4 | <i>n</i> / <i>N</i> (%) | <i>n</i> / <i>N</i> (%) | OR (95% CI) | RR (95% CI) |
| Indirect estimate of effect adjusted for the common reference | – | – | – | OR (95% CI) | RR (95% CI) |

– = not required; CI = confidence interval; *n* = number of participants with event; *N* = total number of participants in group; OR = odds ratio; RR = relative risk

Indirect comparisons of subgroups

See Subsection 2.6.1 for presentation of a subgroup analysis. Present, where possible, an indirect comparison for the whole trial population, the subgroup and its complement. Discuss the results. Explain when this is not possible.

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% CI (eg network meta-analyses, mixed treatment comparisons, meta-regressions, matching-adjusted indirect comparisons or simulated treatment comparisons). Ensure that any additional documented or referenced methods are reproducible and independently verifiable.

Follow these steps to establish the comparative treatment effect:

- Explain the method used.
- Present the statistical code used for the comparison (or the equation in the case where a simple method is used), and explain 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.
- Present the assumptions required for each approach, how the assumptions were tested and the results of such testing.
- Describe and justify the priors where Bayesian methods have been used.
- Present the results, and CIs or intervals to capture the uncertainty in the approach.
- Present heterogeneity statistics or bias statistics.
- Interpret the results and explain any uncertainties.
- Compare the results from the simple indirect comparison method (Bucher's method) and explain any difference.
- Present the individual patient data if these are required by the statistical approach (eg matching-adjusted indirect comparison), or justify their omission.

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

2.6.4 Adjustment for treatment switching

Adjustments to correct for treatment switching may reduce the PBAC's confidence in the estimate of the treatment effect in the absence of switching, and evidence without treatment switching is preferred.

Where one or more of the included studies has participants that switched treatments, check whether the pattern of switching is consistent with current clinical practice for the comparator arm and/or future clinical practice for the intervention. If not, 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 rely on assumptions that are difficult to validate; ensure that the approach provides 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 for each arm of each relevant trial. For each arm, explain:

- the medicine(s) to which switching occurred
- the extent of the switching (see Table 2.6.5)
- 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) resembles current (comparator arm) or future (intervention arm) clinical practice, adjustment for treatment switching in this arm is not appropriate and no further information is required.

If switching (or the extent of switching) does not reflect clinical practice, describe the differences and address the following issues:

- State whether treatment switching and/or specific analyses to adjust for treatment switching were prespecified in the trial 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. Cross-reference the appropriate table in Subsection 2.4 if this has already been discussed, and summarise the differences here. If participants switched primarily as a result of disease or condition 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 or condition progression, toxicity) and the patient numbers for each category.
- Complete Table 2.6.5 to report the extent and timing of treatment switching.

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

| Trial arm | Characteristic | Time point 1 | Time point 2 | Time point 3 |
|------------------------------------|---|--------------------------------|------------------------------------|--------------|
| Proposed medicine arm (<i>N</i>) | Number at risk of switching ^a | s1 | s1 + s2 | [etc] |
| | Number of treatment switches to the comparator arm [percentage of randomised that have switched] | c1 [c1/ <i>N</i> %] | c1 + c2 [(c1 + c2)/ <i>N</i> %] | [etc] |
| | Number of treatment switches to any subsequent active treatments (comparator or nonstudy therapies) [percentage of randomised that have switched] | t1 [t1/ <i>N</i> %] | t1 + t2 [(t1 + t2)/ <i>N</i> %] | [etc] |
| | Proportion of patients at risk of switching who actually switched to the comparator arm (%) | c1/s1 | (c1 + c2)/(s1 + s2) | [etc] |
| | Proportion of patients at risk of switching who actually switched to any subsequent treatments (comparator or nonstudy therapies) (%) | t1/s1 | (t1 + t2)/(s1 + s2) | [etc] |
| Comparator arm (<i>N</i>) | [As for proposed medicine arm] | [As for proposed medicine arm] | [As for proposed medicine arm] | [etc] |

cx = number switched from the medicine to the comparator at time point x; *N* = number randomised; sx = number at risk of switching at time point x; tx = number switched from the medicine to any subsequent therapy at time point x

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

Several methods can be used to adjust survival estimates for treatment switching.³⁰ Using simple methods is acceptable when the estimate of comparative treatment effect is clearly towards the null. More complex methods (eg inverse probability of censoring weights, a rank-preserving structural failure time model, 2-stage methods) have assumptions that can be difficult to validate. Provide details on the approach, the assumptions and how they have been tested, and justify the selection of the approach including a rationale supporting how the assumptions used by each method are reasonable. Provide additional evidence or discussion that will reduce the uncertainty associated with the estimate of the treatment effect following adjustment. If complex methods are used, present the results of several commonly used methods, and clearly justify why a method is not used. Where more complex methods are presented, also present the results of simpler methods as a reference.

Where the discussion of methods is necessarily detailed, present this in a technical attachment.

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% CI. Explain any heterogeneity of treatment effects across the different methods for adjustment. Present the treatment effect and the 95% CI in the absence of switching for comparison.

Where possible, present a Kaplan–Meier graph with curves for each treatment arm with adjustments for treatment switching.³¹ Display 95% CIs for each arm, and include a risk table with the graph to display the numbers of censored patients and patients still at risk in each arm across regular time points for the trial’s follow-up period.

Where complex statistical approaches for adjusting for treatment switching have been used, search the literature 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 nonswitched studies with the modelled Kaplan–Meier curves and discuss where they differ.

In addition, where there is a largely uncontaminated estimate of an outcome that occurred before switching (eg progression-free survival), discuss whether the outcome is a valid surrogate for the clinically relevant outcome (eg overall survival) in Subsection 3A.4. For example, where progression-free survival is a justifiable surrogate for overall survival, compare the estimate of overall survival by transforming progression-free survival with the overall survival determined by statistical methods used above to adjust for switching.

If possible, use a number of different statistical approaches to adjust for switching. A similar result from a number of analyses will reduce uncertainty and increase confidence in the result. Comparison with historical controls or with overall survival calculated from a surrogate measure will also improve confidence in the statistical approaches.

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. Therefore, do not combine these approaches or, if unavoidable, ensure that the results can be clearly interpreted by the PBAC as conservative.

2.7 Assessment of differences between the trial setting and the Australian setting after listing

INFORMATION REQUESTS

- Identify any risk of treatment effect variation that is related to differences between the trial setting and the Australian setting (Subsection 2.7.1)
- Conduct an extended assessment of comparative harms (Subsection 2.7.2)

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 after listing on the PBS.

2.7.1 Identification of important differences across settings

Use Table 2.7.1 to tabulate important differences between the trial setting and the Australian setting. Consider factors relating to differences in the populations, disease or condition, circumstances or treatments as conducted in the trial compared with what would be expected were the proposed medicine reimbursed according to the requested restriction (Subsections 1.1.2 and 1.4) and in accordance with the proposed clinical management algorithm (Subsection 1.2). Table A4.1 (Appendix 4) contains a list of example factors that, when different across settings, may result in a difference in treatment effect, adverse events or patient management across those settings.

Alongside the identified differences, select one of the following conclusions in Table 2.7.1 about the influence of the identified difference across the settings on estimates of effectiveness, safety or patient management:

- differences across the settings are unlikely to have an effect; or
- differences across the settings may have an effect or, where it is unclear whether the differences would have an effect, differences across the settings require further investigation.

For differences across the settings that may have an effect, or for which an effect is unclear, address these in Section 3A.3.2. Provide an explanation of why differences are unlikely to have an effect. Where the explanation requires an analysis of trial or other data, mark this as requiring further investigation and present the translation study in Section 3A.3.2.

Table 2.7.1 Example differences between the trial setting and the Australian setting in terms of population, disease or condition, circumstances or treatments

| Characteristic | Trial setting | Australian setting | Conclusion |
|-------------------------------|---|--|--|
| Disease or condition severity | 42% stage I or II, 58% stage III or IV | 65% stage I or II, 35% stage III or IV | Requires further investigation (optional text: may have an effect on comparative treatment effect) |
| Concomitant treatment | Cisplatin 75 mg/m ² every 4 weeks for 6 cycles | Carboplatin 360 mg/m ² every 4 weeks for 6 cycles | Requires further investigation (optional text: may have an effect on comparative treatment effect) |
| Health care system | United States and Japan | Australia | Requires further investigation (optional text: may have an effect on subsequent lines of therapy, management of side effects and resource use) |
| Age | Average age 54, 4% older than 80 | Average age 61, 12% older than 80 | Unlikely to have an effect |

Differences between the trial setting and the Australian setting that may affect the comparative effectiveness or safety may undermine the key assumptions required to pursue a cost-minimisation approach. Where the submission identifies such differences, present a supplementary analysis in an attachment of the impact of the differences, using the approach outlined in Subsections 3A.3.2 and 3A.3.3, to support the validity of the therapeutic claim in the context of a cost-minimisation approach.

2.7.2 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.

Trial applicability to the Australian setting

Discuss whether any differences between the settings (identified in Subsection 2.7.1) may affect the comparative safety of the proposed medicine if used in the Australian setting.

Factors that will influence the discussion include:

- the prevalence and severity of the adverse event, and whether it is likely to be related to the medicine
- any difference in the rate of the serious adverse events between the patients receiving the proposed medicine and the main comparator
- factors for which the trial setting differs from the Australian setting that may affect the expected rate of the serious adverse event.

Extended safety 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, present additional safety data and an overall conclusion on the safety of the proposed medicine compared with the main comparator.

A broader assessment of harms is especially important for serious adverse reactions that might occur in the long term or rarely; 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.

Where the proposed medicine is registered with the TGA, present the list of important risks and missing information from the approved risk management plan. Discuss these factors in the context of the safety of the proposed medicine compared with the nominated comparator.

Where the proposed medicine is not yet TGA registered, present the following evidence for harms:

- 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 (completed or ongoing postmarket surveillance studies)
- any studies identified in a separate search, including nonrandomised study designs (eg registry data, 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. Only present the most relevant studies, which will tend to be larger or longer than the studies included in Subsection 2.2. Do not report on case studies, small case series, studies of short duration or those that provide little additional value. 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, and provide additional detail or tabulated data in an attachment, if relevant. State whether the source of evidence does not report safety, or the safety conclusions are no different from those in the included studies. Summarise all of

the sources and propose an overall conclusion of comparative safety against the nominated comparator.

If superiority cannot be justified on the basis of trial data from Subsection 2.2, the extended assessment of comparative harms should not be used to form the basis of a claim of superiority for safety of the proposed medicine compared with the nominated comparator.

2.8 Interpretation of the clinical evidence

INFORMATION REQUESTS

- Interpret the evidence by summarising the overall clinical trial evidence presented (Subsection 2.8.1)
- Classify comparative effectiveness and safety (therapeutic conclusion) (Subsection 2.8.2)

2.8.1 Evidence interpretation

Summarise the clinical evidence presented in the submission (without repeating evidence from other sections). Consider:

- 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, since the primary outcome is overall survival and there was little crossover, 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.

2.8.2 Therapeutic conclusion

The interpretation of the clinical data presented in Section 2 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 or noninferior to the comparator).

The therapeutic conclusion should be a simple and unequivocal statement that is supported by evidence provided in the submission.

Example:

[Proposed medicine] is superior/noninferior/inferior in terms of effectiveness compared with [comparator].

[Proposed medicine] is superior/noninferior/inferior in terms of safety compared with [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 [proposed medicine] in combination with [medicine X], and administered until recurrence or for a maximum of 18 cycles is superior in terms of effectiveness compared with [comparator] given in combination with [medicine X] administered until recurrence).

Section 3 Economic evaluation

Introduction

In Section 3, present an economic evaluation of substituting the proposed medicine for the main comparator in the context of the listing requested. Information requests cover a full and transparent description of the economic evaluation, with sensitivity analyses to characterise the uncertainty around the results.

The economic evaluation may be a full cost-effectiveness analysis (CEA) (**Section 3A**) or a cost minimisation (**Section 3B**).

A full CEA is appropriate where the clinical evaluation has concluded that the proposed medicine is:

- therapeutically superior to the main comparator, but likely to result in additional costs to the health system; or
- therapeutically inferior to the main comparator, but likely to result in lower costs to the health system.

This requires a full quantitative analysis of both the incremental health-related costs and health outcomes, associated with the proposed medicine. Ultimately, a full CEA estimates an incremental cost-effectiveness ratio.

A cost-minimisation approach is appropriate where there is a therapeutic claim of noninferiority (or superiority), the safety profile is equivalent or superior (in both nature and magnitude), and use of the proposed medicine is anticipated to result in equivalent or lesser costs to the health system.

For this approach, the difference between the proposed medicine and the main comparator is reduced to a cost comparison.

Go to the relevant version of Section 3 for the submission:

- Section 3A – guidance for preparing a full cost-utility or CEA
- Section 3B – guidance for presenting a cost-minimisation approach.

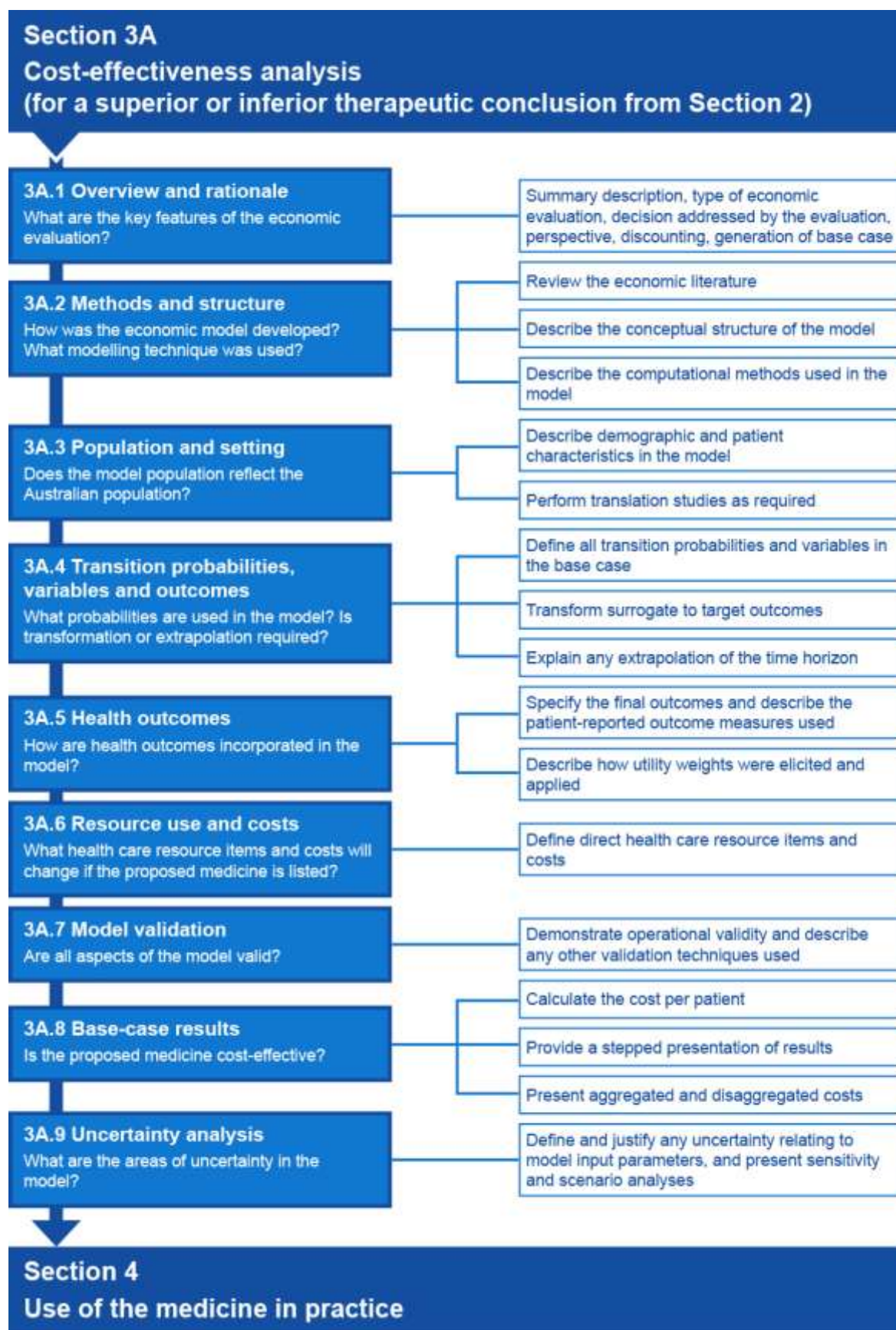
Section 3A Cost-effectiveness analysis

Section 3A provides information requests for preparing a full CEA.

The PBAC prefers that the economic evaluation is based on results from direct randomised trials (see Section 2), with any adjustments or additions to the trial data to account for differences in the population and setting, timeframe of analysis or outcomes of interest presented transparently in a stepped manner. For economic evaluations that rely on results from indirect comparisons of randomised trials or comparisons based on nonrandomised studies, an adaptation of the stepped approach is recommended.

Flowchart 3A.1 shows the key flow of information in Section 3 when there is a superior or inferior therapeutic conclusion leading to a full cost-effectiveness analysis.

Flowchart 3A.1 Overview of information requests for Section 3A of a submission to the PBAC based on a full cost-effectiveness analysis



3A.1 Overview and rationale of the economic evaluation

INFORMATION REQUESTS

- Tabulate the key components of the economic evaluation (Subsection 3A.1.1)
- Justify the type of economic evaluation and outcome measures used (Subsection 3A.1.2)
- Identify the objective and primary decision addressed by the evaluation. Include a decision tree or analytic diagram (Subsection 3A.1.3)
- Use a health care system perspective to inform the base-case analysis, and describe any alternative perspectives provided as supplementary analyses (Subsection 3A.1.4)
- For analyses exceeding one year, confirm the discounting methodology for costs and outcomes in the base case (Subsection 3A.1.5)
- Indicate whether the base case is trial based or modelled, and present a summary of the steps that will be taken to transform from trial to model, where necessary (Subsection 3A.1.6)

3A.1.1 Summary table of economic evaluation

Complete Table 3A.1.1 to summarise the key components of the economic evaluation.

Table 3A.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] |

3A.1.2 Type of economic evaluation

State whether cost-effectiveness will be estimated using a CEA and/or a cost-utility analysis (CUA). Identify the incremental health outcomes (as nominated for the CEA, or as quality-adjusted life years [QALYs] for a CUA) and incremental health costs.

Other economic evaluations (eg cost-benefit analyses or cost-consequences analyses) should not be presented as base-case analyses. However, the various types of economic evaluations are not mutually exclusive and more than one analysis can be presented to make a stronger case for cost-effectiveness (eg both a CEA and a CUA, or cost-consequences analysis and a CUA). (See [Glossary of terms](#)ⁿ for definitions.)

ⁿ www.pbs.gov.au/info/industry/useful-resources/glossary

Cost-utility analysis

A CUA is preferred over a CEA, particularly where:

- there is a claim of incremental life-years gained in the economic evaluation (to assess the impact of quality adjusting that survival gain)
- there is an improvement in quality, but not quantity, of life
- relevant direct randomised trials report results using a multiattribute utility instrument.

Where transformations or external data sources are required to estimate QALYs, present a stepped transformation from a CEA to a CUA, 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 evaluation, justify why the quantified health outcomes are not translated into QALYs and presented as a CUA.

Ensure that the incremental health outcome (eg life-years, other health events) presented in a CEA is patient-relevant. Present the outcome measure that is most closely and validly representative of the overall health of the patient, from their perspective, and in the context of the disease or condition for which they are receiving treatment. Justify the choice of outcome and describe the extent to which the outcome captures all relevant health considerations.

Where a combination of outcomes (either intermediate or final outcomes, or both) are relevant to the patient, capture these collectively. Transform and sum these as QALYs in a CUA, rather than presenting cost-effectiveness analyses for multiple outcomes.

Cost-consequences analysis

A 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. A cost-consequences analysis can be useful where the proposed medicine is demonstrated to have a different profile of effects that are not adequately captured by a single outcome measure, and where there might be trade-offs in effectiveness and safety between the two medicines.

Generally, a cost-consequences analysis should not be presented on its own, but it may be useful as a supplementary or preliminary analysis to a CEA or a CUA. Disaggregated analyses 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 does not incorporate the breadth of considerations that are relevant to PBAC decision making, and there are limitations to the process of eliciting monetary valuations of health, particularly in the context of the Australian health care system where individuals do not face market prices. A cost-benefit analysis should not be presented as the primary analysis. The PBAC is unlikely to be convinced of a cost-effectiveness claim if a cost-benefit analysis is presented without a CUA.

3A.1.3 Decision addressed by the economic evaluation

The purpose of the economic evaluation is to compare the differences in the streams of outcomes and resources that will occur when the proposed medicine or its main comparator are used. This is

expressed as the incremental outcomes and incremental costs between these alternatives in the Australian setting.

Ensure that the decision-tree diagram characterises the primary decision that the economic evaluation addresses, based on the information provided in Subsection 1.1. Use the diagram to provide a conceptual overview rather than the complete computational structure of the economic model. However, after the decision point of the tree, define alternative choices, uncertain events (and probabilities, if practical) and outcomes. Where the model is particularly complex, collapse and summarise branches, and clearly indicate where this has been done. Detail collapsed branches or a more suitable complete diagram of the model structure (eg a health state transition diagram) in Subsection 3A.2.

Ensure that the pathways depicted in the decision tree are consistent with the existing and proposed clinical management algorithms presented in Section 1. Cross-reference to the diagram(s) in Section 1 if they sufficiently represent the decision analytic of the economic model.

Include codependent diagnostic decisions and outcomes, if relevant (see Product type 4).

3A.1.4 Perspective of the economic evaluation

The PBAC's preferred health care system perspective includes health and health-related resource use (costs and cost offsets), and health-related outcomes. Costs include those incurred by the patient, and the public or private health care provider; outcomes are those associated with the patient. Do not include costs and outcomes that are not specifically related to 'health and/or provision of health care' in the base case (see Subsections 3A.5 and 3A.6).

To show a broader societal perspective and quantitatively incorporate considerations beyond the patient and the health care system, present a supplementary analysis in addition to the base case. A well-justified and well-supported analysis will form a more compelling case.

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 beyond the health care system. For example, costs/savings or socially relevant outcomes in domains such as education, housing or justice, or economic productivity impacts. Also, 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.

3A.1.5 Discounting

The values of costs and benefits incurred or received in the future are generally discounted to reflect the present value. Discount both costs and outcomes at a uniform, annual (compounding) rate of 5% per year for all costs and health outcomes that occur or extend beyond one year in the base case.

Present sensitivity analyses using fixed discount rates of 3.5%, and 0% per year (applied to both costs and outcomes). If relevant, present supplementary analyses using other discounting methodologies (eg a different uniform rate, differential rates, time-varying rates) and justify the alternative approach.

3A.1.6 Generation of the base case

Trial-based economic evaluation

A trial-based evaluation is sufficient to provide the base case of the economic evaluation if the trial(s):

- recruited patients who are directly representative of those for whom listing is sought
- tested the proposed medicine in the circumstances of use expected to apply to the requested PBS listing
- directly measured and reported patient-relevant end points over an appropriate time horizon.

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

If the trial(s) did not provide evidence that sufficiently measures the full clinical and economic performance of the proposed medicine compared with its main comparator in the Australian setting, use modelling or adjustments to the trial data to generate the base-case economic evaluation.

Justify and make transparent any translations of the primary effectiveness data and additional assumptions used in the model. Construct economic models in a way that allows the results to be presented sequentially before and after key translational steps.

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

- Present the outcomes and costs as identified in the key trial(s) (see Subsections 3A.5.1 and 3A.6.1).
- Transform trial-based surrogate outcomes to final patient-relevant outcomes (see Subsection 3A.4.2).
- Adjust treatment effects on health care resource use and health outcomes, as would be anticipated in the Australian setting and PBS population according to the restriction (see Subsection 3A.3.1). This may involve one or more steps – for example
 - re-estimate the treatment effect in the PBS population (eg use selected subgroups or weighted trial outcomes to improve applicability to the Australian demographic)
 - incorporate Australian circumstances of use or clinical practice (eg with respect to patterns of resource use)
 - incorporate 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).
- Extrapolate health care resource use and health outcomes (for the proposed PBS use) as required over the appropriate time horizon (see Subsection 3A.4.3).
- Transform health outcomes, if necessary, to the final outcomes used in the economic evaluation (eg using utility weights to obtain QALYs) (detailed in Subsection 3A.5.1).

The last four stages of the stepped approach may vary depending on the nature of the available data. The base-case result is represented by the final incremental costs, outcomes and incremental cost-effectiveness ratio after the evidence from the main trial(s) has been translated.

3A.2 Computational methods and structure of the economic evaluation

INFORMATION REQUESTS

- Review the literature for relevant economic references and any additional clinical or epidemiological literature relevant to the model that has not already been presented, and attach copies of studies and original sources of data used in the economic evaluation (Section 3A.2.1)
- Report and justify the model structure and its development, and justify the time horizon (Subsection 3A.2.2)
- Describe and justify the modelling technique used. If an individual-level model is used instead of a state transition model, explain why (Subsection 3A.2.3)
- Provide a fully editable electronic copy (Subsection 3A.2.4)

3A.2.1 Literature review

Present the results of a literature search for economic evaluations involving the proposed and similar medicines or alternative managements, or similar treatment algorithms, focusing on the structure of the existing models. This may include published reports and models considered by other health technology assessment agencies.

Present any additional literature (eg additional clinical trials, guidelines, natural history studies, burden of disease studies, utility studies, surveys) that informs the model structure or inputs and that has not already been presented in Subsection 1.2 or Section 2, noting what aspect of the model it informs. Provide copies of the original sources of all data not already presented in Section 2, or expert opinion used in the model, in an attachment. Cross-reference the extraction of data from each source to the page, table or figure number of the source document.

3A.2.2 Structure of the economic model

Ensure that the model structure captures all relevant health states or clinical events along the disease or condition pathway, and that it is consistent with the treatment and disease or condition algorithms presented in Subsection 1.2.

Inform the model structure using the results of the literature review of economic evaluations, and other clinical and economic literature, including clinical trials, clinical guidelines, natural history studies and burden of disease studies.

Disaggregate patient-relevant events if there are important differences in mortality, disease or condition progression, associated costs, or quality-of-life effects, and the distribution differs between the intervention and comparator.

During the model development, consider whether, for a given patient, an event experienced in the model should influence the risk of experiencing subsequent events – this may inform the choice of computational method.

Assess the model structure(s) to establish face validity. Justify the exclusion of any potentially relevant states or events identified in the literature, and reference data sources and expert input. Discuss the potential impact of any exclusions on the model outputs. Where the model structure differs from existing models, explain the basis for the selection of the submission's approach.

If relevant, define multiple plausible model structures and test them as part of a structural sensitivity analysis. Examine and address structural uncertainty in Subsection 3A.9.

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. Ensure that the time horizon captures all important differences in costs and outcomes between the intervention and the comparator, as a result of the choice of treatment, but does not extend unnecessarily beyond this.

Where interventions do not affect mortality, and have temporary health or quality-of-life effects, a relatively short time horizon may be appropriate.

Where there is evidence that a treatment affects mortality or long-term/ongoing quality of life, then a lifetime time horizon is appropriate. Note that a lifetime time horizon relates to the life expectancy of the relevant patient population, and reflects the time span required for nearly all of the model cohort to die. The validity of the lifetime horizon is determined by the population of the model, and the inputs; it is not an independently nominated duration. Inputs that are not realistic will result in a model predicting an implausible duration of outcomes or survival and, thus, an implausible lifetime time horizon. The assessment of plausibility should also apply to how the model extrapolates the curves to reach this time horizon (see Subsection 3A.4).

As a modelled time horizon extends – in absolute terms and relative to available data – it is associated with increasing inherent uncertainty. Therefore, economic claims based on models with very extended time horizons and predominantly extrapolated benefits will be less certain and are likely to be less convincing to the PBAC. Subsections 3A.4.3 and 3A.9 address the extrapolation of costs and outcomes for an extended time horizon and associated uncertainty.

Input data

Where possible, input data should be sourced directly from the evidence presented in Section 2.

Where relevant, applicability issues with clinical data from Section 2 are identified (see Subsection 2.7.1), these are discussed and translated to the Australian population and setting, if necessary, in Subsection 3A.3.

Describe the methods used to identify data to populate the model input parameters. 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 method of identifying the data should be robust and transparent. Where multiple sources of data exist, the choice of the source used in the base case should be justified.

Applicability concerns (and any translation) relating to additional data should be described in the relevant subsection. For example, transition probabilities beyond the scope of the clinical trial evidence are described in Subsection 3A.4, health outcomes and utilities are described in Subsection 3A.5, and health care resource use and costs are described in Subsection 3A.6.

If adequate input data are not available to inform the model according to the initially defined structure, review the model structure in the light of the available data, and assess the face validity of alternative model structures that better conform to the available data. If a valid alternative model structure can be defined, describe the revisions to the structural model and discuss the potential effects on the model outputs.

If an alternative valid model structure cannot be defined, use expert opinion to estimate input parameters for which empirical data were not identified (see Subsection 3A.9 and Appendix 1 for more information.)

3A.2.3 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 methods and software used to do this.

For model-based economic evaluations, identify the most appropriate modelling technique for the implementation of the final model structure(s).³² Generally, 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. Note the software used.

Decision trees

Decision trees are useful for models with short time horizons. General spreadsheet software (eg Excel) or specialist software (eg TreeAge) can be used. Follow good-practice guidelines for using decision trees.³³

Cohort-based state transition (or Markov) models

Use cohort-based state transition models 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. General spreadsheet software (eg Excel) or specialist software (eg TreeAge) can be used.

Follow good-practice guidelines for using state transition models.³⁴ In particular, consider the following questions 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 can be used 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 commonly refers to the age of the eligible population, but may include other factors. If relevant factors are not normally distributed, run separate analyses of the model and aggregate the outputs.
- What is the likely impact of alternative cycle lengths on the model outputs? Describe the factors determining the selected cycle length.

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

Use individual-level modelling approaches only when a defined model structure cannot be feasibly implemented as a cohort-based model. Describe the characteristics of the model structure that prevent using a cohort-based model. Potential factors include baseline heterogeneity, continuous disease or condition markers, time-varying event rates and the influence of previous events on

subsequent event rates.³⁵ Also describe how incorporation of these features in an individual-level model are expected to produce a more accurate representation of the disease or condition pathways, costs and patient outcomes.

The most common individual-level approaches include individual-based state transition and discrete event simulation models. Follow published guidelines on good research practices for applying these models.^{34,36} Discuss any requirements for specialist software with the Pharmaceutical Evaluation Branch (PEB) in advance.

Other modelling techniques

If the results from simpler models are robust enough to produce plausible sensitivity and scenario analyses, it is not necessary to use more complex modelling techniques.³⁷ 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 will not demonstrate cost-effectiveness accurately enough.

Note that more complex modelling techniques may be less transparent, and the model assumptions less certain. This might result in the PBAC having less confidence in the cost-effectiveness claim. Discuss the use of complex modelling techniques (including any specialist software) with the PEB in advance.

3A.2.4 Fully editable electronic copy of the economic evaluation

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

The following software packages do not need prearrangement with the PEB:

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

3A.3 Population and setting

INFORMATION REQUESTS

- Describe the setting of the model and the demographic and patient characteristics for the modelled population (Subsection 3A.3.1)
- Translate the important applicability concerns associated with the clinical data in Subsection 2.7.1 and identify any remaining uncertainty (Subsection 3A.3.2)

3A.3.1 Demographic and patient characteristics, and circumstances of use

The setting of the economic evaluation should be the Australian health care setting, with the modelled population representing the target Australian population indicated for use of the proposed medicine (Subsection 1.1.2), and the circumstances of use consistent with the clinical management algorithm (Subsection 1.2) and the proposed restriction or indication (Subsection 1.4).

Describe the demographic and clinical characteristics of the modelled population 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 and severity of the medical condition, and comorbidities. Indicate which patient characteristics are incorporated explicitly and which are implicit (associated with use of other data) or not included.

Describe and justify how heterogeneity in patient characteristics (if relevant) is represented in the cost-effectiveness analysis.

Provide details of any additional circumstances of use relating to the proposed medicine that are relevant to the model setting or population, and detail how they are incorporated into the model. These may include:

- restrictions on the position of the proposed medicine in the clinical management algorithm (eg first-line treatment or second-line treatment), stopping or continuation rules etc
- 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).

3A.3.2 Applicability issues and translation studies associated with the clinical evidence

For each difference between the clinical evidence setting(s) (including population and circumstances of use) and the Australian setting that are identified in Table 2.7.1 as potentially important, design a translation study. The translation study should determine whether a quantitative adjustment to model inputs are necessary and, if so, the nature of the appropriate translation. Where there are inadequate data for a translation study, identify this as an issue that will remain a source of uncertainty in the model.

The translation study should include:

- the issue and the specific question to be addressed
- the data used and their sources (justify the choice of data where there are multiple possible sources)
- the methods of analysis, with sufficient details to enable independent verification of the analysis (common methods are described below)

- the results, including an estimate of the comparative treatment effect (both relative and absolute) and the 95% confidence interval, and a description of how (or whether) the findings are applied in the model
- a description of any residual uncertainty, and sensitivity analyses that are proposed to address this uncertainty (see Subsection 3A.9).

Take care when converting relative treatment effects across jurisdictions with different baseline risks. Ensure that the baseline risk (ie prognostic characteristics) of patients does not differ between the trial evidence and the target population, or that patients are not expected to respond better to the proposed medicine or the main comparator in one setting than in another setting.

Common methods for translation include subgroup analyses, regression analyses, meta-regression or use of other published studies. Justify the selected approach.

Subgroup analysis

For subgroup analyses, follow the same methods outlined in Subsection 2.6.1.

Regression or meta-regression

Regression analysis has an advantage compared with 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, use a meta-regression, if appropriate. Meta-regression may be used at the study level or at the individual patient level (where the study is entered as a covariate). Only use a meta-regression at the study level if the number of trials is large (5–10 trials for each covariate examined).

Where a regression analysis is used, present and interpret the results in the main body of the submission, and provide the following additional details in an attachment:

- 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 in 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).

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. Systematically identify published studies concerning the proposed medicine (or comparator) or the same class of medicines in the proposed eligible population. Present the search strategy and selection criteria in an attachment.

Report the relevant findings from the included studies. Describe the findings in relation to the proposed medicine, and apply the findings to inform the translation.

3A.4 Model transition probabilities or variables, transformation and extrapolation

INFORMATION REQUESTS

- Present the transition probabilities and any other modelled variables that are incorporated into the base-case economic model, and identify data sources and any associated translation requirements (Subsection 3A.4.1)
- Justify and describe the transformation of surrogate to target clinical outcomes (Subsection 3A.4.2)
- Derive extrapolations of data where necessary; explain and justify methods used, and prepare alternatives for sensitivity or scenario analyses (Subsection 3A.4.3)

3A.4.1 Transition probabilities and variables

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 applicability translation in Section 3A.3.2, as appropriate). Cross-reference the relevant subsections for the clinical evidence and note whether further translation studies or extrapolations are required (do these in Subsections 3A.4.2 and 3A.4.3).

Other transition probabilities may be required that describe the progression of a disease or condition following the experience of an intermediate outcome event, and for which the same transition probabilities are applied, regardless of treatment allocation. Where external sources of data (other than the clinical trials from Section 2) are used to inform transition probabilities (or other variables) in the model, assess the applicability of these sources of data with respect to the Australian setting. Note and justify whether the data are applicable, requiring translation (in which case, follow the approach detailed in Subsection 3A.3.2), or is a source of uncertainty within the model.

Detail where the model uses other variables instead of, or in addition to, transition probabilities. Do not include variables associated with the valuation of outcomes or costs; these are described in Subsections 3A.5 and 3A.6, respectively.

Describe and justify the methods used to identify and analyse relevant data to derive transition probabilities and variables.

For each transition probability or variable, present the point estimate and interval estimates (eg 95% confidence intervals). Follow good-practice guidelines when choosing the methods to derive interval estimates (eg using probability distributions based on agreed statistical methods for alternative types of input parameters).³⁸ Ensure that values taken from all sources of evidence are appropriately adjusted to represent the transitions required by the model structure.³⁹ For example, translate reported rates or cumulative probabilities to the probabilities for timeframes associated with a model cycle, if necessary.

Occasionally, secondary outcomes and other trial-derived data (eg adverse event rates) are relevant to outcomes and/or resource use in the economic model, and point estimates are numerically different across the arms, but not statistically significantly different. This may reflect either no 'real'

difference, or a difference but with insufficient power in the trial to demonstrate it statistically. Explain the approach used to inform the probability in the base-case model (eg whether it has been pooled across arms or differentiated between arms), and explain and justify with supporting evidence, if available. Examine the alternative approach in a sensitivity analysis.

Assess the potential correlation between transition probabilities and/or variables. Correlation between parameters is explored further in Section 3A.9 for uncertainty analysis.

3A.4.2 Transformation of 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 for a relevant health outcome that is used in the model (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. Justify and quantify 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.

Present a translation study that follows the framework in Appendix 5 for assessing a proposed surrogate measure if the transformation of a change in a proposed surrogate measure predicts a change in a target clinical outcome.

It may not be necessary to detail, in full, 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 identified in the clinical evidence associated with the transformation that was previously accepted by the PBAC.
- 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 about 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, apply the surrogate and direct data separately to populate the model. If both approaches provide similar estimates of the comparative treatment effect on the target clinical outcome in the longer term, this helps validate the model.

If a proposed surrogate measure is transformed, ensure that the sensitivity analyses in Subsection 3A.9 represents the uncertainty in the estimation of the comparative treatment effect on the proposed surrogate measure, and the uncertainty of the transformation. This is more complex than where direct measures of comparative treatment effect for a target clinical outcome are used.

3A.4.3 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. Detail any extrapolations of data that are required for the base-case economic model.

Where extrapolation is undertaken, use observed time-to-event data in preference to modelled data up to the time point at which the observed data become unreliable as a result of small numbers of patients remaining event-free.

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. Test alternative truncation points in the sensitivity analysis.

Derive appropriately estimated parametric survival curves based on the observed data (using individual patient data, if available) to extrapolate transition probabilities beyond the data truncation point.

Detail each of the following:

- Whether an assumption of proportional hazards is appropriate beyond the observed data.
- Fit a range of alternative survival models to the observed data (eg exponential, Weibull, log-normal, log-logistic, gamma, Gompertz). Include more flexible extrapolation approaches with multiple points of inflexion (eg piecewise spline models) to better facilitate extrapolation based on the section of the Kaplan–Meier curve that is most representative of long-term survival.⁴⁰
- Assess and discuss goodness of fit using visual inspection, Akaike’s information criterion and Bayesian information criterion. Justify the most appropriate model for the base case and test a number of the best-fitting models in the sensitivity analysis.
- The plausibility of the predictions in the unobserved period (eg the ongoing hazard ratio and/or treatment effect, the point of convergence and/or residual survival in each arm).

The treatment effect resulting from the independent extrapolation of the survival curves should be plotted over the time horizon of the model. If the treatment effect is maintained or increasing, and this is not clinically plausible, apply a hazard ratio such that the intervention and comparator curves converge at a plausible time point. The assessment of plausibility should be linked to the justification of the time horizon (see Subsection 3A.2).

When considering the extrapolated treatment effect, give explicit consideration to clinical decisions regarding the cessation or continuation of treatment. State and justify all assumptions in this regard, and apply them consistently when modelling respective treatment costs.

Numerous sources of advice on extrapolation techniques for economic evaluation are available in the literature.⁴¹⁻⁴⁶

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. Include a time covariate in the multinomial logistic model to represent time-varying probabilities, if possible. 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, format the data into categories, or use a generalised estimating equation model.

Extrapolating published time-to-event data

If individual patient time-to-event data are not available, extrapolate survival probabilities from published Kaplan–Meier curves using graph digitiser software. Fit alternative constant (ie exponential), or monotonically increasing and decreasing (eg Weibull or Gompertz) hazard functions to the extracted survival data beyond the last point of inflexion to the time point at which the observed data become unreliable because of small numbers of patients remaining event-free.

Present tests of the relative and absolute goodness of fit of the alternative curves, and use the best-fitting curve in the base case. Test the alternative models in the sensitivity analyses in Subsection 3A.9.

3A.5 Health outcomes

INFORMATION REQUESTS

- Justify and describe the intermediate and clinical health outcomes in the model, and how they inform the final health outcome in the economic evaluation (Subsection 3A.5.1), including:**
 - how utility weights were identified and applied, if applicable
 - details of the multiattribute utility instrument, or other patient-reported outcome measures, used to inform the model, if applicable
 - any other sources of utility data applied in the model

3A.5.1 Health outcomes

Nominate and justify the final health 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 incremental cost-effectiveness ratio (ICER), consistent with the approach justified in Subsection 3A.1.2.

Detail the health outcome(s) (intermediate and/or final) that inform the final outcome in the economic evaluation and whether these were reported directly in the clinical evaluation (Section 2), and, if not, summarise the transformations involved to obtain the final outcome.

If available, use quality-of-life or utility data reported in Section 2 to estimate QALYs in the model, or, justify the use of alternative indirect methods to estimate QALYs when direct data are available. Present both sets of methods and results, and compare the interpretation.

Present the results of any utility study as the point estimate of the mean elicited utility weight for each health state, and include its standard deviation and 95% confidence interval, where available.

If a claim is made for a change in a nonhealth outcome, 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), do not include these in the base-case evaluation; rather, present them as supplementary analyses (see Appendix 6).

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

Estimates of quality of life or utility from the within-trial evidence (from 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.

If a MAUI has been used in an included study to estimate utility weights (as described in Subsection 2.4.3), 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.

If the initial patient-reported outcome measure is not a MAUI, provide detail of the measure and justification of its use in Subsection 2.4.3. In this subsection, describe a validated method of mapping the results into preference weights (see below). 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.

Consider the duration over which the patient-reported outcome measure informing utilities was administered compared with the duration of the condition of interest. If a generic MAUI or patient-reported outcome measure is used, consider whether it captures all important disease- or condition-specific factors that might be relevant.

Address the following questions when incorporating trial-based patient-reported outcome data into the economic model:

- Are the participants representative of the population for whom listing is requested? (Refer to Subsection 3A.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, assess the results with reference to the conclusion from the primary analysis of the trial.
- Is there a ‘healthy cohort effect’? (ie where the sickest patients are least likely to complete patient-reported outcome data forms, and therefore the data obtained has a bias towards healthier patients.) Consider the responder numbers and drop-outs. While generally associated with an overestimate of utility weights, the direction of any associated bias may depend on whether the treatment and comparator are associated with different utilities, the relative extent of the effect across different arms and health states, and the time spent in different health states. Identify any impact on the overall ICER.
- 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 posttreatment states, but not in other circumstances where treatment (rather than disease or condition) directly affects quality of life (eg because of serious adverse events and any associated long-term implications, or imposed limitations). Justify the approach, and, where possible, present results with and without pooling.
- Is there a risk of bias from a regression to the mean effect?⁴⁷ This may be more likely in instances where quality of life for the control arm is drawn from a trial other than a randomised controlled trial (eg instance from a pre-intervention population).

Use of other sources of data to estimate utility weights

Where utility weights or QALY changes cannot be directly estimated from data collected in the clinical studies from Section 2, or there are significant concerns about the reliability and relevance of trial-based utility, transform the Section 2 health outcomes to estimate QALY gains (eg by applying utility weights to the time spent in different health states that represent the experience of clinical outcomes).

Additional studies (either published or done for the submission) may be needed to estimate utility weights for health states in the economic model. These studies should be identified (and copies provided) in Subsection 3A.2.1.

Describe the source(s) and method(s) (as described below) used to derive externally derived health state utilities, and justify their inclusion in the model. Depending on the clinical context and available data, there may be more than one acceptable source of utility weights. Where this is the case, reflect the uncertainty in selecting an optimal source of weights by reporting the sensitivity of the result to switching between the various sources of weights.

Address the questions regarding quality-of-life data derived from the clinical trials (above) that are applicable to any utility estimates obtained from alternative sources and methods.

Mapping of generic and disease-specific scales

Nonpreference-based patient-reported outcome measures will require a mapping algorithm to be transformed into preference-based measures to estimate utilities. Where this occurs, detail the source of the mapping algorithm. Describe the estimation sample (population demographic and clinical characteristics, sample size etc) and whether there is an external validation sample. Provide details of the source and target measures (eg index, dimensional), and the statistical model and methods used to estimate the mapping algorithm. Detail the statistical association or operations that constitute the algorithm. Discuss methods used to measure the algorithm performance and validity. Present the resulting predicted utilities with associated uncertainty. Discuss the applicability to the submission data, particularly in relation to the sample in which the algorithm was developed.

Scenario-based methods to indirectly elicit utility weights

Scenario-based methods use vignettes to describe the symptoms of a health state to a sample population, usually a representative general population sample, from which utility weights are elicited using an accepted preference-based method. Methods to elicit preferences include the standard gamble, time trade-off and discrete choice experiments, and other stated preference methods.

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.

Describe all stages of a scenario-based study in detail and explain efforts to minimise potential bias. It is difficult to minimise the many sources of analyst bias that are intrinsic to the scenario-based utility approach, including the nonblinded 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.

Population matching study method to indirectly elicit utility weights

This 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. 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. See Subsection 2.4.3 for further detail on MAUIs.

Potential sources of bias for such studies include the possibility of systematic 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, the sampled patients should possibly have been 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.

Published sources of utility weights

Utility estimates may be 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, 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.

Using 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.

Presentation of outcomes and health utility value information

If presenting a CUA, a format for summarising the minimum information on all modelled health outcomes (eg intermediate, final outcomes and events) contributing to the final health outcome in the economic evaluation, and any associated utilities or disutilities is suggested in Table 3A.5.1.

Table 3A.5.1 Identification of health outcomes used in the model

| Health state or event | Mean utility (SD and/or 95% CI) or QALY | Nature of estimate and any translations | Source of estimate | Alternative estimates of utility value (and sources) | Average application in the model: proposed medicine | Average application in the model: comparator |
|------------------------------|--|--|---|---|--|---|
| [Health state 1] | [Utility estimates for health state 1] | [eg EQ5D data (Australian value set)] | [eg from Trial 001 (see Section 2)] | [eg nonpooled data from study] | [eg days/months] | [eg days/months] |
| [Health state 2] | [Utility estimates for health state 2] | [eg scenario-based study using standard gamble method] | [eg external publication: Smith et al 2010] | [eg external publication: Jones et al 2008] | [eg days/months] | [eg days/months] |
| [Event 1] | [x QALYs per event] | [eg scenario-based study using time trade-off method] | [eg commissioned study (study report provided in attachment)] | [eg external publication: Jones et al 2008] | [no. of events] | [no. of events] |

CI = confidence interval; QALY = quality-adjusted life year; SD = standard deviation

3A.6 Health care resource use and costs

INFORMATION REQUEST

- 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 (Subsection 3A.6.1)

3A.6.1 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.

Where a special pricing arrangement is proposed, define the costs with and without the proposed arrangement. Describe the details of any special pricing arrangement in Subsection 1.4.

See the [Manual of resource items and their associated costs](#)^o for additional detail about this section.

Health care resource items

Where appropriate, consider the following resource items:

- 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. Justify and explain any calculation of the cost per patient per year, as necessary, for therapies used episodically.

The amount of a medicine or other resource provided (eg dispensed) is the relevant economic measure rather than the amount of resource consumed. Incorporate wastage in the model, because it is a consumption and therefore an incurred cost.

^o www.pbs.gov.au/info/industry/useful-resources/manual

For estimates of health care resource items, describe and justify their basis, and specify the information source. Consider the applicability of the data to the modelled setting. Measure prospectively the pattern of provision of health care resources in the course of a clinical study by:

- retrospectively reviewing relevant records or through linking data with claims data
- administering a questionnaire or survey
- using 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.

Exclude types of health care resources that would not have a material influence on the conclusion of the economic evaluation, if appropriate. This may be because the cost is very small, or because the cost largely cancels out between the intervention and the comparator(s) (eg the costs of dying, if all individuals in the model would die). If resources are excluded for this purpose, state this and justify their exclusion, and outline how the exclusion affects the incremental cost of the intervention.

Allocation of prices (unit costs) to resources

Present all unit prices and costs in Australian dollars with a consistent year of analysis (which should be stated and be as close as possible to the submission date).

Section 3 adopts a broad perspective for the valuation of health care resources, so include 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 – in the economic evaluation. Where available, use the source of costs recommended by the [Manual of resource items and their associated costs](#).^P 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.

Detail all alternative costs, their sources and any assumptions about them. If multiple estimates are identified, justify the estimate used in the base case and present alternative plausible estimates in sensitivity analyses.

If cost conversion is required from non-Australian prices, and is done using a prevailing exchange rate, justify the price comparability between countries.

If using historical estimates of costs, detail the information sources and the methods used to estimate them. Justify the use of the historical cost source as relevant and the best estimate available. Use the most relevant Australian price index (eg total health and health industry-specific price indexes published by the Australian Institute of Health and Welfare) to adjust for inflation and estimate current prices.

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

^P www.pbs.gov.au/info/industry/useful-resources/manual

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 3A.6.1. These are samples for each identified category, which are consistent with the [Manual of resource items and their associated costs](#),^q but are not comprehensive of all types of health care resource items, natural units of measurement or sources of unit costs.

Present all steps taken to calculate costs in the economic evaluation in a way that allows the calculations to be independently verified.

If a complete presentation of costs is very large, present the calculations in an accompanying technical document. Cross-reference between the calculations and the main body of the submission, and include an electronic version of the detailed calculations.

^q www.pbs.gov.au/info/industry/useful-resources/manual

Table 3A.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 |
|-----------------------|--|--------------------------------|-----------------|--|---------------------------------|--------------------------|
| Medicines | Proposed medicine | Quantity of medicine dispensed | x | Proposed dispensed price | [add usage] | [add usage] |
| | Comparator | Quantity of medicine dispensed | x | PBS dispensed price for item code according to current PBS, if PBS-listed medicine | [add usage] | [add usage] |
| Medical services | Type of medical or allied health practitioner attendance or diagnostic / investigational service | Service rendered | x | MBS schedule fee for item code according to current MBS, if MBS-listed service | [add usage] | [add usage] |
| Hospital services | Hospital admission | Episode for identified AR-DRG | x | Average cost weight for DRG item code according to current AR-DRG Public Sector Estimated Cost Weights | [add usage] | [add usage] |
| Residential care | ACFI category | Daily | x | Daily ACFI subsidy rate plus basic daily care fee | [add usage] | [add usage] |

ACFI = Aged Care Funding Instrument; AR-DRG = Australian Refined Diagnosis Related Group; AUD = Australian dollars; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme

3A.7 Model validation

INFORMATION REQUESTS

- Provide model traces and demonstrate the operational validity of the economic model (Subsection 3A.7.1)
- Describe any other methods used to validate the model-based analysis (Subsection 3A.7.2)

Validation of an economic model to demonstrate that the generated results represent what they are intended to represent is best practice. It helps to reduce some of the uncertainty associated with modelling, and a more thoroughly validated model allows more confidence in its predictions.

3A.7.1 Operational validation of the economic model

Model traces for the proposed medicine and its comparator provide a clear depiction of the implications of the model. They can inform the face validity of the model logic, computerisation and external validity.

Use traces to track patients through the model and demonstrate that the logic of the model is correct. 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. If applicable, state the number of events over time where patient-relevant events occur within a health state. Comment on whether each of the model traces is logical – for example, ensure that any traces of overall survival converge to zero at or before the time horizon of the model (see Subsections 3A.2 and 3A.4).

Compare model traces with corresponding empirical data, where possible, to identify whether outcomes are consistent. Consider both data sources used in the model (dependent validation) and data sources not used in the model (independent validation). For example, compare predicted clinical events with observed data on the natural history of the medical condition. Comment on and explain any differences indicated by these comparisons.

In addition, compare modelled outcomes against outcomes from similar models as a cross-validation tool to identify consistencies (or differences that can be explained).

3A.7.2 Other validation techniques

Present or cross-reference any other completed model validation exercises. The Assessment of the Validation Status of Health-Economic Decision Models (AdViSHE) Study Group describe a range of validation processes, and these should be considered.⁴⁸

3A.8 Results of the base-case economic evaluation

INFORMATION REQUESTS

- Calculate the proposed medication cost per patient (Subsection 3A.8.1)
- Provide a stepped presentation of the cost-effectiveness results, and present the base-case incremental cost-effectiveness ratio (Subsection 3A.8.2)
- Present disaggregated and aggregated costs and outcomes for the proposed medicine and its main comparator (Subsection 3A.8.3)
- Summarise the base-case estimate of the incremental cost-effectiveness ratio (Subsection 3A.8.4)

3A.8.1 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.

3A.8.2 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 clinical outcomes
- extrapolation of data over longer time periods
- additional data or assumptions
- transformation of clinical outcomes to final health outcomes (QALYs).

Identify the steps or assumptions of the model that have important impacts on the ICER.

Table 3A.8.1 shows an example of how to present this analysis.

Table 3A.8.1 Presentation of the stepped derivation of the base-case economic evaluation from the clinical study data

| Steps (only included if undertaken) | Proposed medicine costs | Comparator costs | Incremental costs | Proposed medicine health outcomes | Comparator health outcomes | Incremental health outcomes | Incremental cost-effectiveness ratio |
|--|-----------------------------------|-----------------------------------|---------------------------|--------------------------------------|--------------------------------------|-----------------------------|--|
| Comparative study data (as presented in Section 2); Setting: (trial setting); Time horizon: (trial follow-up) | [A] ^a | [B] ^a | [A – B] | [C] (surrogate outcome) ^b | [D] (surrogate outcome) ^b | [C – D] (surrogate outcome) | \$(A – B)/(C – D) per [surrogate outcome] |
| Study evidence transformed from surrogate to clinical outcome (C→E, D→F) ^c | [A] | [B] | [A – B] | [E] (clinical outcome) | [F] (clinical outcome) | [E – F] (clinical outcome) | \$(A – B)/(E – F) per [clinical outcome] |
| Study evidence transformed to clinical outcome and translated to the Australian population and/or Australian setting (may need multiple steps) | [modified A] ^d | [modified B] ^d | [modified A – modified B] | [modified E] ^e | [modified F] ^e | [modified E – modified F] | \$(modified A – modified B)/(modified E – modified F) per [clinical outcome] |
| Study evidence transformed to clinical outcome, translated to the Australian population/setting, and extrapolated to the appropriate time horizon | [modified & extrapolated A] = [G] | [modified & extrapolated B] = [H] | [G – H] | [modified & extrapolated E] = [I] | [modified & extrapolated F] = [J] | [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 | [K – L] | (I + y) = [M] ^g | (J + z) = [N] ^g | [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 a relevant health outcome (eg QALYs)(M→O, N→P) | K | L | [K – L] | [O] | [P] | [O – P] | \$(K – L)/(O – P) per QALY |

QALY = quality-adjusted life year

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 3A.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 that 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 the steps for the translation of the trial-based economic evaluation may vary. Firstly, incorporate the patient-relevant health outcome if the study outcome is a surrogate. Secondly, translate the effect as necessary to match the Australian population.

The final row of Table 3A.8.1 incorporates all translation studies and additional modelling to complete the impacts of translation of the trial-based economic evaluation into a modelled economic evaluation. Ensure that this corresponds to the base-case ICER.

The stepped presentation informs the face validity of the results, and identifies assumptions and approaches to be examined in more detail in sensitivity analyses. For example, if the main impact is achieved by extrapolating the final outcome over time, then 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).

3A.8.3 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, report the proportions of patients predicted to experience alternative target clinical outcomes in the intervention and comparator groups.

Alternative examples of tables showing disaggregated costs are provided in Tables 3A.8.2 and 3A.8.3.

Table 3A.8.2 Health care resource items: disaggregated summary of cost impacts in the economic evaluation

| Type of resource item | Subtype of resource item | Costs ^a for proposed medicine | Costs ^a for main comparator | Incremental cost ^a | % of total incremental cost ^a |
|-----------------------|---|--|--|--------------------------------------|--|
| Medicines | 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] |
| Residential care | ACFI category | A\$x | A\$y | \$x - \$y | z% |
| | Total | A\$x | A\$y | \$x - \$y | 100% |

ACFI = Aged Care Funding Instrument; PBS = Pharmaceutical Benefits Scheme

a Indicate clearly whether cost values are discounted costs (use of discounted costs is appropriate).

Table 3A.8.3 List of health states and disaggregated 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 | Total incremental cost (%) |
|-----------------------|---|-------------------------------|-------------------------------|--|----------------------------|
| Health state 1 | Resource type 1 | \$x1 | \$y1 | \$x1 – \$y1 | z1 |
| | Resource type 2 | \$x2 | \$y2 | \$x2 – \$y2 | z2 |
| | [etc] | \$x etc | \$y etc | \$x etc – \$y etc | z etc |
| | Total for health state 1 | $\sum \$x$ | $\sum \$y$ | $\sum \$x - \sum \y | $\sum z$ |
| Health state 2 | Resource type 1 | \$xx1 | \$yy1 | \$xx1 – \$yy1 | zz1 |
| | Resource type k | \$xxk | \$yyk | \$xxk – \$yyk | zzk |
| | Total for health state 2 | $\sum \$xx$ | $\sum \$yy$ | $\sum \$xx - \sum \yy | $\sum zz$ |
| [etc] | [etc] | [etc] | [etc] | [etc] | [etc] |
| Total | – | $\sum \$x + \sum \xx etc | $\sum \$y + \sum \yy etc | $(\sum \$x + \sum \$xx \text{ etc}) -$ $(\sum \$y + \sum \$yy \text{ etc})$ | 100 |

– = not required

Similarly, an example of a table showing outcomes disaggregated by health state is given in Table 3A.8.4.

Table 3A.8.4 List of health states and disaggregated summary of health outcomes included in the economic evaluation

| Health state in model | Outcome for proposed medicine | Outcome for main comparator | Incremental outcome | Total incremental outcome (%) |
|-----------------------|-------------------------------|-----------------------------|---------------------|-------------------------------|
| Health state 1 | x1 | y1 | x1 – y1 | z1 |
| Health state 2 | x2 | y2 | x2 – y2 | z2 |
| [etc] | [x etc] | [y etc] | [x etc – y etc] | [z etc] |
| Total | x | y | x – y | 100 |

Identify which health states and resources contribute to the greatest incremental differences between the proposed medicine and the comparator.

3A.8.4 Summary of base-case results

Summarise the base-case estimate of the incremental outcome(s), incremental cost and the cost-effectiveness ratio(s) obtained in the economic evaluation(s), including both CUA and CEA where relevant.

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.

3A.9 Uncertainty analysis: model inputs and assumptions

INFORMATION REQUESTS

- Explain the methods used to represent the uncertainty around the model's input parameters, translations and structure. For each, define the uncertainty or alternatives to be tested in sensitivity or scenario analyses (Subsection 3A.9.1)
- Present and discuss the univariate sensitivity and scenario analyses (Subsection 3A.9.2)
- Present and discuss relevant multivariate analyses and any probabilistic sensitivity analysis (Subsection 3A.9.3)
- Summarise the findings of the uncertainty analysis (Subsection 3A.9.4)

3A.9.1 Identifying and defining uncertainty in the model

Present univariate deterministic sensitivity analyses for all uncertain input parameters, or natural groups of input parameters (eg cost or utility weights for all target clinical outcomes). The following requests are based on good-practice guidelines for model parameter estimation and uncertainty analysis.³⁸

Parameter uncertainty

Use commonly adopted statistical standards to represent the uncertainty around the true value of each uncertain input parameter. For example, beta distributions are a natural match for transition probabilities; log-normal for relative risks or hazard ratios; logistic distributions to calculate odds ratios; and gamma or log-normal for costs and utility parameters.

Justify using alternative distributions. Use interval estimates (eg 95% CIs) derived from fitted probability distributions to define the ranges of the parameter values tested in the deterministic sensitivity analyses.

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.

Consider correlation between input parameter values. If applicable, represent the joint uncertainty around the true values of two or more input parameters in the uncertainty analyses. In particular, it is preferable to represent the joint uncertainty around transition probabilities in the intervention group and the comparator group through the application of a relative treatment effect parameter. If a relative treatment effect parameter is not applicable, individual-level data for the comparator and intervention could be bootstrapped to provide more realistic estimates of the joint uncertainty between these.³⁸

The joint estimation of multiple input parameters when using regression analysis produces relevant correlation parameters. Otherwise, model calibration methods may be used to represent joint uncertainty around the true value of model input parameters.

Translational uncertainty

Where clinical data have required translation for applicability issues, transformation or extrapolation for incorporation into the model, systematically consider the assumptions incorporated into the translation and identify any uncertainty in these assumptions. Identify plausible alternatives for testing in scenario analysis.

Examples of analyses that can be used where the data or outcome translations are incorporated into base-case analysis are presented in Table 3A.9.1.

Table 3A.9.1 Examples of potential sources of translational uncertainty in the economic model and suggested scenario analyses

| Translations incorporated into base-case analysis | Suggested uncertainty analysis |
|--|--|
| Transformation of continuous outcome data to a dichotomous outcome | Alternative thresholds (Subsection 2.5.1) |
| Treatment effect with adjustment for switching | Treatment effect without adjustment for switching, and/or using an alternative adjustment technique (Subsection 2.6.4) |
| Treatment effect based on translation (eg subgroup analysis) following applicability study | Treatment effect based on intention-to-treat population (Subsections 2.6.1, 3A.3.2) |
| Selected source(s) of data for treatment effect | Alternative available source(s) of data, and/or meta-analysis of data as source of treatment effect (alternative analyses presented in Subsections 2.5 and 2.6) |
| Transformation of a surrogate to a final outcome | Range of alternative plausible values (as derived establishing STFO relationship; Subsection 3A.4.2) |
| Extrapolation of data beyond the trial | Alternative data truncation point(s), alternative choices of parametric model, or alternative assumptions regarding ongoing treatment effect (Subsection 3A.4.3) |
| Pooled within-trial data to estimate utility values (or alternative approach) | Estimates based on individual arms (or the alternative approach; Subsection 3A.5.1) |
| Externally sourced utility values | Alternative values or sources (Subsection 3A.5.1) |

STFO = surrogate to final outcome

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. Parameterise structural assumptions where there is sufficient clinical evidence or expert opinion to do so. Alternatively, use scenario analyses to assess the impact of assumptions around the structure of the economic model. Report the results of each set of plausible structural assumptions.

Describe and justify the inclusion and exclusion of potential scenario analyses when making alternative assumptions about data translation and model structure.

Include an analysis of the impact of the time horizon.

Use other scenario analyses to 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 are expected to have demographic and patient characteristics and circumstances that differ from the target population and circumstances.

3A.9.2 Presentation of univariate sensitivity and scenario analyses

Tabulate all parameter values and assumptions included in the model, and present the results of univariate sensitivity and scenario analyses in a similar format to Table 3A.9.2.

Use a tornado diagram to represent the relative effect of the uncertainty around alternative input parameters on the base-case incremental cost-effectiveness result.

Identify the input parameters and model assumptions to which the incremental cost-effectiveness results are most sensitive.

3A.9.3 Presentation of multivariate and probabilistic sensitivity analyses

Use multivariate sensitivity analyses to 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 present the results. Justify the inclusion and exclusion of parameters in these analyses.

A probabilistic sensitivity analysis (PSA) may be provided in addition to deterministic sensitivity analysis. Although PSA can usefully characterise parameter uncertainty, it cannot address translational or structural uncertainty.

If undertaking a PSA 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. Provide the random seed associated with the presented results to enable replication, and also ensure that the model permits alternative seeds.

If undertaking a PSA 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 PSA (eg a few hours, rather than a few days).

Use cost-effectiveness planes and acceptability curves to present the results of a PSA, as well as the tabulated presentation of the interval estimates for the ICER or the incremental net benefits of the proposed medicine.

3A.9.4 Summary of the uncertainty analysis

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, identifying the key sources of uncertainty. This range may be informed by a formal PSA, 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 of the base-case ICER estimate.

Discuss the likely overall effect of deficiencies in the evidence base on the reported cost-effectiveness of the proposed medicine.

Table 3A.9.2 Results of the sensitivity and scenario analyses characterising the uncertainty around the ICER

| Variable or assumption | Base-case value | Plausible alternative(s) or range of values | Incremental outcomes | Incremental costs | ICER | Description of impact on ICER |
|---|-------------------------|---|-------------------------|-------------------------|-------------------------|-------------------------------|
| Base case | | | [base case] | [base case] | [base case] | |
| Discounting rate | Outcomes and costs = 5% | Outcomes and costs = 3.5% Outcomes and costs = 0% | [alternative estimates] | [alternative estimates] | [alternative estimates] | [describe as required] |
| Plausible range of treatment effect, if modelled as a variable (eg hazard ratio or relative risk) | [add] | [eg upper and lower 95% confidence intervals around estimate] | [alternative estimates] | [alternative estimates] | [alternative estimates] | [describe as required] |
| Altered patient characteristics, if relevant | [add] | [eg different average age, disease or condition severity] | [alternative estimates] | [alternative estimates] | [alternative estimates] | [describe as required] |
| Transition or event probabilities | [add] | [add] | [alternative estimates] | [alternative estimates] | [alternative estimates] | [describe as required] |
| Outcome-related assumptions or variables [Recommended examples: • alternative estimates of the STFO relationship • alternative methods or sources of utility weights] | [add] | [add] | [alternative estimates] | [alternative estimates] | [alternative estimates] | [describe as required] |
| Cost-related assumptions or variables | [add] | [add] | [alternative estimates] | [alternative estimates] | [alternative estimates] | [describe as required] |
| Alternative extrapolation variables or assumptions [Recommended examples: • start point • choice of parametric model • assumption regarding ongoing treatment effect] | [eg maximum follow-up] | [eg median follow-up] | [alternative estimates] | [alternative estimates] | [alternative estimates] | [describe as required] |
| Any other translation assumptions [eg use of intention-to-treat/nonadjusted data] | [add] | [add] | [alternative estimates] | [alternative estimates] | [alternative estimates] | [describe as required] |
| Alternative assumptions regarding model structure | [add] | [add] | [alternative estimates] | [alternative estimates] | [alternative estimates] | [describe as required] |
| Time horizon | [add] | [eg trial based; 5, 10, 20 years, as appropriate] | [alternative estimates] | [alternative estimates] | [alternative estimates] | [describe as required] |
| Plausible alternatives for other variables or assumptions [eg including leakage beyond the requested restriction] | [add] | [add] | [alternative estimates] | [alternative estimates] | [alternative estimates] | [describe as required] |

ICER = incremental cost-effectiveness ratio; STFO = surrogate to final outcome

Section 3B Cost minimisation

This section provides information requests for preparing Section 3 using a cost-minimisation approach (see Section 3, Introduction).

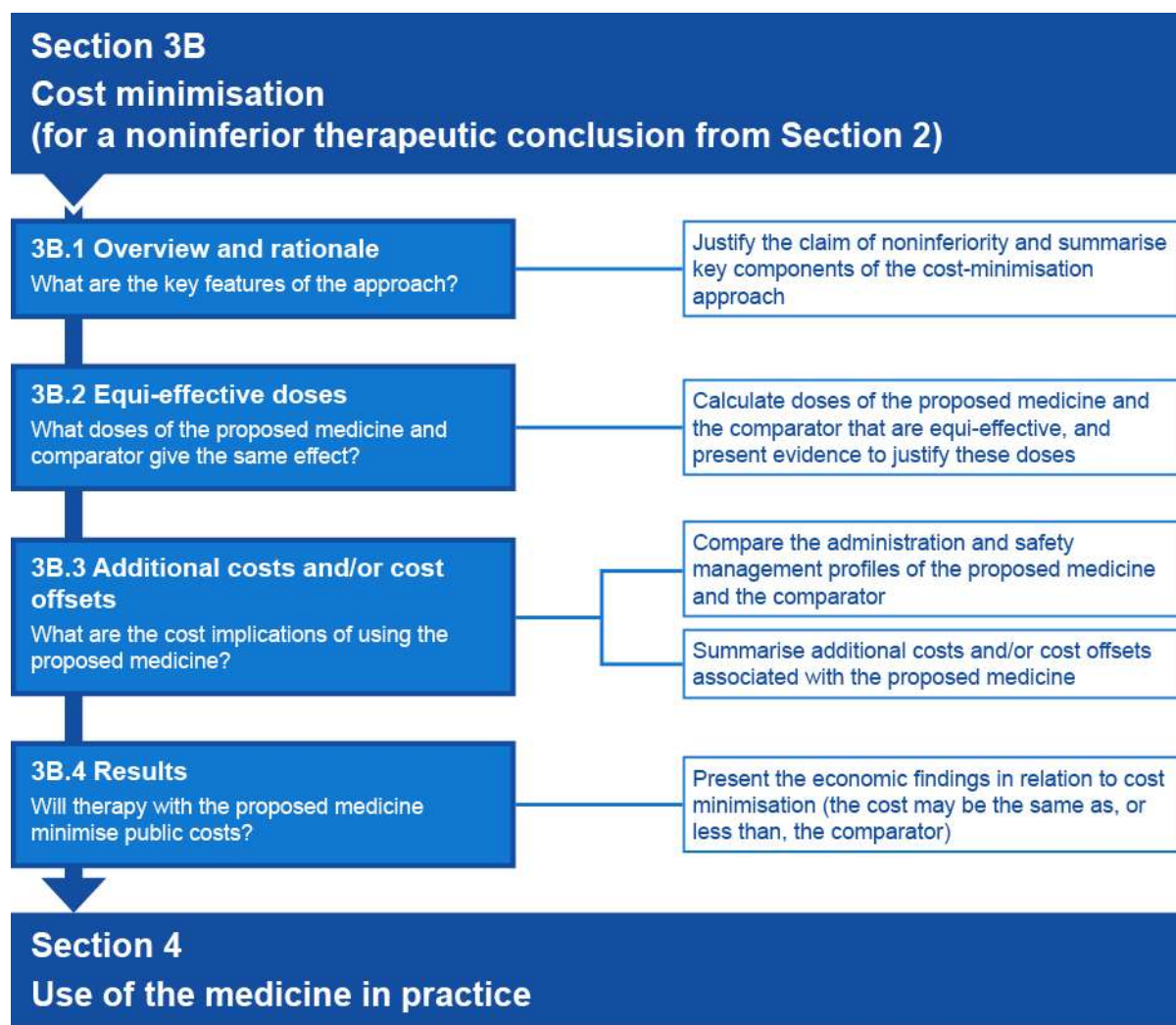
The assumption of noninferiority (or superiority), with respect to both effectiveness and safety, needs to be well justified for the cost-minimisation approach to be accepted. Irrespective of the therapeutic claim, if the adverse effect profiles of a proposed medicine and its main comparator are significantly different in nature, it is unlikely that the cost-minimisation approach will suffice. The implications of these differences, for both health outcomes (ideally, utility) and resource use, should be explored in a full economic evaluation.

The cost-minimisation approach has an abbreviated Section 3, but provide sufficient detail to establish equi-effective doses. Also identify any differences between the proposed medicine and the comparator that are likely to result in a difference in health resource use. This includes identifying differences in:

- the costs of prescribing or administering the medicines
- the costs of monitoring or managing adverse events associated with the medicines
- anything else that may impact health resource use.

Flowchart 3B.1 shows an overview of the cost-minimisation approach.

Flowchart 3B.1 Overview of information requests for Section 3B of a submission to the PBAC based on a cost-minimisation approach



3B.1 Overview and rationale for the cost-minimisation approach

INFORMATION REQUESTS

- Summarise the key components and assumptions of the approach (Subsection 3B.1.1)

3B.1.1 Summary table of cost-minimisation approach

Complete Table 3B.1.1 to summarise the key assumptions and components of the cost-minimisation approach.

Table 3B.1.1 Key assumptions and components of the cost-minimisation approach

| Component | Claim or assumption |
|----------------------------------|---|
| 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) |
| Other costs or cost offsets | [Yes/No] [if yes; brief description – eg adverse effect–related costs, monitoring costs, administration costs] |

3B.2 Estimation of equi-effective doses

INFORMATION REQUESTS

- Calculate equi-effective doses using the best available evidence (Subsection 3B.2.1)

3B.2.1 Equi-effective doses

Identify whether the medicines are intended to be used over a fixed course of treatment or used indefinitely as an ongoing medicine (while indicated).

For medicines set by fixed protocols, compare the total doses required over the entire duration of therapy.

For medicines that are ongoing, the ‘steady state’ dose comparison is generally most relevant. 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, calculate the weighted average dose using the number of participants still on the medicine at steady state as the weighting factor. Generally, it is not justifiable to weight the doses between studies by both the duration of therapy in the study and by the number of participants. Justify the exclusion of any studies not incorporated into the equi-effective dosing calculations.

Where a sponsor does not have access to a study's primary data, present the calculations the way the doses are 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, use the following sources of evidence (presented in order of preference):

- 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 an 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 from prescribing or dispensing data, such as the PBS prescription dataset, rather than using market research data.

Indicate whether these data are consistent with those recommended in each medicine's TGA-approved product information about:

- 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).

3B.3 Additional costs and/or cost offsets

INFORMATION REQUESTS

- Compare the administration profiles of the proposed medicine and the comparator, identify differences, and note if this will result in additional costs or cost offsets (Subsection 3B.3.1)
- Compare the safety management profiles of the proposed medicine and the comparator, identify differences in resource use with monitoring or managing adverse events, and note if this will result in additional costs or cost offsets (Subsection 3B.3.2)

The nature of additional costs and/or cost offsets will differ across submissions. Two common areas for these are costs associated with administration and costs of managing adverse events; however, this does not preclude other possible cost offsets. Justify any other additional costs and/or cost offsets in terms of how they are realisable and/or patient relevant, and show how they differ between the options being considered in the cost-minimisation analysis.

3B.3.1 Comparison of prescribing and administration profiles

Identify differences in the costs of prescribing or administering the medicines.

If the proposed medicine and its main comparator are available in different forms (eg tablets, injections, implants, 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](#)^f for further detail on costing administration-related resource use.

3B.3.2 Comparison of safety and toxicity management profiles

Only use the cost-minimisation approach where the proposed medicine has a safety profile that is superior (preferably) or noninferior to the main comparator.

Identify any differences in the costs of monitoring or managing adverse events associated with the medicines.

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 because of reduced costs of monitoring for, or managing of, adverse reactions. Use clinical trials and the recommendations in the Australian product information 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), present a thorough description of the quantified differences in safety, with a justified estimate of any corresponding resource-use implications.

Where the adverse effect profiles of a proposed medicine and its main comparator are different in nature, a cost-effectiveness or cost-utility analysis is likely to be preferred (Section 3A). However, a cost analysis may be acceptable to quantify a claim that the cost offsets from the reduction in health

^f www.pbs.gov.au/info/industry/useful-resources/manual

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](#)^s for further detail on resource use and costing associated with monitoring and adverse effects.

3B.4 Results

INFORMATION REQUESTS

- Present the results of the cost-minimisation approach (Subsection 3B.4.1)
- Attach copies of relevant papers and original sources of data, and cross-reference from the submission (Subsection 3B.4.2)

3B.4.1 Results of the cost-minimisation approach

List all identified costs associated with both the proposed medicine or the comparator, then aggregate these with the dispensed medicine cost (based on the equi-effective doses) to estimate the net cost difference.

Consult the [PBS Pricing Section](#),^t if necessary, for help in calculating medicine prices (ex-manufacturer and dispensed) from equi-effective doses. The economic claim should 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.

3B.4.2 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 data extracted 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.

^s www.pbs.gov.au/info/industry/useful-resources/manual

^t www.pbs.gov.au/info/contacts/industry#Pricing_enquiries

Section 4 Use of the medicine in practice

Introduction

Section 4 presents a set of budget impact analyses, and provides the most likely extent of use and financial estimates. These analyses are relevant to both the PBAC and the Australian Government. Section 4 is important for estimating 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.

Epidemiological and market-share analyses are the two broad approaches for developing utilisation and financial estimates, 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 if the submission indicates a noninferior therapeutic conclusion in Subsection 2.8.

Justify the approach taken. Demonstrate concordance across both approaches where data inputs from one approach (epidemiological or market share) are uncertain.

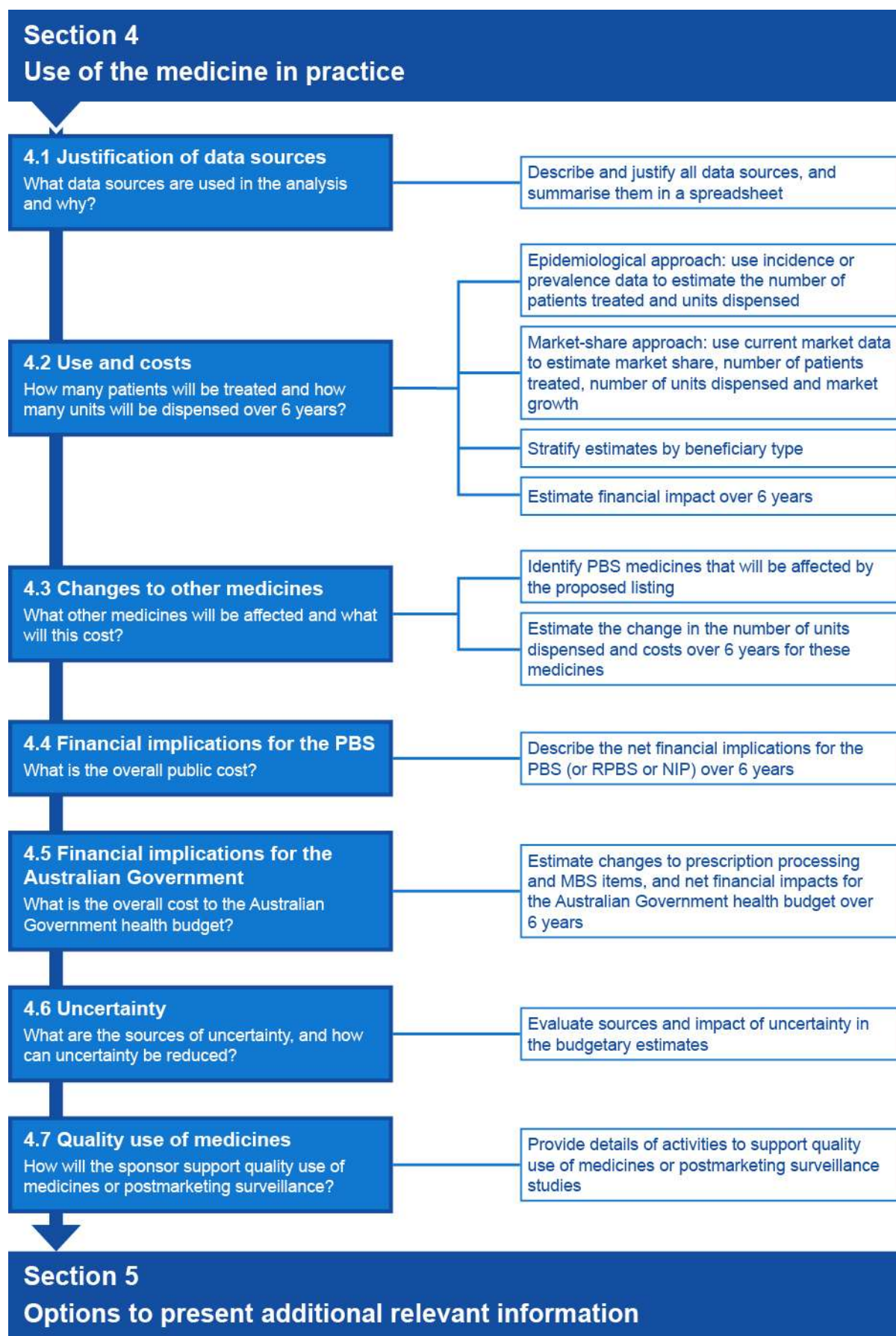
Ensure that any estimates of the extent of use of the medicine (and other medicines and therapies) in the Australian setting are consistent with evidence presented throughout. Ensure that uptake of the medicine, change in the use of alternative medicines and offsets are all consistent with the clinical place of the proposed medicine (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). Explain and justify any discrepancies.

Provide sufficient data in Section 4 so that the steps can be interpreted. Where the calculations used to generate estimates are not transparent in the main body of the submission, present additional data. The standardised Excel workbook for use with the epidemiological approach is available from the 'Downloads' section of the [PBAC Guidelines website](https://pbac.pbs.gov.au).^u

Flowchart 4.1 shows an overview of information requests in Section 4 for both the epidemiological and market-share approaches.

^u <https://pbac.pbs.gov.au>

Flowchart 4.1 Overview of information requests for Section 4 of a submission to the PBAC



Epidemiological approach

An epidemiological approach estimates the number of people with the medical condition, and then estimates the use of the proposed medicine (see Subsection 4.2) and of other medicines (see Subsection 4.3) in the context of the patient group defined by the restriction or the main indication. Subsections 4.2–4.4 request financial analyses of health care resources subsidised through the relevant funding. Subsection 4.5 requests that these analyses be limited 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 copayment from a source other than the identified budget (see the relevant chapter of the [Manual of resource items and their associated costs^v](#)).

The epidemiological approach presented in Section 4 aligns with the utilisation and cost worksheets supplied alongside these guidelines, based on a standardised Excel workbook.

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, aggregated these results across the indications.

Market-share approach

The market-share approach 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. It is likely to be the most suitable approach where a medicine will completely substitute existing PBS-listed medicines.

In contrast with the epidemiological approach, the market-share approach allows an abbreviated presentation of information, where justified by an expectation of no market growth following listing, 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 because 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.

^v www.pbs.gov.au/info/industry/useful-resources/manual

Quality use of medicines

Many factors influence the clinical outcome achieved by an individual after using a medicine. Identifying those factors and addressing them to achieve the quality use of the medicine is an important component of a therapeutic plan, including compliance with any requested restriction. Incorporate quality use of medicines (QUM) initiatives, where possible, throughout the estimates in Section 4. Summarise the activities that will be undertaken to promote QUM in Section 4.7.

Special pricing arrangements

Where a special pricing arrangement has been offered, include spreadsheets (using the supplied template) that show the costs over six years with and without the special pricing arrangement in place. Ensure that any comparators that also have a special pricing arrangement have their costs identified both with and without the special pricing arrangement. Carry the effect of the special pricing arrangement through the entire workbook.

Standardised Excel workbook

An Excel workbook developed for submissions is available at the [PBAC Guidelines website](#),^w to guide sponsors on how to present the utilisation implications and financial implications for the PBS/RPBS, the MBS and Medicare. This workbook enables the PBAC to validate the presented estimates. Create additional spreadsheets to handle complex analyses or provide data to support assumptions, where required.

Ensure that the calculations flow through the spreadsheets, so that changes to any variable flow on to the results. To help understand the spreadsheets, apply clear and unambiguous labels to spreadsheet values, and cross-reference the data source (provide the data sources as an attachment). Provide clear and consistent formulas in the spreadsheets, to facilitate tracing and replicating the calculation flow.

Throughout Section 4, refer to the relevant spreadsheet number (eg Spreadsheet 1 of the standardised Excel workbook for PBAC submissions). Describe the approach, methods, assumptions and potential biases. Where possible, add comments to the Excel workbook to describe these factors, particularly if the approach is complex. Confidence in the estimates is reduced if the interpretation of calculations in the Excel workbook cannot be reconciled with the relevant assumptions or approach.

Copies of the data

To allow independent assessment of the data, attach copies of the data used (published, unpublished and commissioned). Ensure that the responses to Section 4 and the Excel workbook cross-reference 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 for the data request.

^w <https://pbac.pbs.gov.au>

4.1 Justification of the selection of data sources

INFORMATION REQUESTS

- Present and assess available data sources. For commissioned data, describe the information gap that required commissioned analysis (Subsection 4.1.1)
- Summarise background information in the relevant spreadsheet of the Excel workbook (Subsection 4.1.2)

4.1.1 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 data for use in generating utilisation estimates^x](#)).

The main sources of relevant data for the market-share approach are the PBS data, including those supplied by the DHS and data for under-copayment 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 or condition epidemiological data (provide estimates of prevalence or incidence in the population) | <ul style="list-style-type: none"> • Australian case or mortality registers that estimate the incidence or prevalence of a disease or condition • Large, well-designed Australian studies that estimate the incidence or prevalence of a disease or condition • Australian national health surveys that estimate the prevalence of a disease or condition |
| Pharmacoepidemiological data (provide estimates of treated prevalence) | <ul style="list-style-type: none"> • Surveys of the treated prevalence of the disease or condition in Australia • Utilisation databases, including PBS/RPBS data for therapeutically equivalent medicines |
| Market data | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • Medicine usage evaluations • Data requests to registries, epidemiological studies or utilisation studies • Pharmacoepidemiological studies |

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Different sources of data may be required. 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, clearly state that Australian data were not available and discuss the

^x www.pbs.gov.au/info/industry/useful-resources/sources

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

A commissioned study may be used to fill a gap in the data, and may include medicine usage surveys; data from disease or condition registries; or dispensing and medical service claims. Clearly state the original purpose for the collection (eg the data were collected for the primary purpose of understanding treatment choices, or this was an analysis of dispensing claims collected for the primary purpose of administering the PBS). When reporting the results of commissioned data, provide sufficient background and methodological information to adequately interpret the results.

See Appendix 1 for further guidance on presenting commission data from a survey of experts. Provide the method for identifying respondents, the reasons for collecting information, and any potential conflicts of interest of the respondents or the company undertaking the survey. Present the actual questions asked and the range of responses. Where the respondents are experts in treating specific diseases, provide an estimate of the number of patients they treat, what proportion this is of the expected numbers of patients in Australia, and the health area and setting in which the respondents practise (eg public hospital, private hospital, community, regional area, inner urban area).

When analysing administrative data and registries, provide sufficient information about the method used to sample the dataset, the proportion of the affected population included in the dataset, rules for analysis, assumptions used (particularly where elements in the dataset are used as surrogates) and statistical methods (such as censoring or use of propensity scores).

4.1.2 Summary of background information

Summarise the data sources, background information, primary (not calculated) variables and assumptions in the relevant spreadsheet(s) of the Excel workbook.

4.2 Estimation of use and financial impact of the proposed medicine

INFORMATION REQUESTS

- For an epidemiological approach, use the relevant spreadsheets of the Excel workbook to estimate the number of (Subsection 4.2.1):
 - patients with the medical condition targeted by the proposed medicine
 - patients who would be eligible for the requested restriction
 - patients likely to take the proposed medicine
 - units dispensed each year over six years
- For a market-share approach, use the relevant spreadsheet of the Excel workbook to (Subsection 4.2.2):
 - describe the market and estimate the number of units 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 units dispensed each year over six years
 - indicate whether the market or the market growth rate will increase because of listing
- Provide estimates disaggregated according to the PBS and the RPBS, and for beneficiary type (Subsection 4.2.3)
- Estimate the financial impact over six full calendar years for each form and strength of the proposed medicine (Subsection 4.2.4)
- Present special pricing arrangements. Describe any 'caps' on duration of treatment and/or dosage, and any financial impacts with and without this limitation (Subsection 4.2.4)

Justify any estimates of the incidence, prevalence or market growth over six years. Multiple factors may influence growth, and it may not be appropriate to assume linear growth in the estimates, particularly if the proposed medicine is not the first entrant to the market for the specific indication. It is important to base projections on the number of patients, not dispensed packs, wherever possible.

4.2.1 Epidemiological approach

Incidence or prevalence data

For 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 each year.

The choice to use incidence or prevalence data depends on several factors, including the nature of the medical condition, its treatment and the available data. In general, treatments of short duration are best suited to incidence estimates, and long-term treatments (eg for chronic diseases or conditions) may be better suited to prevalence estimates. A combination of prevalence and incidence estimates may be required (eg intermittent treatments for a chronic condition).

Consider the current prevalent patient population in addition to the incident population – for example, a cancer therapy where there are patients receiving best supportive care before the proposed medicine becomes available. Only calculating the incident population would underestimate the likely number of patients treated in the early years of listing.

Detail the impact of any grandfathered use of the proposed medicine when estimating patient numbers.

Estimate the number of patients with the medical condition

Estimate the likely number of patients in the current year and in the six years following listing, using the incidence or prevalence approach, accounting for changes in disease or condition incidence or prevalence trends. If appropriate, present shorter periods (eg monthly or quarterly) in supporting spreadsheets and summarise annually for six years from listing. If using an incidence approach, also estimate the prevalent population (from years before listing) that may add to the treated patient pool in year 1. Justify when the addition of a prevalent population is not required.

If the medical condition has a subjective element in its diagnosis, consider the impact of misdiagnosis for the purposes of rendering patients eligible for treatment with the proposed medicine. Where this is regarded as unlikely because of activities proposed by the sponsor to support QUM, describe these activities in Subsection 4.7.

Estimate the number of patients eligible for the requested restriction

Using the annual numbers of patients with the medical condition for six years, estimate the proportions of patients who would be expected to be eligible for therapy according to each of the proposed restrictions for PBS listing.

Where the proposed restriction contains subjective elements, consider whether patients might be misclassified to be eligible for the proposed medicine. Again, ensure that any proposed QUM activities are described in Subsection 4.7.

Estimate the number of patients likely to take the medicine for the proposed indication

Using the annual numbers of eligible patients, estimate the proportions likely to take the proposed medicine in each of the six years. Ensure that the estimates reflect the rate of uptake of the proposed medicine and include the impact of the use of other medicines. Justify the estimate of uptake and assess variations to this estimate in a sensitivity analysis.

Estimate the units dispensed

The estimate of the units dispensed for each of six years should account for:

- the rate of uptake of the proposed medicine across the six years from listing (described previously)
- the dose, frequency and duration of therapy involving the proposed medicine
- different forms and strengths of the proposed medicine.

Present each of the steps for estimating the units dispensed separately.

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.

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 them. Therefore, disaggregate the estimated utilisation for each of the forms, strengths and maximum quantities.

4.2.2 Market-share approach

Describe the market

To generate estimates of expected utilisation and costs, ensure that the market-share approach relies 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.

Units dispensed for currently listed medicines

Estimate the units dispensed in the most recent 12 months of the relevant PBS market. This estimate should be based on data from the DHS for the currently listed medicines.

Where possible, present the units dispensed **and** the number of patients this represents according to the evidence provided in Section 2. 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, because this is often calculated from patient-level data rather than units dispensed. Consider the impact of wastage, discontinuations and noncompliance when back-calculating the number of patients from units dispensed, or justify when these factors are unlikely to be important. However, if the duration of therapy or the units dispensed per patient per course of treatment is uncertain, do not back-calculate to patients, as it can introduce significant errors into the patient numbers.

Estimate the rate of growth in this market over six years following listing. Base this on historical trends in the market or other influences, but ensure that it is unrelated to the listing of the proposed medicine. Justify 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, present the market share and rate of growth for each item, if required. Disaggregating the estimated growth according to each PBS item 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 according to 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 six 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. Clearly communicate and justify the likely extent of market uptake following listing of the proposed medicine. Ensure that substitution is consistent with the equi-effective dose calculated in Section 3B.2, when presented.

Present the estimate of the rate of substitution for each of the following, if required:

- 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.

Present a table in the submission for overall estimates, if appropriate. Also present a table in the Excel workbook, stratified by individual PBS items, and clearly show the steps for aggregating the

data. Ensure that the proportions of each PBS item and PBS-listed medicine likely to be substituted by the proposed medicine are clear on the spreadsheet.

Estimate the growth of the market after listing

Estimate the units 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 units for each form, strength and duration for the proposed medicine.

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.

Provide references to data of similar circumstances in similar markets, and discuss risks associated with market growth, to increase the certainty of the financial implications of listing the proposed medicine.

4.2.3 Estimates by beneficiary type

For both the epidemiological and market-share approaches, present estimates for the proposed medicine stratified by 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.

Apply the proportions (available from the [DHS website](#)^y) in each beneficiary type for the closest therapy that is currently listed (the main comparator, if it is PBS listed), if appropriate. Present different weights if they are likely to apply.

These estimates may assist in determining the copayment to be removed from the dispensed price for maximum quantity (DPMQ) or the dispensed price for maximum amount (DPMA).

4.2.4 Financial impact over six years

Financial impact disaggregated according to beneficiary type

In most circumstances, apply two sets of unit costs to the estimates stratified by beneficiary type for each of the forms and strengths of the proposed medicine:

- the DPMQ or the DPMA
- the DPMQ or the DPMA with appropriate patient copayments removed. A weighted copayment can be used, but it should distinguish between PBS and RPBS patients. For medicines listed under section 100 Efficient Funding of Chemotherapy, only one copayment is payable per course

^y <https://www.humanservices.gov.au/corporate/statistical-information-and-data/medicare-statistics/pharmaceutical-benefits-schedule-statistics>

of treatment. (Copayments are stated in the Schedule of Pharmaceutical Benefits and are available on the [PBS website](#).^z)

Where these prices do not apply (eg for products to be funded under the National Immunisation Program [NIP]), apply the price to the Australian Government.

For these calculations, use constant prices, make no allowance for inflation and use a zero discount rate. See the [Manual of resource items and their associated costs](#)^{aa} for further guidance.

Overall costs

Present the total estimated financial impact for each of the forms and strengths of the proposed medicine to the PBS and the RPBS, for both the DPMQ or the DPMA, **and** the DPMQ or the DPMA with appropriate patient copayments subtracted.

Calculate the above sets of estimates of units dispensed and costs in the relevant spreadsheet of the standardised Excel workbook.

4.3 Estimation of changes in use and financial impact of other medicines

INFORMATION REQUESTS

- Name the PBS medicines likely to be affected by listing the proposed medicine (Subsection 4.3.1)
- For each affected medicine, estimate the change in the units (of each form and strength) in each year over six years (disaggregated into proportions for the PBS and the RPBS, and by beneficiary type) using the relevant spreadsheet of the Excel workbook (Subsection 4.3.2)
- Estimate the costs of each form and strength of each affected medicine in each year over six years using the relevant spreadsheet of the Excel workbook (Subsection 4.3.3)

4.3.1 Identify PBS medicines likely to be affected

If using a market-share approach, PBS-listed medicines that are likely to be substituted by the proposed medicine will have been identified in Subsection 4.2.2. However, identifying 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.

List all PBS-listed medicines that fall into each of these three categories. Include the PBS-listed medicines identified as comparators in Subsection 1.1 and as other relevant therapies in Subsection 1.2, and disaggregate by form and strength. Where the proposed medicine is replacing a medical procedure or has no comparator medicine, or where patients are receiving best supportive care in the absence of the proposed medicine, there will be no substituted medicines.

^z www.pbs.gov.au/info/healthpro/explanatory-notes/front/fee

^{aa} www.pbs.gov.au/info/industry/useful-resources/manual

If there is 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. 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
- used to treat adverse reactions to substituted medicines
- 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
- used to treat adverse reactions to the proposed medicine.

The impact of adverse reactions might have less weight if the evidence 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. Note 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.

4.3.2 Change in the units dispensed over six years

If using an epidemiological approach, 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 units for each of these medicines over six years. Reference how the estimates were generated and the data on which the estimates are based. Present estimates by beneficiary type, as described in Subsection 4.2.3.

Section 3 may incorporate a change in PBS-listed medicines because of listing the proposed medicine. Justify any inconsistencies between Sections 3 and 4 in terms of the identified medicines or the estimated extent of change of usage over the six years following listing of the proposed medicine.

If using a market-share approach, the change in the units for substituted PBS-listed medicines will represent the market share lost to the proposed medicine. State and justify the proportion of the market gained by the proposed medicine and lost by each substituted PBS-listed medicine in Subsection 4.2. Justify any estimates of a different rate of substitution across different PBS-listed medicines, particularly where there is differential pricing across the PBS-listed medicines.

Estimates disaggregated according to beneficiary type

Base any disaggregation into proportions for the PBS and the RPBS, and by beneficiary type on the most recent 12 months of usage data [from the DHS](#).^{bb} If the expected substitution is for a distinctive subgroup of current use of the substituted medicine(s), base the disaggregation on the subgroup.

Use the relevant spreadsheet of the standardised Excel workbook to calculate the results of this subsection.

4.3.3 Financial impact over six years

Based on estimated utilisation changes, estimate the financial impact in each year over six years for each of the forms and strengths of each medicine substituted, decreased and increased. Refer to Subsection 4.2 for the suggested approach. Present the disaggregated and aggregated costs, applying both the DPMQ or the DPMA, **and** the DPMQ or the DPMA with appropriate patient copayment subtracted, as per Subsection 4.2.

Use the relevant spreadsheet of the standardised Excel workbook to calculate the results of this subsection.

4.4 Estimated financial impact for the PBS/RPBS or the NIP

INFORMATION REQUESTS

- Calculate net financial implications for the PBS/RPBS or the NIP in each year over six years using the relevant spreadsheet of the Excel workbook (Subsection 4.4.1)

4.4.1 Net financial implications

Present the net financial implications for the PBS/RPBS or the NIP over six 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.

For most medicines, this financial estimate uses the DPMQ or the DPMA with appropriate patient copayments removed. For vaccines to be funded under the NIP, the estimate is based on the price to the Australian Government.

Use the relevant spreadsheet of the standardised Excel workbook to calculate net financial implications.

^{bb} <https://www.humanservices.gov.au/corporate/statistical-information-and-data/medicare-statistics/pharmaceutical-benefits-schedule-statistics>

4.5 Estimated financial implications for the health budget

INFORMATION REQUESTS

- Estimate the net change in the number of prescriptions processed by the DHS for payment (and, if appropriate, the net change in the number of authorities by the DHS) for six years using the relevant spreadsheet of the Excel workbook (Subsection 4.5.1)
- Estimate the extent of net change in the number of each type of affected MBS items provided for six years, and the net financial implications for the MBS in each year over six years using the relevant spreadsheet of the Excel workbook (Subsection 4.5.2)
- Estimate net financial implications for the Australian Government health budget for six years using the relevant spreadsheet of the Excel workbook (Subsections 4.5.3)

This section extends the financial analyses presented in Subsection 4.4 for a PBAC recommendation that has financial implications for other parts of the Australian Government's health budget, including the DHS and the MBS. If implications for other components of government health budgets are identified, use the same approach outlined here.

4.5.1 Net prescription processing changes for the DHS

To estimate the numbers of prescriptions processed by the DHS, use the estimates of the dispensed units of the proposed medicine (from Subsection 4.2) and the net changes in the units of other medicines dispensed (from Subsection 4.3). If using a market-share approach, the number of prescriptions estimated in Subsection 4.2 will be entirely offset by that estimated in Subsection 4.3. However, complete this section if there is likely to be growth in the overall market because of listing of the proposed medicine.

Where the proposed medicine or the medicines considered in Subsection 4.3 include medicines with a relevant restriction requiring authorisation by the DHS, estimate the extent of net change in the number of authorisations in each year over six years, taking into account the number of repeats permitted per authorisation. Where applicable, distinguish between authorisations requiring a written application and those requiring a telephone application, and estimate each type separately.

Use the relevant spreadsheet of the standardised Excel workbook to calculate the sets of net financial implications to the DHS.

4.5.2 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.

Perform this analysis for a cost-minimisation approach, if necessary. For example, if any expected increase in the rate of growth in the overall market because of 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 Sections 3 and 4 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 six years of listing. Show the total change in service volumes by MBS item to allow analysis and costing, if necessary.

Apply the costs of MBS items

The appropriate benefit varies depending on the setting for the particular MBS service (see the MBS 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 the relevant spreadsheet of the standardised Excel workbook to calculate the two sets of financial implications (100% schedule fee, and 75% or 85% of the schedule fee based on the treatment setting). Indicate the proportion of public versus private hospital use, and inpatient and outpatient services.

4.5.3 Net implications for the health budget

Identify and justify any other financial implications for the Australian Government health budget. Present the calculations and follow a stepwise approach to:

1. estimate the numbers, in their natural units, of the disaggregated health care resources provided or freed
2. apply the appropriate unit cost(s) to each type of health care resource to estimate the net financial implications for each type
3. aggregate the newly identified financial implications in each year over six years.

Combine PBS and RPBS estimates, using the DPMQ or the DPMA, with the MBS estimates, using the schedule fee. Separately combine financial implications with appropriate copayments removed. Incorporate any other identified financial implications for the Australian Government health budget.

Use the relevant spreadsheet of the standardised Excel workbook to calculate the aggregated sets of net financial implications. If the proposed medicine has a special pricing arrangement, show the net financial implications with and without the special pricing arrangement.

4.6 Identification, estimation and reduction of uncertainty

INFORMATION REQUESTS

- Evaluate sources of uncertainty, and distinguish the type and degree of uncertainty in utilisation and financial estimates (Subsection 4.6.1)
- Describe the direction and magnitude of the impact of uncertainty on the overall estimates (Subsection 4.6.2)
- Estimate the level of the uncertainty and propose ways to reduce it (Subsection 4.6.3)
- Use a separate spreadsheet to calculate the impact of uncertainty, and summarise the results in the relevant spreadsheet of the Excel workbook (Subsection 4.6.4)

4.6.1 Sources of uncertainty

Uncertainty arises when estimating utilisation and financial implications because of the potential for usage that differs from expectations, and usage that extends beyond the restriction.

Address both of these sources of uncertainty and clearly differentiate 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'), minimise the impact of the uncertainty by proposing a risk-sharing arrangement.

Where uncertainty arises because of the risk of inappropriate usage, or usage beyond the restriction, propose measures in Subsection 4.7 that are designed to reduce this risk.

Factors affecting uncertainty

The following subsections list some factors to consider when assessing uncertainties in predicted utilisation patterns and financial implications resulting from listing of a proposed medicine as requested. The lists are not exhaustive; they reflect general factors that have been considered previously by the Drug Utilisation Sub-Committee and the PBAC. Factors may arise from epidemiological data, pharmacoepidemiological data, expert opinion and assumptions used in generating the quantified predictions. Present any of these factors to increase understanding of the uncertainties present in utilisation estimates. It might not be necessary to address any or all of these factors, because the uncertainties might be very small or of little importance to the overall cost to the PBS, so consider how relevant each of the factors might be.

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 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 a positive or negative effect on uptake of the proposed medicine. The effects could emerge at the time the submission is lodged or within six 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, convenience).

- Limited access to designated types of PBS prescribers or to designated diagnostic procedures in a requested restriction might limit uptake and usage.
- The duration of therapy might be longer than expected from the randomised trials, particularly if 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 varying over time from those expected from the randomised trials.
- 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 in the previous subsection 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 consider the following factors:

- 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.
- Prescribers could find it difficult to determine 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), which might result in the misclassification of patients as eligible.
- Patient advocacy groups may have an influence on determination of eligibility by prescribers.

4.6.2 Impact of uncertainty

Address the following factors in any uncertainty consideration:

- 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, provide approximate assessments, if required. Note where the effects of some uncertainties are difficult to quantify. 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.

4.6.3 Reducing uncertainty

Uncertainty can be reduced by using data from multiple sources, if available, which is sometimes 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 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 or condition, determined from a pharmacoepidemiological database, is used as a surrogate for the true prevalence).

Risk-sharing arrangements

Uncertainties, such as about cost-effectiveness, expected usage and overall financial impact, may affect the PBAC's decision. In some instances, the sponsor may propose a risk-sharing arrangement (RSA) to enable access to a proposed medicine, while addressing uncertainties. An RSA is a restriction specifying continuation rules or stopping rules for obtaining subsidised medicine, or a Managed Access Program, or a combination of these two approaches.

RSAs are generally financial- or performance-based financial arrangements. Performance-based RSAs have been described as arrangements that 'involve a plan by which the performance of the medicinal product is tracked in a defined patient population over a specified period of time and the level or continuation of reimbursement is based on the health and economic outcomes achieved'.⁴⁹

RSAs are also established through deeds of agreement between the Australian Government and the sponsor of the medicine. This deed must be in place before the PBS listing date. In the case of a cost-minimisation submission, where the comparator of the medicine has an RSA in place, the sponsor of the new medicine will usually share the same conditions as the existing RSA.

RSAs can address, for example, the following types of uncertainties:

- number of eligible patients
- potential use in non-cost-effective populations
- potential for dose escalation beyond that expected in the submission
- potential for use beyond disease or condition progression, for a longer duration than is cost-effective or in nonresponding patients
- risk of use in combination with, or in addition to, current therapy rather than replacing existing therapies.

Describe the RSA proposed and explain which uncertainties will be addressed through the proposed arrangement. Consult with the officers in the Pharmaceutical Evaluation Branch, Department of Health, while preparing the submission. Refer to [Procedures for listing medicines on the PBS](#).^{cc}

Present the consequences of the RSA on the financial estimates using relevant scenarios under which the RSA would be applied. Ensure that the effect of the RSA is also captured in Section 3.

^{cc} www.pbs.gov.au/info/industry/listing/listing-steps

4.6.4 Summary of calculations

Summarise the results of any calculations (eg sensitivity or scenario analyses), to quantitatively examine the impact of uncertainty, in the relevant spreadsheet of the standardised Excel workbook. Do not include the supporting calculations in that spreadsheet. If additional calculations need to be explained, provide a separate workbook for any analysis other than the base-case (most likely) analysis. The first spreadsheet of the separate workbook should highlight the differences from the base-case workbook.

4.7 Quality use of medicines

INFORMATION REQUESTS

- Describe activities to support QUM related to appropriate uptake of the proposed medicine (Subsection 4.7.1)
- Describe any proposed postmarketing surveillance studies (Subsection 4.7.2)

4.7.1 Activities to support the quality use of medicines

QUM means deciding whether it is appropriate to use a medicine, determining which is the most appropriate medicine and then monitoring the safety and effectiveness of the medicine to ensure that the best possible results are achieved. Identify and discuss possible risks to achieving QUM, and offer solutions to mitigate the possibility of inappropriate or potentially harmful use of the proposed medicine. Where appropriate, present these discussions throughout the submission if the QUM issue is most relevant in a particular section.

Current or future sponsor activities to support QUM may include activities integrated with other QUM service providers. Discuss any of the following activities that are or will be implemented, and cross-reference the uncertainties from Section 4 they are addressing. Justify if any of the following activities are not required:

- educational activities that help to identify patients eligible for treatment, and that are consistent with the proposed restriction (and avoid leakage outside the restriction or indication) and with the therapeutic conclusion in the submission
- activities that ensure the population and circumstances of use in which the proposed medicine is to be used is consistent with the evidence presented in the submission
- activities that minimise the sources of uncertainty identified in estimating uptake and overall usage patterns of the proposed medicine
- activities that minimise misuse of the medicine in eligible patients (eg development and distribution of consumer medicine information, appropriate packaging, appropriate labelling)
- any monitoring or evaluation of practices to ensure that QUM is being achieved
- pathways that allow prescribers, patients or treating staff to report concerns about QUM
- activities that may help to develop behaviours in patients, prescribers or the community that support QUM in general.

When discussing the proposed QUM activities, state when these will be implemented (approximately), and whether such activities will be available to all prescribers, hospitals and patients. Identify and describe any other risks to QUM and methods that are currently being, or are planned to be, used. These activities could reassure both the PBAC and the government that uncertainty about cost-effectiveness and usage within the requested restriction will be minimised.

The [National Strategy for Quality Use of Medicines](#)^{dd} explains QUM in Australia.

4.7.2 Postmarketing surveillance study

Where the efficacy, safety or long-term safety of the medicine is uncertain, propose a postmarketing surveillance 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.

^{dd} www.health.gov.au/internet/main/publishing.nsf/Content/nmp-pdf-natstrateng-cnt.htm

Section 5 Options to present additional relevant information

INFORMATION REQUESTS

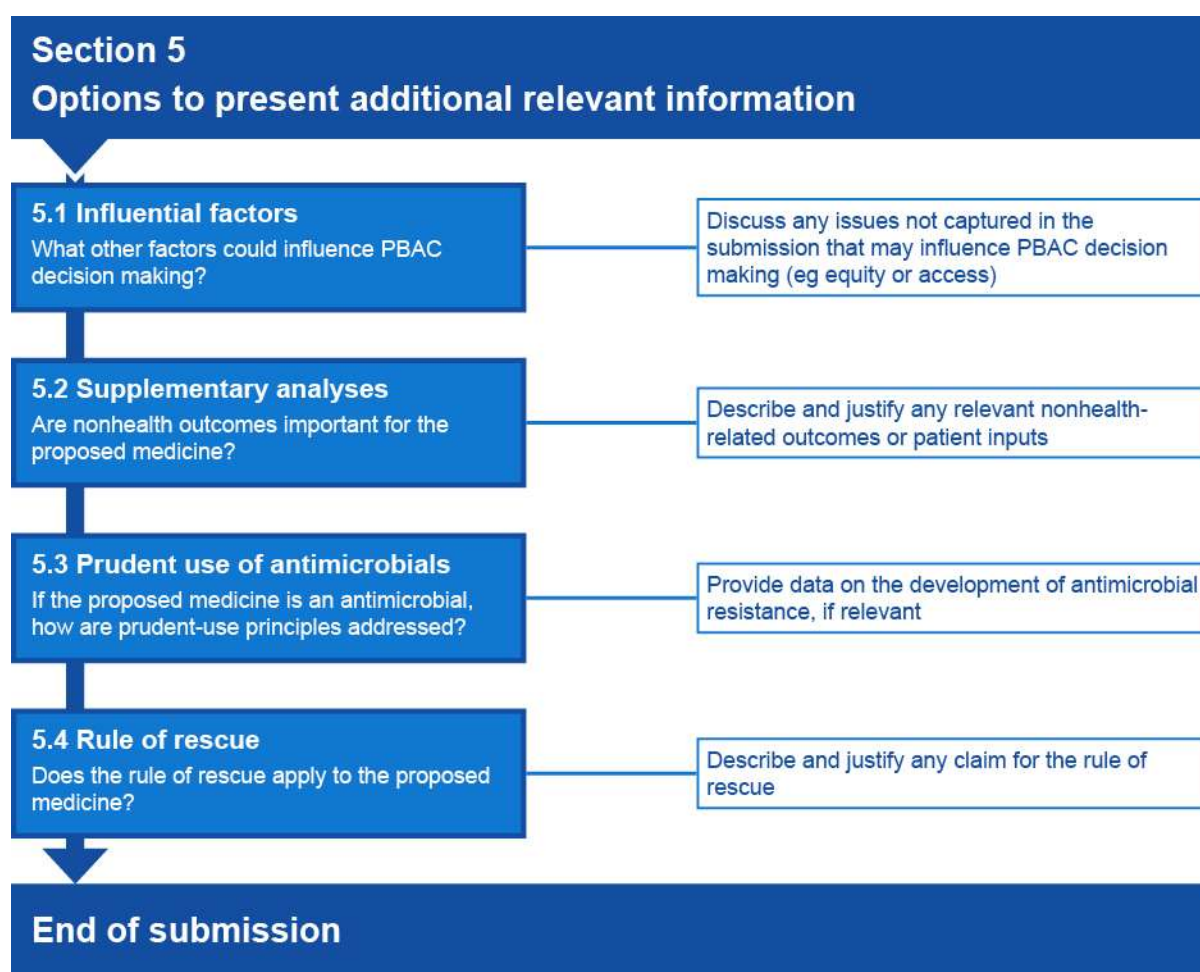
- Provide any additional relevant information, such as:
 - issues influencing decision making (Subsection 5.1)
 - supplementary analyses (Subsection 5.2)
 - prudent-use principles for antimicrobial agents (Subsection 5.3)
 - basis for a claim for the 'rule of rescue' (Subsection 5.4).

Introduction

Although the PBAC primarily focuses on health outcomes, additional factors that may be relevant to the submission can be presented in Section 5. Evidence presented in this section should be clearly presented and reasoned. Where possible, evidence should be generated using high-quality methods or sourced systematically. Inadequately supported claims, or the presentation of evidence prone to bias as a result of the methods of generation or collection, will be difficult to interpret.

Flowchart 5.1 shows an overview of the information requests for Section 5.

Flowchart 5.1 Overview of information requests for Section 5 of a submission to the PBAC



5.1 Issues influencing decision making

If applicable, provide relevant information not captured in the submission that may influence PBAC decision making. Refer to ‘Key factors influencing decision making by the PBAC’ in the introduction to these guidelines. For example, discuss how the proposed medicine might promote (or hinder) patient equity or access.

5.2 Supplementary analyses

For some medicines and/or indications, nonhealth-related outcomes may be relevant to present. When required, clearly present nonhealth-related outcomes and support them with good-quality evidence and sound reasoning.

Where data derived from patient input are provided as supplementary evidence, ensure that they are systematically sourced or generated using high-quality methods. Describe the supplementary evidence so that the uncertainty associated with the evidence is minimised. Interpret and discuss this evidence alongside the clinical and economic evidence presented in Sections 2 and 3.

5.3 Prudent-use principles for antimicrobial agents

Ensure that the submission for a new antimicrobial agent considers the government-endorsed prudent-use principles proposed by the 1999 report of the Joint Expert Advisory Committee on Antibiotic Resistance⁵⁰ and the 'General principles of antimicrobial use' contained in *Therapeutic guidelines: antibiotic*⁵¹ when considering target populations. Provide relevant data about the development of resistance, as appropriate (cross-reference Section 2 if the development or potential development of resistance has been demonstrated to affect health outcomes). Address any issues, and indicate whether any aspect of any restriction requested in response to Subsection 1.4 is designed to minimise the development of resistance.

5.4 Basis for any claim for the 'rule of rescue'

The four factors described below apply in exceptional circumstances and are particularly influential in favour of listing. When all four factors apply concurrently, this is called the 'rule of rescue':

- 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 deliberately kept narrow. Although there are relevant arguments for broadening the guidance, the PBAC is concerned that doing so would reduce the relative influence of the rule of rescue if 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.

Part B – Information requests for specific product types

Product type 1 – Fixed-dose combination products

This subsection applies to a submission for a fixed-dose combination of active component medicines seeking subsidisation under the 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 composite packaging.

Address all the information requests in this section. Explain and justify where an information request is not addressed. Explain, and present evidence for, the value of the fixed-dose combination product compared with 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.

Ensure that the labelling of the combination product clearly identifies the component-generic medicines.

P1.1 Listing fixed-dose combination products

ADDITIONAL INFORMATION REQUESTS

- Comply with all information requests in Part A of these guidelines, where applicable
- Provide additional information for Section 1:
 - the main comparator products (Subsection 1.1)
 - the 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 beneficial effectiveness of the components (Section 2)
- Substantiate other claims, such as:
 - 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 (Section 4)

Requests for information in this subsection are in addition to the requests in the main body of the submission, which should be completed for the combination product.

P1.1.1 Additional information for Section 1

Main comparators (Subsection 1.1)

In the context of the guidance provided in Subsection 1.1, nominate the following main comparators identified in the following comparisons:

- The combination product versus 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 composite packaging).
- The combination product (or its components given concomitantly) versus each of the component products given alone, as the basis for establishing at least an additive beneficial effectiveness.
- The combination product versus the therapy that prescribers would most replace in practice, if 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, or within 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 the 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.

P1.1.2 Additive effectiveness (Section 2)

Demonstrate an additive effect of the combination product using any of the following methods:

- The outcome(s) upon which the components were listed.
- If it is not feasible to measure this outcome, a validated surrogate outcome (eg blood pressure, 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).
- Where the proposed fixed-dose combination product contains medicines for different indications, present evidence for relevant outcomes related to all indications.

P1.1.3 Substantiate other claims (Sections 2 and 3)

To inform a cost-minimisation approach, demonstrate equivalence (or noninferiority) of the combination product to its component medicines. If using a cost-minimisation approach, the pricing

of a combination product would normally be no greater than the sum of its individual components (at the current price to pharmacy 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, ensure that the price to pharmacy reflects 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 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 compared with 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 PBAC to advise the Minister for Health when the committee is satisfied that therapy involving a combination item, compared with alternative therapies, provides one of the following for some patients:

- a significant improvement in patient compliance with the therapy
- 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.

Justify these claims in the submission. Unsupported or inadequately substantiated claims of improved compliance, improved health outcomes or reduced 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, the PBAC evaluates the evidence on the extent of compliance with medicines and the effect on health outcomes when considering therapies to be recommended for subsidy.

This section provides guidance on the approach required for supporting a claim of a significant improvement in compliance for a combination product compared with its comparator. To support this claim, provide evidence:

1. of improved compliance
2. 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 (eg taking a medicine that has been prescribed).⁵²
- Adherence – the extent to which the consumer conforms to the agreed behaviours, with respect to timing, dosage and frequency of medication taking.⁵³

- Persistence – the duration of time from initiation to discontinuation of therapy.⁵³

Approach to support a claim of improved compliance

Address the following to support a claim of improved compliance for the combination product compared with the main comparator:

- Provide information 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 the product used in combination with additional components.
- Where the main comparator is not the components of the combination product, clearly establish this 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 medicine. Relevant sources of information may include:

- a structured literature review or 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.

Estimate the compliance and state the source of information used. 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. Estimate the uncertainty for the data provided.

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 – for example:

- patient or caregiver characteristics or behaviours
- disease or condition 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. State whether the factor predicting compliance is not relevant to the proposed population, proposed use of the medicine or the Australian health care system.

Although factors that affect compliance should be relevant to the use of the proposed medicine, provide some supporting evidence that the factors identified are relevant across other medicines or settings. Explain any difficulties in establishing the effect of certain factors on compliance, where there is not a consistent relationship across alternative scenarios. Relevant sources of information for addressing this 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 using the combination product, compared with its alternative(s), affects the factors contributing to noncompliance in the population of interest. Include a plausible explanation of the link between the use of the combination product and the factors affecting compliance. Support the explanation with published studies, prescriber surveys and/or consumer surveys.

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.

Source evidence of improved compliance from comparative studies of compliance (observational or pragmatic trials) for the combination item compared with alternative therapies. Ensure 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. Compare 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 that the extent of improvement in compliance (previously described) would have an effect on health outcomes. State whether the difference in health outcomes that is likely to occur 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, present the estimate

on PBS expenditure at the currently listed price and 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 compared with alternative therapies, supply information about 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.

P1.1.4 Inappropriate usage (Section 4)

Ensure that any growth in the market that may occur in response to listing the fixed-dose combination product is captured in Section 4. Discuss whether the predicted growth in the market represents an inappropriate increase in overall use of its individual components, or an inappropriate use of one or more of the components in specific patient groups.

P1.1.5 Quality use of medicines (Section 4)

Fixed-dose combination products may have unique QUM issues, such as starting patients on combination drugs without trialling a single agent in the first-line setting (where this is required by the listing), inadvertent duplication of fixed-dose combination product and single agent prescriptions, and patient confusion. Discuss these and other potential QUM issues associated with the proposed listing of the fixed-dose combination product according to the guidance provided in Subsection 4.7.

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 a main comparator for a nutritional product.

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

- Comply with all information requests in Part A of these guidelines, where applicable
- Describe the main comparator(s) (Subsection 1.1)
- Provide additional information for the following medical conditions (Subsection 1.1):
 - multifoed allergy
 - patients requiring products with modified carbohydrate, protein or fat for malabsorption or disorders of metabolism
 - patients requiring ketogenic diets
 - infant formula products, such as a formula used in infants younger than 12 months
- Confirm regulatory compliance with the Australia New Zealand Food Standards Code (Subsection 1.3)
- Provide additional information about the proposed product and its use (Subsection 1.4):
 - a list of all ingredients
 - justification for the requested maximum quantity allowed and repeats
 - macronutrient and micronutrient content per 100 kcal of product and per 100 mg or 100 mL of product
 - 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, including the proposed dilution and scoop size
 - a comparison of the proposed product against the nutritional needs of patients, whether given in conjunction with other foods or not

P2.1.1 Main comparator(s) (Subsection 1.1)

The main comparator for a nutritional product is identified according to guidance in Subsection 1.1.3, and is commonly 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 product(s).

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, use the product in the class that is prescribed on the PBS for the largest number of patients in the appropriate age group as the main comparator. A comparison with a more appropriate form (similar in mechanism of action) that is not necessarily subsidised on the PBS, but is 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), use the product that is prescribed on the PBS to treat that indication for the largest number of patients in the appropriate age group as the main comparator. 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 to make 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, use standard medical management (this could include special dietary restrictions) as the main comparator. This should be clearly and consistently defined in both the submission and the direct randomised trials.

P2.1.2 Specific medical conditions, if applicable (Subsection 1.1)

Multifood allergy

Confirm that the formula of the proposed product will supply the protein, energy, fatty acid, vitamin and mineral requirements for a child younger than two years of age. Note that such a child might consume a limited range and amount of food, and so greater volumes of formula might be necessary than for a child on a normal diet.

Malabsorption or disorders of metabolism

Confirm that the formula of the proposed product, containing modified carbohydrate, protein and/or fat content, will supply the protein, energy, fatty acid, vitamin and mineral requirements for the patient if used as a sole source of nutrition. Identify any additional nutritional needs (eg for catch-up growth, other necessary ingredients to meet nutritional needs).

Patients requiring ketogenic diets

Confirm that the formula of the proposed product will supply the patient's protein, energy, fatty acid, vitamin and mineral requirements if used as a sole source of nutrition. For this to occur, the formula could be multi-ingredient and individually calculated, and a fat source may need to be

added (eg 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, but address the nutritional contribution of the formula in the submission.

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](#),^{ee} 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.

P2.1.3 Regulatory compliance (Subsection 1.3)

The Australia New Zealand Food Standards Code – [Standard 2.9.5: Food for Special Medical Purposes](#)^{ff} sets out the requirements under these standards for foods that have medical purposes. Confirm that these requirements have been met in Subsection 1.3.

P2.1.4 Product and use (Subsection 1.4)

List of ingredients

For nutritional products, provide information about all the ingredients. In the case of products that will be used to treat allergies or food intolerances, include information on the origin of the ingredients.

Provide a table that lists the micronutrient and macronutrient content per 100 kcal, and per 100 g or 100 mL of product.

Maximum quantity and repeats

Justify the requested maximum quantity and repeats for the proposed product, 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 the [Nutrient reference values for Australia and New Zealand](#).^{gg}

^{ee} www.legislation.gov.au/Series/F2008B00658

^{ff} www.legislation.gov.au/Series/F2012L01347

^{gg} www.nhmrc.gov.au/guidelines-publications/n35-n36-n37

Present the nutrient contents 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. Include the following age ranges, as applicable:

- 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 >20 years.

Use the midpoint of the age range. For the non-adult age ranges, compare the nutrient calculations for a child whose weight is on the 50th percentile for weight, using accepted growth charts (eg from the [World Health Organization](#)^{hh} [0–2 years] or the [Centers for Disease Control and Prevention](#)ⁱⁱ [>2 years]). For the adult age range, include pregnancy and lactation tables 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](#).^{jj}

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. Provide the osmolality of the ‘normal’ dilution.

^{hh} www.who.int/childgrowth/standards/en/

ⁱⁱ www.cdc.gov/growthcharts/

^{jj} www.legislation.gov.au/Series/F2008B00658

P2.2 Clinical evaluation (Section 2)

ADDITIONAL INFORMATION REQUEST

- Present trial or study data to support the use of the proposed product in patients (Section 2)

P2.2.1 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.

Provide direct 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 funding under the NIP or listing under the PBS.

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 the disease to be prevented (Subsection 1.1)
- Specify the proposed schedule of administration of the vaccine and any consequential programmatic requirements for administration (Subsections 1.1 and 1.2)
- Define the main comparator(s). Where the defined main comparator is an alternative vaccine, identify differences between the vaccines (Subsection 1.1)
- Provide information about funding, restrictions and catch-up programs (Subsection 1.4)

P3.1.1 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:

- the nature of the immunising agent(s) (eg live, attenuated or killed; absorbed or nonabsorbed; viral or bacterial)
- whether this is a new vaccine for a new condition or an alternative for a vaccine already included in the NIP
- requirements for cold chain management
- the external dimensions of the vaccine packed for storage
- vaccine presentation (eg single vial, prefilled syringe, multidose vial).

See Product type 1 for 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.

P3.1.2 Treatment details (Subsection 1.1)

Specify the proposed schedule of administration of the vaccine, including details of doses, for each of the age or population groups to be used in the context of the NIP, and whether primary immunisation and/or booster vaccinations are requested. Specify any consequential programmatic requirements for administration (eg within and/or beyond current NIP arrangements). Indicate when programmatic requirements are expected to include other delivery systems (which might vary across states and territories), such as clinics, community centres and schools.

Where appropriate, discuss whether a vaccination course that begins with the proposed vaccine can be completed with a competing or alternative vaccine (or vice versa).

Identify and justify any differences from treatment recommendations in the TGA-approved product information or the [Australian immunisation handbook](#)^{kk} (the Handbook). The Handbook is endorsed by the National Health and Medical Research Council, following its preparation by the Australian Technical Advisory Group on Immunisation (ATAGI), and is updated online annually. 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.

P3.1.3 Main comparator (Subsection 1.1)

If an alternative vaccine is available on the NIP or the PBS, or has a positive PBAC recommendation for potential use on the NIP or the PBS, this will usually be the main comparator. If an alternative vaccine is available but not currently funded, seek the advice of the department. If there is currently no vaccine available, the main comparator would usually be standard medical management.

Address different comparators that may be relevant for different age and/or population groups that are proposed to be included on the NIP.

Where the main comparator is an alternative vaccine, present a table to help compare 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, the fit with the current vaccine schedule). If the trials presented in Section 2 involve co-administration or sequential administration of other vaccines, include these in the comparative table.

P3.1.4 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 specifically, a favourable submission for NIP funding considers the following factors:

- The target for the proposed vaccine is the whole population within a specific age cohort or cohorts.

^{kk} www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home

- Selection of the target cohort(s) is based on epidemiology of the vaccine-preventable disease, including consideration of specific risk factors such as age, sex, ethnicity, geography, chronic disease, pregnancy and/or disease-transmission pattern.
- There is a reason to maximise population coverage of the proposed vaccine, because the proposed vaccine results, or is anticipated to result, in indirect (herd immunity) protection of unimmunised individuals by reducing one or more of:
 - the proportion of susceptible individuals
 - carriage of the pathogen(s) targeted by the vaccine
 - transmission of the pathogen(s) (including nosocomial infections, or infections in other institutional settings, such as childcare centres, schools or nursing homes).

Relevant evidence supporting likely herd immunity benefits may include any or all of the following factors:

- The proposed vaccine protects against a new infection/disease and/or reactivation of an existing infectious pathogen to cause disease.
- The efficacy of the proposed vaccine is sufficient to reduce the proportion of susceptible individuals, carriage of the relevant pathogen and/or transmission of the pathogen to susceptible nonimmunised individuals.
- The disease is sufficiently severe or prevalent in an unimmunised population to justify maximising the use of the proposed vaccine to achieve a broader community health benefit.

PBS listing is a less common route for subsidised vaccine provision, but might be appropriate 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 where vaccination relates to a higher disease risk associated with the presence of specific risk factors, for which assessment of eligibility is less straightforward (eg where 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 use of the proposed vaccine to certain populations, seasons, geographical distribution, ethnic groups and/or risk factors (eg medical conditions).

A restriction under the NIP is generally applied to a broad population, and should involve a straightforward assessment of risk factors at an individual level (eg age, sex, ethnicity, geography). Usually, the aim is to enable provision of vaccine to all eligible individuals – for example, an age-based cohort. This occurs 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 may be more appropriate.

Describe any requested PBS restriction or NIP scheduling in relation to the TGA-approved indication and the Handbook, and justify any discrepancies.

Advise on any age limit or circumstances after which there would be no benefit in giving the vaccine.

Catch-up program

If a catch-up program is also requested, define and justify its duration from the start of the overall funding arrangement, and its extent in terms of the additional 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 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).

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.

For both ongoing and catch-up programs, comment on and justify the anticipated vaccine uptake in the proposed cohort(s).

Also justify whether there should be perpetual eligibility for catch-up individuals in cohorts who were eligible for the primary program but did not receive the recommended dose(s) in time. This is particularly relevant if the anticipated on-time uptake for an ongoing cohort is suboptimal in early years.

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 their antigen content and their dosage schedules. A new vaccine program funded under the NIP should take into consideration integration with current programs as much as possible, to maximise coverage and efficient delivery of the overall vaccination schedule. Also address the impact on vaccine efficacy/effectiveness and/or safety arising from co-administration with other vaccines, if relevant.

Relationships with other medications

Explain if there are any additional medicines that are recommended as part of the vaccine administration (eg paracetamol to manage adverse events). If relevant, also outline any additional concerns, precautions and resources or costs associated with the additional treatment.

P3.2 Clinical evaluation (Section 2)

ADDITIONAL INFORMATION REQUESTS

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 (Section 2)

To assess comparative harms:

explain how adverse events were ascertained in the trials (Subsection 2.5)

provide any information on adverse reactions that might have arisen following launch of the proposed vaccine in other markets (Subsection 2.7)

Where the assessment of a vaccine is based on short-term surrogates, discuss long-term outcomes, such as waning of effect and resulting disease, and long-term sequelae.

Discuss any implications of co-administration with other vaccines.

P3.2.1 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, 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.

Subsection 2.4.5 contains guidance for comparing the proposed combination vaccine product with each of its individual components (ie assessing noninferiority). Further guidance on assessing fixed-dose combination products is given in Sections P1.1.1–P1.1.5.

P3.2.2 Superiority claims based on immunogenicity surrogates/correlates

Unless there are internationally accepted standards of measurement, the criteria developed to support any claims of superiority based on immunogenicity surrogates/correlates rather than clinically important outcomes must be prespecified and justified, and their limitations addressed. (See also Subsection 3A.5.)

P3.2.3 Comparative harms and adverse reactions (Subsections 2.5–2.7)

Ensure that the assessment of comparative harms extends 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, disease because of changes in disease epidemiology and individual susceptibility at a population level at a certain time.

Present evidence of the effectiveness of the vaccine for individuals in the primary and catch-up populations.

P3.3 Economic evaluation (Section 3)

ADDITIONAL INFORMATION REQUESTS

- Consider and explain whether herd activity or community activity influence the time horizon of the model. Detail whether the model is static or dynamic, and whether joint analysis is relevant (Subsection 3A.2)
- Define the relevant Australian population(s) for the model (Subsection 3A.3)
- Present a systematic review to support key variables associated with effectiveness, such as waning and the duration of vaccine effectiveness, and any herd immunity implications (Subsection 3A.4)
- Transform immunogenicity outcomes to patient-relevant outcomes. Include any regulatory standards for immunogenicity outcomes that would inform the transformation of these surrogate outcomes (Subsection 3A.4)
- Include additional vaccine program resource use and costs (Subsection 3A.6)
- Ensure that the model validation process has attempted to validate the duration of vaccine effectiveness and any herd immunity assumptions (Subsection 3A.7)
- Include sensitivity analyses of alternative discounting approaches and scenario analyses of potential vaccination catch-up programs (Subsection 3A.9).

P3.3.1 Computational methods and structure for economic models of vaccines (Subsection 3A.2)

Time horizon of the model

Ensure that the duration of a model extends to the point where the estimate of cost-effectiveness is stable. Explain if herd immunity and community activity are involved, and follow a different pattern to other medicines, and ensure the information is well supported.

Present model traces (in Section 3) of the incremental cost-effectiveness ratio and key variables over time, to help assess the impact of varying the time horizon of the model. This may also help to assess the consequences of any waning or limited duration of vaccine effectiveness or herd immunity implications.

Structural assumptions and computational methods

State whether the model is static or dynamic, and justify the approach.

Use a static model when 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).

A static model is appropriate where a small proportion of the population is to be vaccinated, either through low coverage or targeted vaccination, or the proposed vaccine does not prevent circulation of the pathogen, and herd immunity effects are expected to be negligible.

Use a dynamic model when the force of infection depends on the number of infectious individuals in the population at each time point and this number is expected to decline following immunisation. Dynamic models allow herd immunity and age shift to be assessed; use this model when the force of infection is likely to change after vaccination (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.

Joint analysis

A joint analysis includes analysis of changes in costs and outcomes associated with other medicines or vaccines. In this context, a joint analysis may be appropriate across all other affected vaccinations where the proposed vaccine may affect the cost of delivery or the coverage rate across multiple vaccinations. 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.

P3.3.2 Population and circumstances in the model (Subsection 3A.3)

Ensure that the base-case population of the model reflects the primary population proposed for eligibility for the proposed vaccine, accounting for anticipated uptake patterns, if relevant. The population for vaccination would generally be considerably larger than (and not necessarily well reflected by any epidemiological data) the number of patients who acquire the disease.

To assess the evidence on effectiveness, consider the applicability of the baseline risk (population at risk) and the applicability of the disease pattern described by the evidence. Possible sources of epidemiological evidence include routine surveillance data, seroprevalence studies and surveys.

P3.3.3 Transition probabilities and variables (Subsection 3A.4)

Use a systematic basis to support key assumptions and variables relating to vaccine effectiveness, including:

- duration of vaccine effectiveness/waning effectiveness (eg include surveillance studies on the need for booster doses)
- herd immunity assumptions and implications (eg observational studies identifying level of coverage required to obtain some degree of herd immunity).

Present and assess these nonrandomised studies for extrapolation purposes separately.

P3.3.4 Translation of immunogenicity outcomes (Subsection 3A.4)

For the proposed vaccine, translating an immunogenicity outcome from a vaccine trial usually requires two separate analyses:

- 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.
- Identify a limit to the duration of the effect or characterise waning of the effect over time.

Provide relevant regulatory standards for immunogenicity outcomes; however, these may not be sufficient to 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.

P3.3.5 Additional program costs (Subsection 3A.6)

Consider the following resources and costs specifically associated with an immunisation program listing:

- any required amendments to Australian immunisation registers, including the addition of new vaccine types or brands, and potential system changes relating to new or existing vaccine schedule points
- costs associated with delivery/changes to the delivery of the proposed vaccine through clinics, community centres and schools
- initiation or enhancement of a surveillance program for effectiveness and/or safety assessments (which may be requested or advised by ATAGI) as an essential component of funding the proposed vaccine under the NIP; include the costs of the resources for such a program.

Seek the advice of the department, particularly the Immunisation Policy Section, to identify relevant costs to include in the economic model.

P3.3.6 Validating the model (Subsection 3A.7)

The duration of effectiveness of a vaccine before any waning of effect, and the extent of any herd immunity are often particularly important factors in the economic evaluation of vaccines. Cross-reference supporting evidence presented in Section 3A.3 and look for any relevant external data that may provide additional evidence on the patterns of these matters over time. If additional external data incorporating these effects are identified during the validation process, it may be appropriate to recalibrate the model outputs based on such evidence.

P3.3.7 Sensitivity analyses (Subsection 3A.9)

Note that sensitivity analyses using alternative discount rates may be particularly relevant for cost-effectiveness models of vaccines.

Where catch-up programs are requested, present scenario analyses in Subsection 3A.9 to examine the effect on the base case if adding a catch-up program, extending the catch-up population and/or lengthening the duration of the catch-up program.

P3.4 Budgetary implications (Section 4)

ADDITIONAL INFORMATION REQUESTS

- Estimate financial implications using the basis for pricing that applies to the NIP or the PBS, as relevant (Subsection 4.4)
- Estimate extent of use and costs for primary vaccination program. Where the proposed vaccine is to replace an existing product, estimate the extent of use based on data from current estimates of vaccinated cohorts. Where the proposed vaccine is indicated for a new disease, estimate the extent of use based on standard population estimates (Subsection 4.2)
- Estimate extent of use and costs for any catch-up cohorts (Subsection 4.2)
- Estimate administration costs, including delivery through general practice (Subsection 4.5)

P3.4.1 Financial implications for the NIP (Subsection 4.4)

Where NIP funding is sought, estimate the costs presented in Section 4 using the price to the Australian Government that applies to vaccines funded under the NIP. Where PBS listing is sought, use the dispensed price for maximum quantity, with appropriate patient copayments removed, that applies to vaccines listed on the PBS.

P3.4.2 Extent of use and costs for primary vaccination program (Subsection 4.2)

Where NIP funding is sought, estimate wastage and usage beyond the target population. Seek the advice of the department, particularly the Immunisation Policy Section. 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 for information in response to Subsection 4.2 for possible sources of epidemiological evidence.

Specify any new or additional requirements that are likely to have an impact on the financial implications of listing the proposed vaccine.

P3.4.3 Extent of use and costs for any catch-up cohorts (Subsection 4.2)

Consistent with the additional requests for information in response to Subsection 4.2, 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.

P3.4.4 Administration costs (Subsection 4.5)

Estimate any administration costs. Present separately any cost-consequence estimates (which may vary across states and territories) to government budgets beyond the health sector (eg clinics, community centres, schools).

Product type 4 – Codependent technologies

Introduction

This section provides guidance on the preparation of a submission to the PBAC that involves codependent technologies.

What are codependent technologies?

Health technologies are codependent where the patient health outcomes related to the use of one health technology (eg a medicine) are improved by the use of another health technology (eg a pathology test or an imaging technology). The use of the technologies needs to be combined (either sequentially or simultaneously) to achieve or enhance the intended clinical effect of either technology. Therefore, the net clinical benefits of the joint use of the technologies, as distinct from the net clinical benefit of each technology in isolation, needs to be determined for a health technology assessment. The cost-effectiveness and financial implications of the joint use of the technologies are also considered as part of the reimbursement decision.

The most common example of a codependent technology is a medicine-test combination where a new medicine seeking listing on the PBS has a related pathology test that may help to determine the population group eligible for that medicine. The Medical Services Advisory Committee (MSAC) classifies such tests as ‘investigative medical services’.

An investigative medical service can have several purposes,⁵⁴ of which the following are most likely to be relevant to codependent technologies:

- establishing a predisposition or estimating a prognosis
- identifying a patient as suitable for a therapeutic medical service by predicting a variation in the effect of the therapeutic medical service
- measuring an early treatment effect on a surrogate outcome as the basis for predicting the extent of a later treatment effect on more patient-relevant outcomes
- monitoring a patient over time after an initial investigation to guide subsequent treatment decisions if the service needs to be repeated.

To achieve an improvement in health outcomes, the investigative information from the test must result in a change in the management of a subsequent therapeutic service. In this sense, the test can only indirectly improve health outcomes and any improvement also needs to be balanced against any harm that the service might cause. This purpose defines the need for a codependent technology to be assessed.

When is a codependent submission required?

A material codependency requiring a codependent submission arises when the Minister for Health requires advice from two different expert advisory committees because listing of the codependent technologies would involve two separate reimbursement schemes. For example, codependent technologies that require new listings or amendments to both the PBS and the Medicare Benefits Schedule (MBS) would need advice from both the PBAC and MSAC.

There are two different processes by which advice relating to the two reimbursement schemes can be formulated for the minister:

- **integrated codependent submission** – a combined submission for the two technologies is prepared and considered *jointly* by MSAC and the PBAC
- **streamlined codependent submissions** – individual submissions for each of the technologies (one for the test and one for the medicine) are lodged at the same time and are considered by MSAC and the PBAC, respectively, in parallel.

Further details of each process are provided below. Flowchart P4.1 shows the scenarios in which technologies with a material codependency have been considered for reimbursement by MSAC and the PBAC using an integrated or streamlined approach.

Integrated codependent submissions

Integrated submissions involve a submission of a medicine to the PBAC which also involves a codependent test or other investigative service that either:

- is not listed in the MBS; or
- requires a substantial amendment to the MBS to list it as intended, and thus entails joint consideration by both the PBAC and MSAC.

The format outlined in Subsection P4.2 is sufficient to meet the expectations of both the PBAC and MSAC with regard to a submission for PBS listing of the medicine and also a submission-based assessment for the MBS listing of the codependent pathology test or other investigative service.

In particular, lodge an integrated codependent submission when:

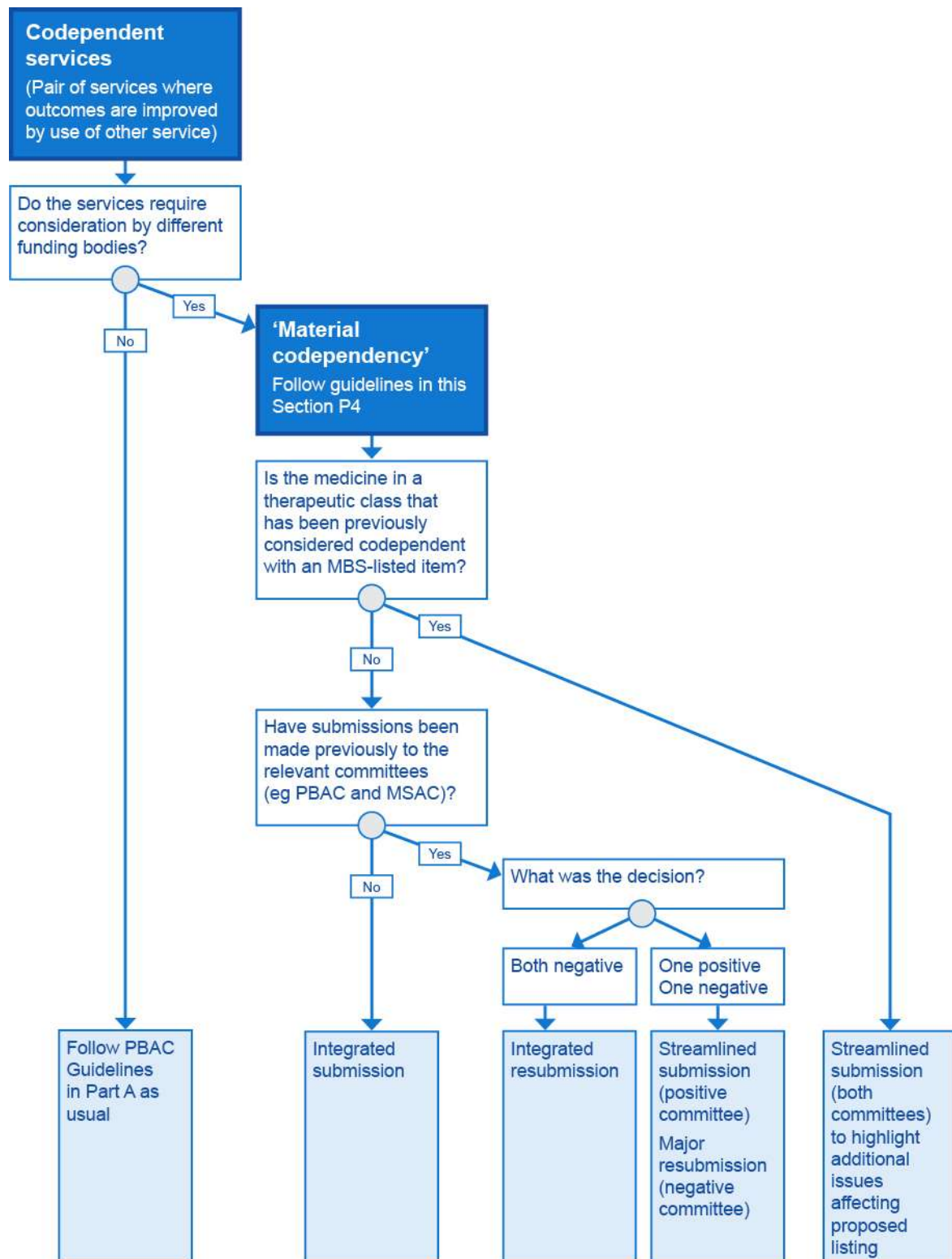
- the test and the medicine require a listing on the MBS and the PBS, respectively, and neither technology has been considered previously by either committee (MSAC or the PBAC)
- an integrated codependent resubmission is needed (ie both committees have indicated they are not satisfied with the information in the previous submission)
- the medicine is of a different therapeutic class to one that has been previously considered to be codependent with the MBS-listed companion test.

Streamlined codependent submissions

Codependent technologies can be efficiently *reconsidered* when, after previous consideration, only one committee has foreshadowed support for a technology in the pairing. For example, if MSAC has foreshadowed support for a codependent test or other investigative service, the lodgment of a resubmission to the PBAC may occur separately but in parallel to the lodgment of a streamlined resubmission to MSAC to ensure that MSAC's advice is expeditiously aligned with the circumstances of any PBAC recommendation for the codependent medicine. Similarly, if an MBS item descriptor for a test or other investigative service needs minor amendment to accommodate access to a codependent medicine in the same therapeutic class as one that has been previously PBS listed, then a streamlined codependent submission to amend this item descriptor may be lodged with MSAC alongside the submission to the PBAC for the codependent medicine.

Flowchart P4.1

Classification of integrated and streamlined codependent submissions



MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; PBAC = Pharmaceutical Benefits Advisory Committee

Note: In the situation where the medicine is listed but the test is not, a material codependency does not exist because the decision to list the test falls to MSAC alone.

P4.1 Overview of information requested in codependent submissions

As already indicated, the amount of information to include in a codependent submission is contingent on any previous MSAC and PBAC consideration of public funding of the test and/or the medicine for the specific clinical condition under review.

Types of evidence

The approach to presenting evidence in an integrated codependent submission will differ according to whether direct evidence or linked evidence is available (see Figure P4.2 and Subsection P4.2 in Section 2 – Clinical evaluation).

Direct evidence

‘Direct evidence’ describes studies that compare groups of people receiving either the currently used diagnostic test/test strategy or the proposed diagnostic test/test strategy and measures the differential impact of the diagnostic method on patient health outcomes. If patients are randomised to receive the test, then biomarker status would be known and, on that basis, subsequent targeted therapy or usual care could be decided. If patients are randomised to not having the test, then a treatment would be received that is not targeted by the biomarker result.

Linked evidence

The ‘linked-evidence approach’ was proposed by MSAC whereby evidence of test accuracy comparing the proposed and current test/test strategy could be linked (if considered to be appropriately transferable) to separately sourced evidence of treatment effectiveness to approximate the likely clinical effectiveness of the proposed test/test strategy.

For example, this might involve linking evidence of the test’s performance (eg diagnostic accuracy) with evidence demonstrating that the test result changes the medicines or treatment prescribed, and with evidence that the alternative medicines have different effectiveness and safety profiles.

Integrated codependent submissions

If lodging an initial integrated codependent submission, consider addressing all the items outlined in Subsection P4.2. If lodging an integrated codependent *resubmission*, pay particular attention to the issues raised by both committees in deciding not to support the proposed codependent technologies.

The key to the evaluation of codependent technologies is to establish the basis of the codependency claim.⁵⁵ Make the relationship between the test for the biomarker (investigative medical service) and the medicine explicit, particularly whether it is based on treatment effect modification and/or a prognostic effect. An integrated codependent submission must demonstrate that the medicine interacts with the biomarker that is identified by the test to improve patient health outcomes. That is, there must be an improved treatment effect because the medicine targets either an intrinsic property of the biomarker, or a physiological process for which the biomarker is a proxy.⁵⁵

If the codependent technologies have evidence of both a background prognostic effect (tied to a specific biomarker) and treatment effect modification, present the net treatment effect (ie treatment effect modification controlling or adjusting for the background prognostic effect) in the submission.

Where a new codependent test and medicine targeting an as yet unproven biomarker are submitted for reimbursement, complete all information items in Subsection P4.2.

When a new biomarker(s) is proposed as part of a group of biomarkers in a submission, the aim is to gauge whether the addition of this new biomarker(s), when targeted by the medicine, results in further improvements in patient health outcomes. For a submission of this type, focus on the multiple biomarkers identified by a single test (rather than sequential testing). It is probable that the committees will have already addressed a codependent relationship between at least one of the biomarkers and the medicine and, in the interim, knowledge has advanced on how biomarkers work together to interact with the medicine. This scenario could encompass the possibility of a new or currently listed medicine, as well as a new or currently listed test. In this situation, all the items in Subsection P4.2 need to be addressed. Also seek advice from the Pharmaceutical Evaluation Branch on how to address these types of codependent technologies.

The preferred structure for an integrated codependent submission is given in Figures P4.2–P4.4. This is an adaptation of the preferred structure for submissions to the PBAC for medicines outlined in these guidelines.

Figure P4.2 Preferred structure of an integrated codependent submission for Section 1

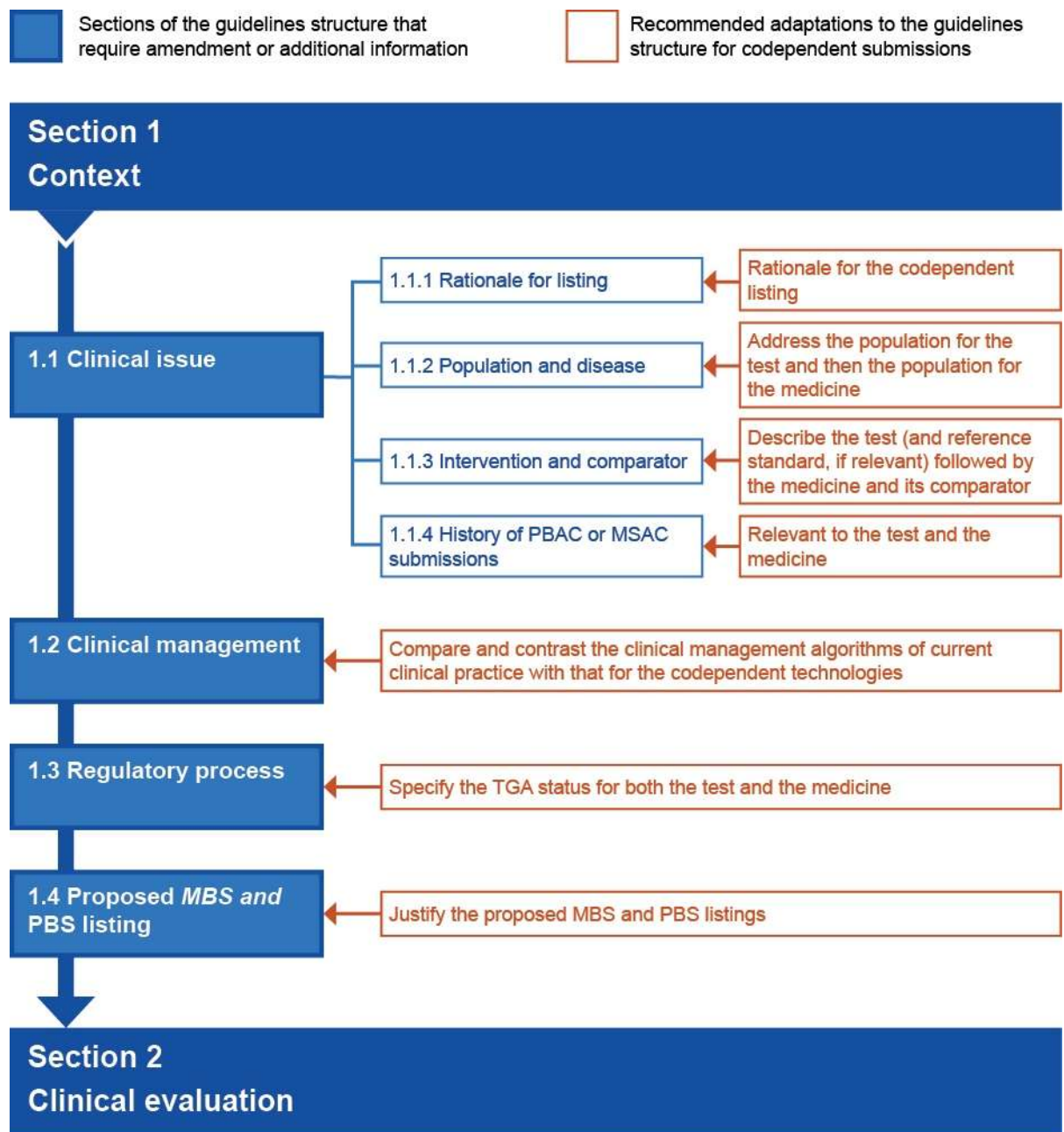
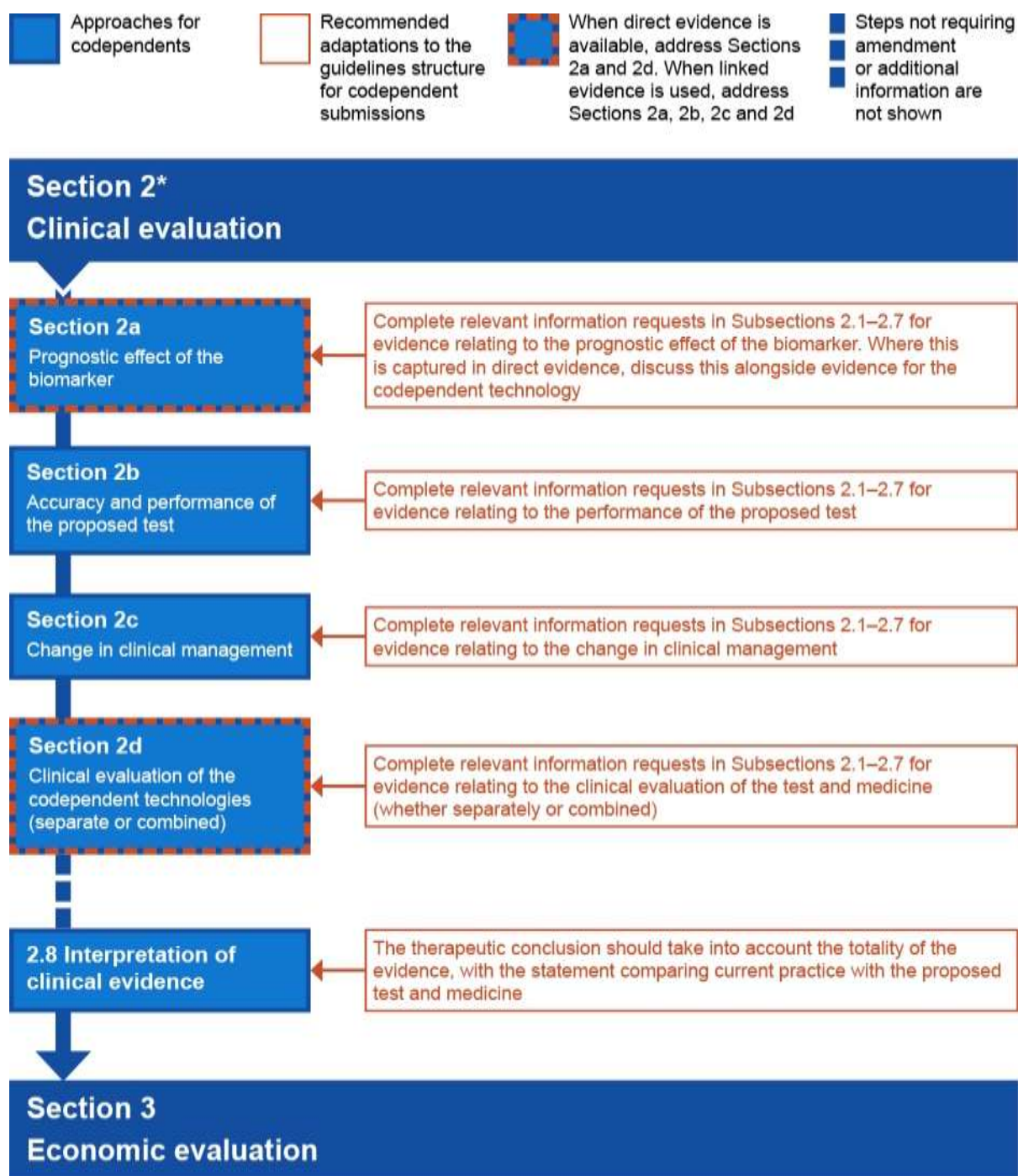
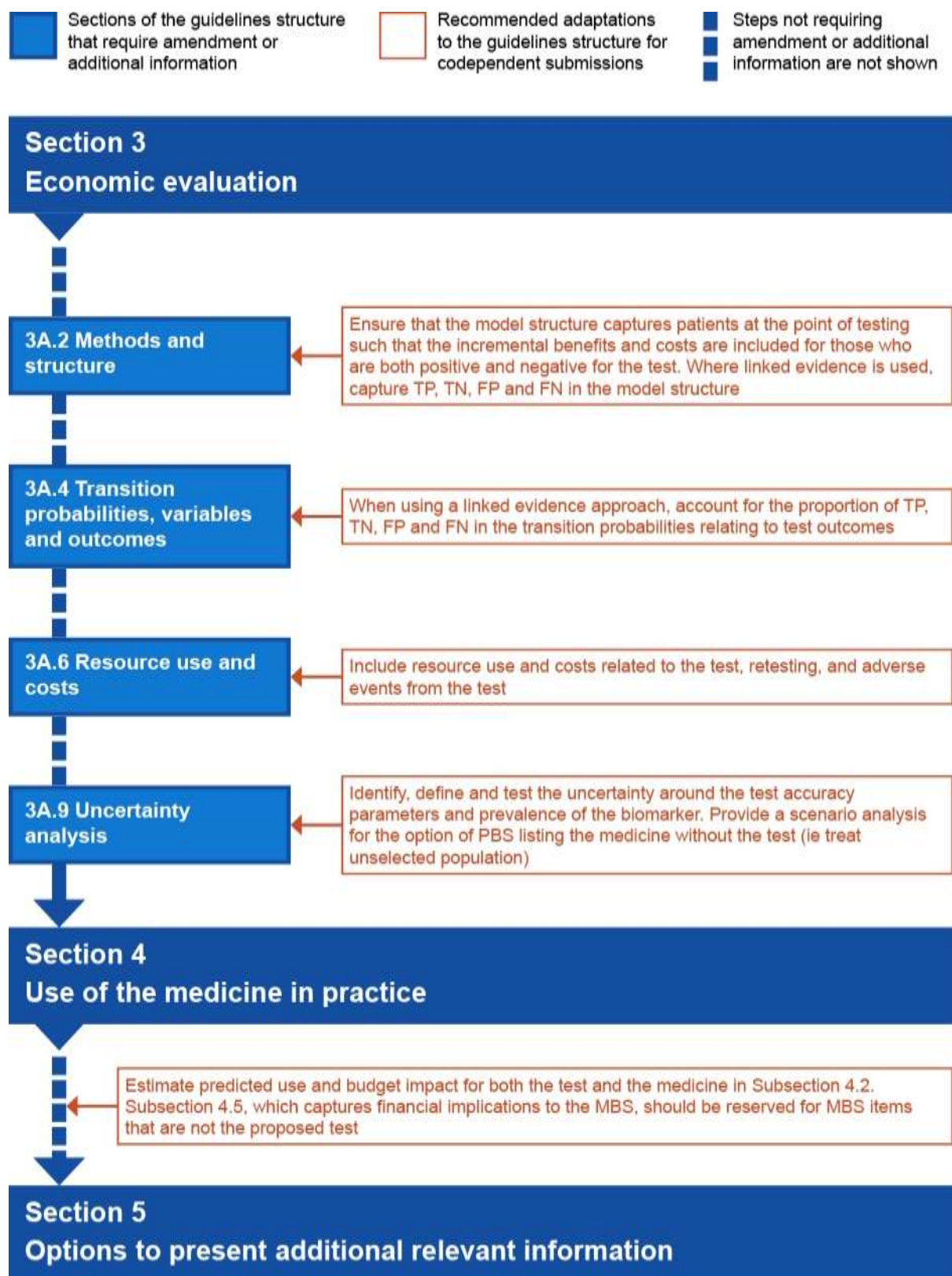


Figure P4.3 Preferred structure of an integrated codependent submission for Section 2



* The approach taken in Section 2 will depend on the available evidence. Perform a literature search to find direct evidence (of current practice vs the proposed test/medicine). Where this is not available, perform a literature review for each of Sections 2a, 2b, 2c and 2d.

Figure P4.4 Preferred structure of an integrated codependent submission for Sections 3 and 4



FN = false negative; FP = false positive; TN = true negative; TP = true positive

Streamlined codependent submissions

The principle of streamlined codependent submissions is to ensure that the substantive submission to seek the advice of one committee is coordinated with a less substantive submission to the other committee which has already signalled some support for the other codependent technology. In practice so far, the substantive submissions have had to be lodged with the PBAC, and streamlined submissions have been needed to ensure timely alignment of MSAC advice in the event of a PBAC recommendation.

Most experience has occurred where the PBAC has decided to defer or not to recommend a codependent medicine. In this circumstance, the purpose of the resubmission to the PBAC is to address the issues raised by the PBAC in reaching this outcome. There is also experience in the situation where the proposed medicine is in the same therapeutic class as a PBS-listed medicine, and listing is sought for essentially the same population, including with reference to patient eligibility being informed by biomarker test results. In this circumstance, the submission to the PBAC should address the items in Subsection P4.2 to the extent that is relevant, especially in relation to determining the individuals for inclusion in the proposed PBS restriction, in the submitted clinical evidence, and in the estimates of cost-effectiveness and financial implications.

Where a resubmission is being made to the PBAC, address the following matters in the streamlined resubmission to MSAC:

- a request to create or amend the MBS item for the proposed investigational medical service corresponding to the proposed medicine
- proposed wording for the MBS item descriptor (which should reflect the requested PBS restriction and the existing MBS item and/or the previous MSAC advice relevant to the proposed investigative medical service)
- a proposed MBS fee
- the costs to the MBS of the proposed listing (which should reflect the corresponding costs in the submission to the PBAC)
- a summary of the previous MSAC advice relevant to the proposed investigational medical service, and either
 - confirming that the applicant agrees with each aspect of the advice (including, where appropriate, indicating how it has followed it in the submission to the PBAC and/or MSAC); or
 - indicating where the applicant disagrees with any particular aspect of the advice, providing reasons (and an assessment of the consequences of adopting the applicant's alternative approach rather than MSAC's advice).

Where a submission is being made for a proposed medicine that is in the same therapeutic class as a PBS-listed medicine, and listing is sought for essentially the same population, including with reference to patient eligibility being informed by biomarker test results, address the first four of the matters listed above in the streamlined resubmission to MSAC. Also provide a detailed description of the testing strategy used in the trials presented in the submission to the PBAC, and the testing strategy for the corresponding trial of the comparator medicine – so that MSAC can assess any differences between these 'evidentiary standards'.

P4.2 Specific codependent technology information requests

Subsection P4.2 contains 62 item numbers (information requests) intended to meet the evidence requirements of the PBAC and MSAC when assessing codependent technologies for aligned reimbursement decisions. These items are accompanied by additional clarification on what is meant by the information request, as well as where it would be appropriate to present the information throughout the integrated codependent submission.

Item numbers are tagged with (T), (M) or (O), which indicate whether the item number is relevant to the test, the medicine or overlaps both. This flags the information that is primarily relevant to MSAC (T), the PBAC (M) and both committees (O).

Since listing circumstances will vary between the codependent technologies, the information needed to reduce decision-maker uncertainty will also vary. Follow the guidance given in Part A, Sections 1–5, about the medicine for all integrated codependent submissions. In addition, new items and/or expanded information are requested to address specific codependency issues. These are organised here by the main sections of a submission (ie Sections 1–5). Refer to Subsection P4.1 for an overview of which codependency information items apply to an integrated or streamlined submission, and to Figure P4.2 for how the submission should be structured.

Section 1 – Context

The following information requests are relevant to Part A, Section 1, of a submission to the PBAC.

Details about the biomarker, the test and the medicine

ADDITIONAL INFORMATION REQUESTS

- 1 (O) Describe current reimbursement arrangements for the test and the medicine
- 2 (T) Identify the sponsor of the test
- 3 (M) Identify the sponsor of the medicine
- 4 (O) Describe the biomarker
- 5 (T) Describe the proposed test
- 6 (O) Describe the medical condition or problem being managed
- 7 (O) Describe the relevant clinical management pathways

1 (O) *Current reimbursement arrangements*

Include in Subsection 1.4

Indicate whether the proposed biomarker(s) has been previously accepted as valid by MSAC and the PBAC for the proposed clinical indication (eg validated using another test). Describe current reimbursement arrangements for the test and the medicine.

The response to this item defines whether the submission is integrated or streamlined (see Subsection P4.1).

2 (T) Test sponsor

Include in Subsection 1.1.1 or 1.1.3

Identify the source(s) of the test options (eg commercial sponsor, research laboratory, National Association of Testing Authorities [NATA]-accredited pathology provider, pathology practice). This includes clinical sponsors of tests, given that tests guide both the initiation and cessation of therapy. If a specific test (eg the evidentiary standard; see Item 5) is not specified, this item is not needed.

3 (M) Medicine sponsor

Include in Subsection 1.1.1 or 1.1.3

Identify the sponsor of the medicine. This enables a different sponsor to be identified, if necessary, for each component of the codependent technology.

4 (O) Biomarker

Include in Subsection 1.1.2

Describe the biomarker in a way that is consistent with the proposed MBS item descriptor and to enable differentiation from other possible biomarkers. Additional detail can be provided at Item 8.

The most common type of integrated codependent submission has involved pharmacogenetic technologies assessing genetic DNA biomarkers whereby one genetic locus at a time is evaluated. However, codependent technologies that include genetic panel testing or genomic testing (ie assessment across the genome, testing hundreds or thousands of loci simultaneously) can also be submitted.

5 (T) Proposed test(s)

Include in Subsections 1.1 and 1.4

First describe the evidentiary standard test method (ie the test used in the key evidence supporting the requested listing). Include sufficient detail for a laboratory technician to be able to perform it. If more than one test is proposed or available, then specify the range of techniques used to measure the biomarker (eg polymerase chain reaction, high-resolution melting), and indicate which method, if any, is regarded as the reference or 'gold standard' test.

List the other available test options that fall within the scope of the proposed MBS item descriptor. If other test options are available in Australia, or the evidentiary standard test is not available in Australia, then provide a comparison of all available tests for the biomarker that fall within the scope of the requested MBS item descriptor.

Include the proposed MBS item descriptor by modifying Subsection 1.4 to 'Proposed MBS and PBS listing'.

6 (O) Medical condition or problem being managed

Include in Subsection 1.1.2

Describe the population proposed for testing for the biomarker in terms of what previous tests have been undertaken or what clinical signs are present. Describe whether the proposed population has been enriched in terms of biomarker prevalence.

Issues to consider when judging the value of adopting any enrichment or triaging strategy include:

- the quantified effect on the Australian prevalence of being test positive (and hence on the number of patients who would need to be tested to target treatment)
- the confidence in the clinical diagnosis being able to identify likely patients with the biomarker and to minimise erroneous inclusions and exclusions from the patient pool selected as eligible for the test
- the consequences of misallocation of treatment due to false positive or false negative test results brought about by these erroneous inclusions and exclusions, which can vary across clinical settings – for example, between first-line therapy (where there are effective alternative treatments) and last-line therapy (where there are not)
- the amount of tissue needed to make multiple types of diagnosis when tumour tissue is limited (eg via fine needle aspirate biopsy) and so the need for larger tumour samples or re-sampling has implications for harm to patients and costs to the health care system
- whether the clinical diagnosis itself might also modify the treatment effect, independent of the testing strategy (eg the effect of the proposed medicine might vary according to histology type, in addition to biomarker status).

If different test result thresholds are likely to determine eligibility for the medicine, or if eligibility for the medicine is determined subjectively, consider providing alternative requested PBS listings in Subsection 1.4.

7 (O) Clinical management pathways

Include in Subsection 1.2

Describe and compare the proposed clinical management of a typical patient up to the point of being offered the proposed test and subsequent therapy with the proposed medicine, as compared with the currently existing clinical pathway(s) where the proposed test and/or medicine is not available.

Ensure that the clinical management pathways outline all alternative tests/test strategies (whether the tests occur in series or concurrently) and all alternative treatments (including nonmedicine treatments) for the target clinical indication, both with and without knowledge of the patient's biomarker status.

Identify tests and treatments that are commonly used and likely to be supplemented or replaced by the codependent technologies (see Item 14).

If it is important for patients with a rapidly progressive disease or condition to ensure that a timely test result is available to determine eligibility for the medicine, indicate whether the test is likely to be performed earlier in disease or condition progression than currently (also see Item 12).

The nomination of when to test compared with when to treat can be influenced by many factors, including:

- the urgency of knowing the test result to inform the start of medicine therapy
- the costs of block retrieval and costs (and patient harms) of obtaining new samples
- the confidence that the sample or previously obtained test result represents the status of the patient at the time of deciding which treatment to start (eg the stability of a mutation over time or in response to previous treatment, or between the primary tumour and metastatic disease)

- the clinical and cost-effectiveness consequences of misallocation of treatment due to false positive or false negative conclusions based on changes in mutation status.

A 'no testing' pathway and dealing with data scarcity

To demonstrate the test's impact on patient health outcomes, indicate a pathway where testing for the biomarker is not undertaken. Then estimate the effectiveness (and cost-effectiveness) of the medicine using the economic model both with and without use of the test (see Item 37). This approach is requested because it may be more cost-effective to provide the medicine without the test if the test has poor accuracy and/or the medical condition is prevalent.

Because data are often scarce, the aim of codependent technology evaluation is to maximise the use of the available evidence on the two technologies. If the effect of the medicine in the total population is being estimated and data are not available on the biomarker negative population, it may be sufficient to use data/transition probabilities associated with the total population (ie biomarker positive and negative) if the prevalence of the biomarker is low in the total population and if sensitivity analyses are conducted to vary the estimates/inputs within a plausible range.

If the prevalence of the biomarker is high in the total population, it will be important to test whether it would be more cost-effective to deliver the medicine without use of the test. If the 'biomarker negative' arm is receiving usual care, then an effect that was consistent with treatment effects before the introduction of the new medicine would be expected. When the new medicine is replacing usual care and there are no data on the biomarker negative population, or in the event that there is a fairly even distribution of the biomarker negative and positive in the total population, then collect and extract data on false positive patients (ie true negatives with incorrect test result) to determine response to therapy in the alternative condition (biomarker negative group).

Rationale for the codependency

ADDITIONAL INFORMATION REQUESTS

- 8 (O) Define the biomarker**
- 9 (O) Provide a biological rationale for targeting the proposed biomarker with the proposed medicine**
- 10 (O) Define any other biomarker(s) that modify the comparative treatment effect of the medicine**
- 11 (O) Define the prevalence of the condition being targeted in the population that is likely to receive the test**

8 (O) Definition of the biomarker(s)

Include in Subsections 1.1.2 or 1.1.3, and 5.3

Describe the nature of the biomarker (eg single nucleotide polymorphisms, mutation, copy number variation).

Where relevant, include the following elements describing the context for the biomarker:

- the disease or condition
- the specific function of the biomarker
- the critical parameters which define when and how the biomarker should be identified.

If the biomarker is a specific genetic mutation, describe exactly what the test is identifying (eg an expression microarray of tumour tissue that identifies a cancer that can be inhibited by activating a particular pathway). Categorise any mutation biomarker as germline or somatic, or both. If a mutation biomarker is classified as germline, then consider issues related to heritability in Subsection 5.2 (eg testing of relatives and genetic counselling, ethical and medico-legal implications of testing).

Issues to be considered when judging the optimal definition of the biomarker include the following:

- the patient and cost consequences of different sampling needs to support different test options when it is difficult to obtain sufficient material to test for the biomarker (eg tumour samples)
- the prevalence of the different types of mutations in the disease or condition identified, noting that the evidence is likely to be greater for common mutations compared with rare mutations
- the frequency and predictive consequences of multiple mutations in a single sample (eg tumour heterogeneity and mosaicism), or indeed the impact of mutations in genes other than those nominated that may influence the effectiveness of the proposed medicine
- the evidence of impact on health outcomes for each type of mutation, either directly (eg if it is included in the evidentiary standard definition and ideally shows treatment effect modification), or from in vitro studies, or by inference (eg if there is a biologically plausible basis to differentiate among different types of mutations, such as activating or inactivating mutations, or mutations that predict resistance, sensitivity or neutrality to the medicine effect)
- the clinical and cost-effectiveness consequences of misallocation of treatment because of false positive or false negative results based on these conclusions.

9 (O) Biological rationale for targeting that biomarker(s)

Include in Subsection 1.1

Present the initial evidence that was used to select the biomarker for targeting with the proposed medicine. Describe and explain the overall approach to the selection of the biomarker, including methods and relevant aspects of study design and statistical analysis. Describe the rationale for selection of the population sample studied in the biomarker qualification.

Where the biomarker is genetic, present the criteria used for selecting candidate genes (eg candidate by position or by function, based on expression profiling data). Justify, using molecular biological or pharmacological principles, the plausibility of treatment effect modification (ie interaction) between the biomarker itself and the medicine, or, alternatively, between the medicine and another factor for which the biomarker is a proxy. Advise whether this biological rationale preceded the data collection underpinning the key evidence.

10 (O) Other biomarker(s) that modify the comparative treatment effect of the medicine

Include in Subsections 1.1 and 5.3

If testing for any other biomarkers is already reimbursed for targeted treatment with the medicine for the same condition, consider these codependent technologies in the choice of comparator.

If another biomarker is a genetic mutation, then:

- provide details on the specific mutation and the nature of the mutation
- explain whether the treatment effect in patients with this other mutation is consistent with the effect under consideration.

Note: This item may be relevant even if these other biomarker(s) are claimed but a test for the biomarker is not yet reimbursed.

11 (O) Prevalence of the condition being targeted in the population that is likely to receive the test

Include in Subsections 1.1 and 3A.4

Estimate the prevalence of the condition being targeted as measured by the true positive biomarker; this is relevant to calculate the performance of a test in terms of its negative and positive predictive value.

Indicate in Subsection 1.1 whether there is a 'gold standard' or reference standard test to determine whether a patient is true positive for the biomarker. Provide evidence to estimate the prevalence of the biomarker in an Australian population.

In the absence of an accepted reference standard test to correctly identify biomarker status, use an alternative appropriate methodology to estimate the prevalence (eg adjudication by a third test or sensitivity analyses of the prevalence of the biomarker given different assumptions).

The denominator for the prevalence calculation (the source population) is the number of patients considered eligible for the test according to the proposed MBS item descriptor. The source population consists of patients in the clinical pathway up to the point of being offered the test or the medicine in the absence of the test.

Proposed impact of codependent technologies on current clinical practice

ADDITIONAL INFORMATION REQUESTS

- 12 (T)** State whether the proposed test results are expected to be consistent over time, including over the course of the disease or condition
- 13 (T)** Indicate whether the proposed test could be used with other treatments and/or for other purposes
- 14 (T)** State whether the proposed test is additional to another test(s) currently defining the condition, or a replacement test, or both (ie depending on the test result, replace some tests or be additional to other tests)
- 15 (T)** Describe how the proposed test will be offered in Australia
- 16 (T)** Identify the biospecimen or sample needed for the test, and whether this specimen needs to be collected specifically for the test or has already been collected for another purpose
- 17 (T)** Describe the need for subsequent testing to monitor the development of new somatic mutations and/or to guide dosage or cessation of therapy with the codependent medicine (if relevant)
- 18 (O)** Indicate whether the proposed medicine can be used with other specific tests for that biomarker, other than the test proposed. Describe the available methods for testing for the biomarker

12 (T) Consistency of the test results over time

Include in Subsections 1.1 and 1.2

Where test results for a patient may change over time (eg between a primary tumour and subsequent metastases in cancer), provide sufficient detail to clarify the relationship and timeframes between test results and the appropriateness of treatment.

For example, rat sarcoma viral oncogene homolog testing of the primary colorectal cancer tumour is usually representative of the findings in metastases, regardless of therapy. In another example, epidermal growth factor receptor results change with, for example, exposure to radiotherapy, so the results of testing the primary tumour may not be representative of what is happening in non-small cell lung cancer metastases.

13 (T) Use of the proposed test with other treatments and/or for other purposes

Discuss in Subsections 1.2 and 4.2

If other treatments or purposes are relevant, consider whether their use is currently reimbursed or whether there is the possibility of leakage. Refer to the clinical management pathways provided in response to Item 7.

14 (T) Use of the test in the clinical management pathway

Include in Subsections 1.2, 3A.6, 4.2 and 4.5

Refer to the clinical management pathways provided in response to Item 7. The test is most likely to be an additional test, although occasionally, if the biomarker is a strong predictor, it could replace another test in the pathway.

15 (T) Provision of the test in Australia

Include in Subsections 1.2 and 1.3

Indicate whether the test is likely to be widely accessible or available in a few selected laboratories across the country. Explain how the test would be undertaken in practice, and what impact it would have on the patient and health professionals (Subsection 1.2).

Specify the TGA status of the proposed test options (if relevant). Assess access and quality assurance issues. Identify how many laboratories offering the test have NATA accreditation for that test (Subsection 1.3).

16 (T) Specimen or sample collection

Include in Subsection 1.1 (plus Subsections 2.5, 2.6, 2.7, 3A.6, 4.2 and 5.1 if a new specimen needs to be collected)

Identify the biospecimen or sample needed for the test – for example, blood, tumour material (formalin-fixed paraffin embedded [FFPE] or fresh), bone marrow, cytology specimen or mouth swab.

Identify whether this specimen needs to be collected specifically for the test or has already been collected for another purpose. For example, tumour already removed can be tested if archival FFPE is available and the test can identify the biomarker from this tissue.

If a new specimen needs to be collected, specify the costs (Subsections 3A.6 and 4.2), risks (Subsections 2.5–2.7) and feasibility of collecting the sample (Subsection 5.1). In some instances, such as a blood sample, the costs and risks would be trivial. In other instances, such as when a new biopsy is required, there may be significant costs as well as safety risks for the patient.

17 (T) Use of the test for monitoring purposes (if relevant)

Include in Sections 1.1–1.4, 3A.4 and 4.2

If relevant, describe the need for subsequent testing to monitor the development of new somatic mutations and/or to guide dosage or cessation of therapy with the codependent medicine.

This will impact on the clinical need for the proposed test (discuss in Subsections 1.1–1.4), as well as associated transition probabilities (Subsection 3A.4) and costs (Subsections 3A.6 and 4.2). If a new biopsy is required, cross-reference to Item 16.

18 (O) Availability of other tests for the biomarker

Include in Subsection 1.1 (if other tests are publicly funded) or Subsection 5.1 (if other tests are not publicly funded)

Indicate whether the proposed medicine can be used with other specific tests for that biomarker, other than the test proposed. Describe the available methods for testing for the biomarker.

If other tests are publicly funded to identify the biomarker, amalgamate this item with Item 10. If other tests are available or are emerging but are not yet publicly funded, address this item in Subsection 5.1.

Section 2 – Clinical evaluation

The following section contains information requests for establishing the clinical benefit of the codependent technologies in terms of patient health outcomes.

An integrated codependent submission may need to present more than one Section 2 to support the proposed listing of the medicine and the test. The extent of information requested is discussed in Subsection P4.1, and will be further contingent upon the availability of direct evidence or the need to use linked evidence. An overview is shown in Figure P4.2.

The following general approach to presenting a submission may be appropriate:

Approach based on direct evidence

- Section 2a – prognostic effect of the biomarker
- Section 2d – clinical evaluation of the codependent technologies (evidence of combined use)

and/or

Approach based on linked evidence

- Section 2a – prognostic effect of the biomarker
- Section 2b – performance and accuracy of the proposed test
- Section 2c – change in clinical management
- Section 2d – clinical evaluation of the codependent technologies (separate)

Each Section 2 should follow the steps presented in Part A of these guidelines.

Direct evidence approach

ADDITIONAL INFORMATION REQUESTS: DIRECT EVIDENCE

- 19 (0) Determine whether the biomarker test can predict differences in patient health outcomes irrespective of the clinical management provided
- 20 (0) Indicate whether the search for direct evidence was comprehensive and whether the selection process was unbiased
- 21 (0) Assess bias, confounding and the impact of chance on the findings presented in the direct evidence

Section 2a Evidence of prognostic effect of the biomarker

19 (0) Prognostic effect of the biomarker

Include in Section 2

Determine whether the biomarker test can predict differences in patient health outcomes irrespective of the clinical management provided.

It is important to discriminate the background prognostic effect of biomarker status from the impact of any treatment effect modification associated with the biomarker. This requires a comparison of outcomes in patients receiving usual care conditioned on the presence or absence of the biomarker.

Use the approach described in Section 2 to systematically review the evidence of the presence or absence of a prognostic effect of the biomarker, as identified by the proposed test. Searching the literature for prognostic information is typically more complex than searching for intervention (treatment) studies. For example, literature searches would not be limited to randomised controlled trials. Advice from an information specialist is recommended.

Section 2d Clinical evaluation of the codependent technologies (combined)

Most of the information needed for this section is already covered by the information requests in Part A of the PBAC Guidelines. Additional requests are given below.

When 'direct evidence' is available this should be presented in the submission. Direct evidence can include the following trial designs (illustrations of the different trial designs are provided in Merlin et al,⁵⁵ supplemental data 1 file):

- **Double-randomised controlled trial:** A trial that randomises patients to use of the test or not, then randomises to use of the medicine or its main comparator, and then follows patients to measure the effect of the treatment on clinical (health) outcomes.
- **Single-randomised controlled trial of test:** A trial that randomises patients to use of the test or not, and then follows patients to measure the effect of targeted treatment with the new medicine on clinical (health) outcomes.
- **Prospective biomarker-stratified design:** A trial that prospectively tests eligible patients, then randomises those that are test positive or negative to use of the medicine or its main comparator, and then follows participants to measure the effect of treatment on clinical (health) outcomes. The 'no test' or 'alternative test' arm is not included in this biomarker-stratified design.
- **Retrospective biomarker-stratified design:** A trial that randomises eligible patients to use of the medicine or its main comparator, then follows participants to measure the effect of treatment on clinical (health) outcomes, and then analyses results across subgroups of patients defined by

whether they are positive for the test (or biomarker) or whether they are negative to the test (or biomarker).

The design of a double-randomised controlled trial can be used as a template within which the available direct clinical evidence can be hypothetically mapped (see Merlin et al,⁵⁵ supplemental data 2 file). Identify areas where information is missing in the economic modelling in Section 3.

For example, given that a single-randomised controlled trial of a test does not provide information on the test (biomarker)-medicine relationship (ie evidence that the biomarker is a treatment effect modifier and/or has a prognostic effect), consider supplementing this evidence with information from prospective and/or retrospective biomarker-stratified study designs.

As prospective and retrospective biomarker-stratified study designs are without a 'no testing' trial arm (ie to determine biomarker status), the impact of false positive and false negative test findings cannot be determined from the reported patient health outcomes. Consider providing supplementary information from the linked-evidence approach described below, so that a comparison of the proposed test/test strategy and existing test/test strategy can be made with respect to their relative diagnostic accuracy or test performance.

Retrospective biomarker-stratified study designs may use archival tissue/sampling to determine biomarker status. Exercise caution when interpreting results from these studies, because biomarker status might change over time, particularly if there is evidence that an intervening treatment may modify the biomarker result.

20 (O) Selection of the direct evidence

Include in Subsections 2.1 and 2.2

Indicate whether the search for direct evidence was comprehensive and whether the selection process was unbiased. Present a systematic review of direct evidence (study designs given above) concerning the proposed biomarker test and the proposed medicine, with prespecified inclusion/exclusion criteria and study selection outlined in a PRISMA flowchart¹ (ie indicating how trials were selected and the reasons why any potentially relevant trials were excluded).

21 (O) Quality of the direct evidence

Include in Subsections 2.3 and 2.6

Assess bias, confounding and the impact of chance on the findings presented in the direct evidence. Give particular attention to the impact of selection bias and confounding with respect to any subgroup analyses. For example, were the subgroup analyses prespecified (involving stratified randomisation) and was blinding maintained? Was the subgroup analysis exploratory (eg determined on the basis of retrospectively obtained samples)? Were the results adjusted for potential confounders?

Linked-evidence approach

ADDITIONAL INFORMATION REQUESTS: LINKED EVIDENCE

- 22 (T) Describe the analytical performance of the proposed test
- 23 (T) Define the reference standard or a gold standard against which the performance of the proposed test will be measured
- 24 (T) Indicate whether the search for evidence on the diagnostic accuracy or predictive accuracy of the proposed test was comprehensive, and whether the evidence selection process was unbiased
- 25 (T) Indicate whether the evidence reporting on the diagnostic accuracy or predictive accuracy of the proposed test is (i) of good quality and (ii) applicable to the requested MBS target population
- 26 (T) Report on the performance of the proposed test in terms of its diagnostic accuracy or predictive accuracy. If several tests are proposed or no specific test is specified, indicate which test has the best performance. If test accuracy cannot be determined, calculate agreement or concordance between tests
- 27 (T) Indicate which test is the most accessible/available/used. (Only relevant if several tests are proposed or no specific test is specified)

A full linked-evidence approach is only meaningful when the evidence for the proposed test and the evidence for the proposed medicine have been generated in similar patient populations, and so it is clinically sensible to link the two datasets. If the test identifies patients earlier or with a different spectrum of disease than the patients in whom the medicine has been trialled, then it is not clinically sensible to link this evidence. In this circumstance, present direct evidence of the impact of biomarker testing on patient health outcomes.

Section 2b Test performance and accuracy

22 (T) Analytical test performance

Include alongside Subsection 2.5

Analytical test performance assesses how accurately and how consistently the test identifies biomarker status (eg the coefficient of variation and other appropriate statistics). Present any differences across laboratories in how they characterise test results (eg a kappa statistic or other concordance statistic). Identify whether there is an external quality assurance program by which laboratories can benchmark their assays, and whether the test is performed and interpreted accurately and reliably. An assessment of the analytic validity of the evidentiary standard test, relative to other existing test options, would be helpful for decision making.

23 (T) Reference standard or a gold standard for test performance

Include in Subsection 1.1

Define the reference standard or a gold standard against which the performance of the proposed test will be measured. Provide evidence that the reference standard is considered to be accurate and is an appropriate benchmark. (This is not needed if the reference standard has already been identified and ratified by the Protocol Advisory Sub-committee [PASC].)

Note: The reference standard is not necessarily the same as the relevant comparator for the codependent test. The comparator is the current test/test strategy being used in the absence of the proposed test; this may be different to the benchmark (reference standard) test for determining test

accuracy. For example, a reference standard for a new genetic test might be Sanger sequencing, but the comparator for the new genetic test might be a high-resolution melting method.

Also note that the comparator for the test is different to the comparator for the medicine.

Test accuracy

In the instance where a reference standard is available

If a reference standard is available, test performance is determined using diagnostic accuracy measures (eg using a cross-sectional study design). Compare the proposed test to the designated reference standard by cross-classifying the test results of patients who are representative of the intended population receiving the test. The proposed test will be referred to as the 'evidentiary standard' if it is the test used in the key evidence presented in the submission.

Use the reference standard designated by the PASC, or select and justify the choice of a reference standard if this has not been previously specified by the PASC.

In the instance where no reference standard is available

If no reference standard is available, test performance can be determined using predictive accuracy (eg using a longitudinal study design, with the clinical outcome providing the benchmark for identifying whether the patient does or does not have the condition).

If a reference standard is not available or is unacceptable for the requested use and/or the requested population, consider the various options for dealing with imperfect or missing reference standards in the guidance provided by Reitsma et al.⁵⁶ If the guidance by Reitsma et al is not followed, justify the approach used.

Note that if sensitivity and specificity of the proposed test are to be estimated using a composite/constructed standard, the new reference standard should be developed independently from the analysis of results of the proposed test (ideally, in advance of collecting any specimens). Consult with statisticians and health professionals before constructing the reference standard.

If measures of concordance or agreement (positive per cent agreement and negative per cent agreement) are calculated instead of measures of test performance, ensure that the terms 'sensitivity' and 'specificity' are not used, as these estimates are not of test accuracy but of agreement between the proposed test with the nonreference standard.⁵⁷

24 (T) Selection of the evidence on test accuracy

Include in Subsections 2.1 and 2.2

Indicate whether the search for evidence on the diagnostic accuracy or predictive accuracy of the proposed test was comprehensive and whether the evidence selection process was unbiased.

For example, systematically review test performance studies for the proposed test (evidentiary standard) with prespecified inclusion/exclusion criteria and a PRISMA flowchart.¹ Indicate how test performance studies were selected and the reasons why any potentially relevant studies were excluded.

Note that literature searching for test performance studies will need to be more exhaustive than for treatment trials, because indexing and filtering of these studies is less reliable in bibliographic

databases. Suggestions for identifying test accuracy studies in literature searches is given in Chapter 7 of the *Cochrane handbook for systematic reviews of diagnostic test accuracy*.⁵⁸

25 (T) Quality of the test accuracy studies

Include in Subsection 2.3

Indicate whether the evidence reporting on the diagnostic accuracy or predictive accuracy of the proposed test is of good quality and applicable to the requested MBS target population.

This can be done using a [QUADAS-2 assessment](#)^{ll} for each test accuracy study in terms of risk of bias and applicability for use in Australia on the domains of patient selection, index test, reference standard, and flow and timing.⁵⁹ Display the results as a table or graph. Note that QUADAS-2 is a critical appraisal tool, whereas tools like STARD and the ACCE framework are used for reporting test accuracy studies and genetic test interventions, respectively.

26 (T) Performance of the proposed test

Include in modified version of Subsection 2.5

Report on the diagnostic accuracy or predictive accuracy of the proposed test. If several tests are proposed or no specific test is specified, indicate which of the tests has the best performance. If test accuracy cannot be determined, calculate agreement or concordance between tests.

Diagnostic accuracy or predictive accuracy

Provide test performance measures such as sensitivity, specificity, likelihood ratios, positive and negative predictive values, or area under the receiver-operator characteristic curve. Ensure that test failure (invalid results) for either test is documented (proportion of failures), but do not include these results in the test accuracy estimates.

Summarise (if a meta-analysis is performed) test accuracy measures and approaches, as appropriate to the available evidence base. Consider the presence of heterogeneity and/or test threshold effects. Various methods are described by Takwoingi et al.⁶⁰

When interpreting the results of the studies, prioritise assessing the trade-offs in false positive and false negative test findings. For example, consider whether there is a clinically accepted test performance level below which a new test should not be used (ie either false positives are too great or false negatives are too great) for the intended purpose.

The main issues to consider are that:

- false negatives are of greater concern when the clinical setting of the proposed medicine is as last line with best supportive care as its comparator
- false positives are of greater concern when the proposed medicine is being compared with effective alternatives.

If the reference standard being used to determine test accuracy is imperfect, and it is therefore unclear whether the false positives or false negatives ascertained using the codependent test are actually true positives and true negatives, provide evidence of the clinical (health) outcomes of those patients found to be false positive or false negative and report these under the 'Direct evidence' section, if possible.

^{ll} www.bristol.ac.uk/social-community-medicine/projects/quadas/quadas-2

The positive predictive value and negative predictive value should also be calculated, since these data are key to the calculation of transition probabilities in Subsection 3A.4.

Calculate estimates of sensitivity and specificity, adjusted to correct for any (verification or partial verification) bias that may have been introduced by not using the reference standard to its fullest extent (ie to verify all the results obtained with the new test).⁵⁶

Agreement or concordance

If agreement data are provided, rather than test accuracy data, measures such as positive predictive value and negative predictive value (used in Section 3) cannot be calculated since the subjects' condition (as determined by a reference standard) is unknown. In this situation, report the 2 × 2 table of results, comparing the candidate test with the nonreference standard test, and report the agreement measures along with their confidence intervals or kappa statistics. Alternatively, odds ratios could be reported indicating the likelihood of an outcome, given that particular test result.

27 (T) Test availability

Include in Subsection 5.1

Consider which test is the most accessible/available/used. (Only relevant if several tests are proposed or no specific test is specified.)

Where testing is both complex and uncommon, there are important quality and pathology laboratory performance considerations that need to be addressed – for example, biospecimens may need to be shipped to a small number of high-throughput pathology laboratories.

Where biospecimens are relatively transportable, it may not always be an access advantage to bring the test closer to the patient.

Section 2c Change in clinical management

ADDITIONAL INFORMATION REQUESTS: LINKED EVIDENCE

- 28 (O) Substantiate whether knowledge of the test result will cause a change in the management of the patient by the treating clinician. Identify instances where management would not change, despite the test indicating that the biomarker is present**

28 (O) Change in management of the patient because of knowledge of test result

Include in Subsections 2.1–2.5

Substantiate whether knowledge of the test result will cause a change in the management of the patient by the treating clinician. Identify instances where management would not change, despite the test indicating that the biomarker is present.

There may be 'leakage' issues identified through an assessment of the 'change in management' part of the linked evidence. Often a test is done to rule out use of a medicine (eg to avoid potential medicine-related adverse events or the development of resistance), but the medicine is given anyway, or, alternatively, the test is used to select a specific medicine, but the medicine is not provided. Since codependent tests are used to guide therapeutic decisions, explicitly address this by searching for literature that reports on the management of patients identified with and without the biomarker.

Section 2d Clinical evaluation of the codependent technologies (separate)

ADDITIONAL INFORMATION REQUESTS: LINKED EVIDENCE

- 29 (T) Identify any safety considerations that will impact on the entire process of testing
- 30 (M) Indicate whether the search for evidence on the therapeutic effectiveness of the proposed medicine was comprehensive and whether the evidence selection process was unbiased
- 31 (M) Indicate whether the evidence reporting on the therapeutic effectiveness of the proposed medicine is of good quality
- 32 (O) Provide evidence (if relevant) of treatment effect modification (ie interaction) as a consequence of biomarker status
- 33 (O) Provide evidence (if relevant) that using the test results in better targeting of patients that are likely to respond most to the medicine (ie by using the prognostic effect of the biomarker to determine the baseline risk of disease or condition progression)
- 34 (O) Indicate whether the effect of the medicine, as conditioned by the test or biomarker result, has a clinically important and statistically significant effect on patient-relevant health outcomes (both safety and effectiveness)

29 (T) Safety concerns regarding the proposed test

Include in Subsection 2.7

Identify any safety considerations that will impact on the entire process of testing. For example, patient contraindications to the testing procedure, required biospecimen size, additional risk of harm (with reference to Item 16), or processing time impacting on treatment initiation.

30 (M) Selection of the evidence on the therapeutic effectiveness of the medicine

Include in Subsections 2.1 and 2.2

Indicate whether the search for evidence on the therapeutic effectiveness of the proposed medicine was comprehensive and whether the evidence selection process was unbiased.

This evidence should include:

- the therapeutic effectiveness of the medicine when conditioned by the test or biomarker result
- the therapeutic effectiveness of the medicine in unselected patients (where biomarker status has not been determined).

For example, present a systematic review of the available comparative clinical evidence of the proposed medicine versus its comparator in patients with and without the biomarker, as well as the available comparative clinical evidence of the proposed medicine versus its comparator when patient biomarker status is not known.

Ensure that the systematic review has study inclusion/exclusion criteria delineated, and include a PRISMA flowchart¹ indicating how trials were selected and the reasons why any potentially relevant trials were excluded.

31 (M) Quality of therapeutic effectiveness evidence

Include in Subsection 2.3

Indicate whether the evidence reporting on the therapeutic effectiveness of the proposed medicine is of good quality.

Assess bias, confounding and the impact of chance on the results. Particular attention should be given to the impact of selection bias and confounding on any subgroup analyses. For example, were the subgroup analyses prespecified (stratified randomisation) and was blinding maintained? Or was the subgroup analysis exploratory (determined on the basis of retrospectively obtained samples)? Were the results adjusted for potential confounders? Where the study design involves biomarker positive patients only, assess study quality according to the usual guidance in Subsection 2.3.

Depending on the study design, confounding may occur where biomarker status is a prognostic factor and when there are imbalances in biomarker status in the proposed medicine and comparator medicine trial arms.

32 (O) Evidence of treatment effect modification

Include in Subsection 2.6

Provide evidence (where available) of treatment effect modification (ie interaction) as a consequence of biomarker status.

For example, is there evidence of substantial variation in a measure of relative treatment effect between the proposed medicine and comparator/usual care trial arms after stratifying on biomarker status?

Treatment effect modification in this setting identifies a relationship between the biomarker and the medicine, which is likely to be unique or limited to companion tests assessing a particular biomarker and medicines with a particular mechanism of action (cross-reference to Item 9). This means that both technologies are needed to produce or optimise a clinical benefit.

33 (O) Evidence of prognostic effect

Include in Subsection 2.6

Provide evidence (if relevant) that using the test results in better targeting of patients that are likely to respond most to the medicine (ie by using the prognostic effect of the biomarker to determine the baseline risk of disease or condition progression).

For example, is there evidence of minimal variation in a measure of relative treatment effect between the proposed medicine and comparator/usual care trial arms, but determining biomarker status helps identify patients at greatest risk of an event, which, in turn, helps maximise the absolute treatment effect?

Amalgamate with Item 19 if this issue has been addressed there.

If an improvement in treatment effect is a result of better targeting of those patients that are likely to respond most, this identifies a relationship between the biomarker and a potentially broader range of existing and future treatment options (potentially including nonmedicine treatment options) than is likely to apply for treatment effect modification. This may allow reimbursement of either the test or the medicine of both technologies.

This apparent improvement in treatment effect is simply because a certain patient subgroup (flagged by a specific biomarker) will always do better, so the biomarker is considered prognostic.

It is possible for both treatment effect modification and prognostic effect to coexist. In this case, to assess the unique contribution of the medicine, an assessment of its effect must be made relative to usual care and an adjustment made for the background prognostic effect of the biomarker.

34 (O) Size of the treatment effect on patient-relevant health outcomes

Include in Subsections 2.6 and 2.8

Indicate whether the effect of the medicine, as conditioned by the test or biomarker result, has a clinically important and statistically significant effect on patient-relevant health outcomes (both safety and effectiveness). Relate this to the following factors:

- factors intrinsic to the proposed medicine
 - treatment effect modification when prognostic effect is not present in the medicine/biomarker relationship (see Item 32)
 - absolute treatment effect when prognostic effect is present in the medicine/biomarker relationship (see Item 33)
- the factor intrinsic to the proposed test
 - accuracy of identification of biomarker status given the test result (ie positive predictive value and negative predictive value), and the impact of inappropriately treating or not treating patients who received an inaccurate biomarker test result.

When the proposed MBS listing either cannot include the test used in the evidence base or also encompasses other test options, delineate the consequences of using the other test options in place of the evidentiary standard test for health outcomes and the provision of subsequent health care resources in Subsection 2.7.

Applicability of the effectiveness of the codependent technology

ADDITIONAL INFORMATION REQUESTS

- 35 (O) Indicate whether the evidence supporting the clinical effectiveness of the codependent technology is applicable to the Australian population and to the circumstances of using each of the technologies**

35 (O) Applicability of the evidence

Include in Subsection 2.7, with any economic implications included in Subsection 3A.3

Indicate whether the evidence supporting the clinical effectiveness of the codependent technology is applicable to the Australian population and to the circumstances of using each of the technologies. For example, is the biomarker prevalence in the trial similar to that in the target MBS population? Is the medicine, dosage and frequency of use in the trial similar to that proposed for the target PBS population? How are any inconsistencies identified in the submission addressed?

Section 3 – Economic evaluation

The following section contains information requests for establishing the cost-effectiveness of the codependent technologies in terms of patient health outcomes.

Structure of the model

ADDITIONAL INFORMATION REQUESTS

- 36 (O)** Indicate whether the model structure is consistent with other published economic evaluations in the same broad clinical management setting, initiating before the decision to test or treat
- 37 (O)** Indicate whether the model structure is consistent with the clinical pathways provided in response to Item 7
- 38 (O)** If relevant, provide a supplementary analysis of the nonhealth-related impacts associated with using the proposed test

36 (O) Consistency with other published economic evaluations

Include in Subsection 3A.2

Indicate whether the model structure is consistent with other published economic evaluations in the same broad clinical management setting, initiating before the decision to test or treat.

Indicate whether and why there are differences in model structure compared with the identified economic evaluations.

37 (O) Consistency with the clinical management pathways

Include in Subsection 3A.2

Indicate whether the model structure is consistent with the clinical pathways provided in response to Item 7. Indicate whether and why there are differences between the model structure and the clinical pathways, considering the following factors:

- The start point is testing of the eligible population (ie only a subset of the tested population goes forward to receive the proposed medicine). The less-preferred alternative is to start with the treatment and back-calculate the number (and costs) of testing the larger population.
- Where the model is constructed using a linked-evidence approach, include model arms to account for both accurate and inaccurate test results (see Items 39–42). This is not necessary if a single-randomised trial of the test is available (ie randomised to test versus no test trial arms) and only the evidentiary standard test is to be listed in the MBS – then the impact of inaccurate testing is incorporated in the health outcomes of the patients (this is analogous to a trial-based economic evaluation of the test and medicine pair). Where true positive, false positive, true negative and false negative test results are accounted for in the model, present a table specifying what source of estimates is used for each of the health outcomes and the health care resource provision in each of these four situations.
- A scenario analysis is provided where the proposed medicine is used without testing to show the extent of improvement in the incremental cost-effectiveness ratio (ICER) associated with using the test (see Items 7 and 58).

38 (O) Nonhealth-related impacts

Include in Subsection 3A.2

If relevant, provide a supplementary analysis of the nonhealth-related impacts associated with using the proposed test.

The same considerations for caregiver impact apply to codependent technologies as for other technologies, so the guidance provided in Part A of these guidelines will apply. The base-case economic model should be from a health system perspective. If other significant nonhealth impacts are expected, provide a supplementary analysis from a societal perspective. Discuss this in a supplementary analysis section. This could include the value to patients of being informed of their biomarker status.

Transition probabilities relating to test outcomes

ADDITIONAL INFORMATION REQUESTS

If a linked-evidence approach was used in Section 2, calculate and include in the model:

- 39 (O) the positive predictive value (PPV) of the proposed test
- 40 (O) the complement of the PPV of the proposed test
- 41 (O) the negative predictive value (NPV) of the proposed test
- 42 (O) the complement of the NPV of the proposed test

43 (O) In the model, provide the incidence of adverse events associated with (i) the proposed medicine in patients with correct (true positive) and incorrect (false positive) positive test results, and (ii) the comparator medicine in patients with correct (true negative) and incorrect (false negative) negative test results; or (iii) reported from the direct evidence (ie in the circumstance that a double or single-randomised controlled trial of the test is available – analogous to a trial-based economic evaluation of the test/medicine pair)

44 (O) In the model, include the incidence of test-related adverse events for *all those tested*

45 (O) Where prognostic effect is operating in addition to treatment effect modification, ensure that the model adjusts for this factor when presenting absolute treatment effects

Calculate the following values for inclusion in the model using prevalence of the biomarker in the 'tested' population, and the sensitivity and specificity of the proposed test reported in Section 2:

- positive predictive value (PPV)
- negative predictive value (NPV)
- complement of PPV (1-PPV)
- complement of NPV (1-NPV).

39 (O) Positive predictive value of the proposed test

Include in Subsections 3A.4 and 3A.8

Calculating the PPV requires information on the sensitivity and specificity of the proposed test – as reported in the clinical evaluation section of the submission – and the prevalence (probability) of the biomarker in the target MBS population. It is the probability that a test positive result for the biomarker is correct. The PPV is used in a Bayesian manner to condition the model and calculate the transition probability associated with a true positive (use in Subsection 3A.4).

$$PPV = \frac{SN \times P}{SN \times P + (1 - SP) \times (1 - P)}$$

where SN = sensitivity, P = prevalence of the biomarker, SP = specificity

If agreement or concordance data are provided, rather than test accuracy data, measures such as the PPV cannot be accurately calculated since the subjects' condition (as determined by a valid reference standard) is unknown. In this situation, a range of indicative PPVs (using a test nominated as the reference standard) might be used as transition probabilities and tested in sensitivity analyses. These analyses would explore the impact on the ICER of discrepancies in the agreement between the evidentiary standard test and other nominated reference standard tests that will be used in Australia to identify the biomarker.

40 (O) Complement of positive predictive value of the proposed test

Include in Subsections 3A.4 and 3A.8

One minus positive predictive value (1 – PPV) is the probability that a test positive result for the biomarker is incorrect (false positive). It predicts the consequence that patients will be treated unnecessarily, with a consequent decrement in expected treatment effectiveness and increment in harms. It is used in a Bayesian manner to condition the model and calculate transition probabilities.

If agreement or concordance data are provided rather than test accuracy data, present the complement of the range of indicative PPVs used to address Item 39.

41 (O) Negative predictive value of the proposed test

Include in Subsection 3A.4 and 3A.8

To calculate the NPV also requires information on the sensitivity and specificity of the proposed test – as reported in the clinical evaluation section of the submission – and the prevalence (probability) of the biomarker (eg phenotypic expression of mutation) in the target MBS population.

The NPV is the probability that a test negative result for the biomarker is correct. It is used in a Bayesian manner to condition the model and calculate transition probabilities.

$$NPV = \frac{SP \times (1 - P)}{(1 - SN) \times P + SP \times (1 - P)}$$

where SN = sensitivity, P = prevalence of the biomarker, SP = specificity

If agreement or concordance data are provided rather than test accuracy data, refer to guidance provided at Item 39.

42 (O) Complement of negative predictive value of the proposed test

Include in Subsection 3A.4 and 3A.8

One minus negative predictive value (1 – NPV) is the probability that a test negative is incorrect (false negative) and predicts the scenario where patients receive usual care instead of the proposed medicine with a consequent decrement in expected treatment effectiveness. It is used in a Bayesian manner to condition the model and calculate transition probabilities.

If agreement or concordance data are provided rather than test accuracy data, present the complement of the range of indicative NPVs used to address Item 41.

43 (O) Medicine-related adverse events in patients according to test result

Include in Subsection 2.5 or 2.6, and Section 3

In the model, provide the incidence of adverse events associated with (i) the proposed medicine in patients with correct (true positive) and incorrect (false positive) positive test results, and (ii) the comparator medicine in patients with correct (true negative) and incorrect (false negative) negative test results; or (iii) reported from the direct evidence (ie in the circumstance that a direct randomised trial of the test is available – analogous to a trial-based economic evaluation of the test–medicine pair).

Determine whether biomarker test status predicts or does not predict any comparative treatment effect variation in terms of adverse events (Subsection 2.5 or 2.6) and incorporate in the model (eg Subsections 3A.2 and 3A.4). Include the impact of medicine-related adverse events on patients with a positive test result.

44 (O) Incidence of test-related adverse events

Include in Subsections 3A.4 and 3A.6

In the model, include the incidence of test-related adverse events for **all those tested**. Refer to Items 16 and 29 (Subsection 3A.4). This includes adverse events from resampling to perform or reperform the test. Sometimes the original sample is not available or not of sufficient size to allow retesting, and a new sample is needed to reperform the test. Account for the costs associated with resampling in the model (Subsection 3A.6).

45 (O) Incorporation of net treatment effects (if relevant)

Include in Subsections 3A.2–3A.5

Where prognostic effect is operating in addition to treatment effect modification, ensure that the model adjusts for this factor when presenting absolute treatment effects.

Resource items and costs included in the model

ADDITIONAL INFORMATION REQUESTS

Include the following costs in the model:

- 46 (O) unit test costs
- 47 (O) cost of sampling (if relevant)
- 48 (O) test administration costs
- 49 (O) costs of patient consultations with medical personnel regarding the test results and treatment planning
- 50 (O) costs of retesting and nonassessable results
- 51 (O) costs for adverse events associated with testing
- 52 (O) costs of additional and further testing as a result of the proposed test
- 53 (O) costs of medicine-related adverse events, including those where the test result was false positive
- 54 (O) costs of other relevant health care resources (eg diagnostic, medical, hospital, allied health)

46 (O) Unit test costs

Include in Subsection 3A.6

In estimating the cost of testing, include the cost of tests undertaken on all patients for whom the medicine is being considered, not just the cost of the test for those who were found to be suitable for the medicine. Include all relevant sources of costs (eg infrastructure, training, quality assurance) that need to be captured in, and associated with, rendering an MBS-funded test (eg a pathology test).

47 (O) Cost of sampling (if relevant)

Include in Subsection 3A.6

For example, taking, storing, retrieving and transporting biopsy samples.

48 (O) Other relevant costs of test administration

Include in Subsection 3A.6

49 (O) Costs for patient consultations with medical personnel

Include in Subsection 3A.6

Include costs of patient consultations with medical personnel regarding the test results and treatment planning. Include an explanation as to the extent that these costs overlap with the already-occurring consultations for medical management.

50 (O) Costs of retesting and nonassessable results

Include in Subsection 3A.6

This could be covered at Item 46. In some cases, the test result is invalid or not assessable, and retesting of the sample is required. Ensure that any costs associated with retesting are in the model.

51 (O) Costs for adverse events associated with testing

Include in Subsection 3A.6

Provide costs for the items mentioned at Item 44.

52 (O) Costs of additional and further testing as a result of the proposed test

Include in Subsection 3A.6

This includes costs associated with any changes in subsequent types of testing for other purposes brought about by the use of the proposed test.

53 (O) Cost of medicine-related adverse events

Include in Subsection 3A.6

Provide costs for the items mentioned at Item 43. Include these costs in all arms of the model, including false positive test result arms.

54 (O) Costs of other relevant health care resources

Include in Subsection 3A.6.

For example, costs for diagnostic, medical, hospital and allied health resources.

Uncertainties in the model

ADDITIONAL INFORMATION REQUESTS

- 55 (O) Assess the uncertainty around the medicine's therapeutic effectiveness**
- 56 (O) If a linked-evidence approach was used in Section 2, assess the uncertainty around test accuracy**
- 57 (O) If a linked-evidence approach was used in Section 2, assess the uncertainty around the prevalence of the biomarker**
- 58 (O) If relevant, provide a scenario analysis for the option of PBS listing the medicine without the proposed test as a prerequisite**

55 (O) Uncertainty around therapeutic effectiveness

Include in Subsection 3A.9

In instances where both treatment effect modification and prognostic effect are operating in the medicine-biomarker relationship, assess the uncertainty of the estimated incremental treatment effect and model this uncertainty.

56 (O) Uncertainty around test accuracy (if relevant)

Include in Subsection 3A.9

If a linked-evidence approach was used in Section 2, assess the uncertainty around test accuracy. In instances where there is heterogeneity in plausible test accuracy measures (sensitivity and specificity) in the collated evidence base, particularly for different eligible test options, vary these measures when calculating the PPV and NPV transition probabilities and assess the impact of this uncertainty on the estimated absolute treatment effect.

57 (O) Uncertainty around biomarker prevalence (if relevant)

Include in Subsection 3A.9

In instances where there is limited or heterogeneous information on the prevalence of the biomarker in the target MBS population, vary the plausible prevalence rate when calculating the PPV and NPV transition probabilities, and assess the impact of this uncertainty on the estimated absolute treatment effect.

58 (O) PBS listing the medicine without the biomarker test as a prerequisite

Include in Subsection 3A.9

Depending on the prevalence of the biomarker, in some cases there may be a net clinical benefit – which may be more cost-effective – to provide the medicine to patients without the use of biomarker testing. A scenario analysis should be used to make this explicit (see Item 7).

Section 4 – Use of the medicine in practice

ADDITIONAL INFORMATION REQUESTS

- 59 (O) Present a budget impact analysis incorporating both MBS and PBS components, with results split by sector (public, private, patient, other)
- 60 (O) Calculate an epidemiologic estimate for disease burden that is based on the prevalence of the biomarker as determined by the proposed test
- 61 (O) Estimate the cost of testing all patients eligible for the test and the cost of retesting when indeterminate or nonassessable results are produced. If testing is also required after therapy is initiated (ie to monitor therapy or to determine when therapy should cease), these costs should also be included. If relevant, provide a scenario analysis for the option of PBS listing the medicine without the proposed test as a prerequisite
- 62 (O) Estimate any other MBS costs that would be incurred if the test and medicine were listed

This section contains information requests for establishing the predicted use of codependent technologies and the financial implications to the Australian Government budget.

59 (O) Budget impact analysis incorporating both MBS and PBS components

Include in Subsections 4.1–4.6

Present a budget impact analysis incorporating both MBS and PBS components, with results split by sector (public, private, patient, other).

Present the cost of the proposed test alongside the proposed medicine in Subsection 4.2, if appropriate, and use Subsection 4.5 to present utilisation of, and costs associated with, other MBS items.

60 (O) Epidemiology estimate for disease burden

Include in Subsection 4.2

Calculate an epidemiologic estimate for disease burden that is based on the prevalence of the biomarker as determined by the proposed test.

A market-share estimate for a new biomarker scenario is likely to be inappropriate, because previous medicine utilisation will not have been targeted to this biomarker. Seek expert epidemiological advice on whether prevalence is expected to remain constant after listing.

First, estimate the number(s) of patients likely to be considered for the test (eg with the medical condition as defined). Second, based on the prevalence of the biomarker, estimate the proportion of patients likely to receive a positive test result with the proposed test (and be eligible for use of the medicine).

Where the biomarker has been validated using another test and is targeted by other reimbursed medicines, a market-share approach may be reasonable.

61 (T) Likely use and overall financial cost of the test

Include in Subsections 4.2 and 4.6

Estimate the cost of testing all patients eligible for the test (ie biomarker positive, biomarker negative and indeterminate biomarker status) and the cost of retesting when indeterminate or nonassessable results are produced. Include these costs if testing is also required after therapy is initiated (ie to monitor therapy or to determine when therapy should cease).

Any uncertainty about use of the test (ie biomarker prevalence) or changing availability of the test should be explored in Subsection 4.6. There may be 'leakage' issues identified through an assessment of the 'change in management' part of the linked evidence. A codependent technology is meant to target the use of a medicine to a patient who is biomarker positive, but, in some cases, the medicine is given even if the patient is negative for the biomarker. Similarly, a test may be done to rule out use of a medicine (eg to avoid potential medicine-related adverse events or the development of resistance), but the medicine is given anyway.

62 (O) Other MBS costs

Include in Subsection 4.5

Estimate any other MBS costs that would be incurred if the test and medicine were listed. Consider procedures for administration of the medicine and consultations for adverse events, consultations for resampling, genetic counselling and so on.

Appendixes

Appendix 1 Expert opinion

Uses of expert opinion

Consider providing expert opinion to supplement or support the observed data from randomised trials or nonrandomised studies (including drug usage evaluations, cross-sectional studies or case studies).

Determining an appropriate body of experts will depend on the nature of the information gap that requires filling. Experts may be panels of medical practitioners, a medical specialty group or consumers. Consumers may provide advice on factors such as the patient relevance of outcomes (particularly if elicited at the time of trial design) or how medicines might be used. Expert opinion can be useful in several aspects of preparing submissions to the PBAC – for example, to help:

- define the clinical need for the proposed medicine and inform the main indication (Subsection 1.4)
- determine how the medicine is most likely to alter the clinical management algorithm (Subsection 1.2) and support the choice of the main comparator (Subsection 1.1), noting that a comparator should not be determined by expert opinion alone
- interpret the clinical importance and patient relevance of the outcome measures reported in the trials (Subsections 2.4 and 2.8)
- modify the patterns of health care resource use measured in randomised trials conducted in different settings, such as in other countries (Subsection 3A.6)
- predict which health care resources would be used and how often each would be used to manage outcomes reported in the randomised trials, but were not followed up (Subsection 3A.6)
- estimate the proportion of patients with the medical condition that would be eligible according to the requested listing, and predict uptake rates (Subsection 4.2)
- predict the extent of increases or decreases of other PBS-listed medicines (Subsection 4.3).

In several examples above, trial data, registry data or analyses of data from other countries, where available, would be used in preference to expert opinion, and it would be expected that the expert opinion supports the applicability of the observed data. An example is to support the representativeness of a drug usage evaluation conducted in another country. In this case, expert opinion reduces uncertainty.

Presenting expert opinion

Justify the use of expert opinion in the introduction of the appropriate section. Include a clear rationale for, and the aims of, eliciting the expert opinion. Where expert opinion is used to fill a gap in information, clearly describe the nature of this gap and indicate the other steps that have been taken to address the gap, such as a literature search.

Describing the collection and collation of expert opinion

Using a well-designed methodology to elicit expert opinion helps to reduce uncertainty. The methods used may vary from large, published questionnaires and surveys with statistical analysis to

a summary of interviews with a panel of clinical experts. Present expert opinion as qualitative or quantitative (but not statistically analysed) information.

Include copies of administered surveys or hypothetical scenarios that were presented to experts.

When summarising expert opinions and their variability, interpret the findings, and discuss the limitations and biases of the method chosen. Qualitative studies and interviews should follow best practice for reporting and analysis.⁶¹⁻⁶³ Indicate how the opinions have been used in the main body of the submission.

Where multiple sources of expert opinion are available to address a single assumption or estimate, compare the results, and assess their concordance or lack of it. Present a summary table that compares multiple sources or multiple variables. Table A1.1 provides guidance on the details that should be included. Where multiple estimates (or data) are generated to fill a gap in the information – either from multiple sources of expert opinion or a combination of expert opinion and observed data – compare the estimates (or data) and justify the choice of data used in the submission.

Where expert opinion is used in place of observed data, as may occur when observed data are generated from other health care systems or are historical, present both and clearly justify the use of expert opinion. State if expert opinion (compared with alternative sources of data) is likely to lead to a more favourable clinical, economic or financial assessment of the proposed medicine.

The PBAC is concerned when information used within the clinical, economic or financial analysis of the proposed medicine is uncertain. Where expert opinion is sought for a disease or condition for which the number of prescribers is likely to be large, do not rely on surveys of small numbers of prescribers because this leads to highly uncertain results. In all cases where expert opinion is used to derive estimates for the submission, use the final estimate to minimise the risk to the PBAC of relying on an overestimation of the effectiveness or cost-effectiveness, or underestimation of the financial implications to the Australian Government. To reduce uncertainty associated with expert opinion, provide sensitivity analyses around the derived estimates, or clearly state where the results in the submission are not sensitive to different estimates.

Table A1.1 Methods to collect and collate expert opinion

| Information to be provided | Notes |
|---|---|
| Criteria for selecting experts | Prefer a random or comprehensive set of prescribers likely to prescribe the proposed medicine, or the appropriate medical specialty group. In general, an advisory board created by the sponsor, or for advising on the drug development program or marketing may not be representative of experts in Australian clinical practice. The generalisability of expert opinion derived from such boards is difficult to assess |
| Number of experts approached ^a | Where the likely number of prescribers is large, it is less acceptable to provide expert opinion derived from a small number of prescribers |
| Number of experts who participated ^a | Assess whether the extent and characteristics of the nonresponders are likely to diminish the representativeness of the opinions provided, compared with the intended sample approached |
| Declaration of potential conflicts of interest from each expert or medical specialty group whose opinion was sought | Provide a signed statement from each expert and specialty group specifying any potential conflict of interest and stating the nature of any contractual arrangement, including how much payment was offered and accepted. Where the collection of expert opinion has been contracted out, the contractor should provide this statement, reporting on both the arrangements made between the sponsor and the contractor, and the arrangements made between the contractor and those whose opinions were sought |
| Background information provided and its consistency with the totality of the evidence provided in the submission | Include a copy of any background information provided in the technical document or attachment. If background information has been provided, ask the experts to define the comparative clinical place of the proposed medicine and the main comparator based on this background information. Including the experts' definitions in the technical document or attachment allows an assessment of the consistency of the background information with the evidence provided in the submission |
| Method used to collect opinions | For example, were the experts approached individually or was a meeting convened? Was any incentive used to maximise responses? |
| Medium used to collect opinions | For example, was information gathered by direct interview, telephone interview or self-administered questionnaire? |
| Questions asked ^b | Explain the design of the tool (quantitative or qualitative). Describe its development. Indicate whether it was pilot tested and, if so, provide the results of that testing and explain how the results were used to improve the questions. On a question-by-question basis, assess the extent to which each question is neutral or biased, and the extent to which each question is open or closed. To allow an independent assessment, include the questionnaire or an outline of the interview questions in the technical document (or attach a copy) |
| Whether iteration was used in the collation of opinions and, if so, how it was used | The Delphi technique, for example, uses an iterative approach |
| Number of responses received for each question ^a | Assess whether the extent of any nonresponse is likely to diminish the representativeness of the opinions provided to particular questions, compared with the intended sample approached |
| Whether all experts agreed with each response | If not, specify (i) the approach used to finalise the estimates (eg the majority opinion or a Delphi technique could be applied; for quantitative results, point estimates [such as the mean, median or mode] could be presented), and (ii) the approach used to present the variability in the opinions (eg present the range of opinions expressed, including common and outlying views; for quantitative results, measures of variance [such as confidence intervals, range, centiles] could be presented) |

a Tabulate these information items.

b The way the questions are asked is an important source of potential bias in obtaining expert opinion. A particularly influential extension question extends the respondent beyond 'what' the opinion is (eg what would be done, what extent of benefit would be clinically important) to ask 'why' (eg explain why would you do this, explain why this is important). Conveying these reasons alongside expert opinion-based estimates might help improve their acceptability. Including these explanations in the technical document or attachment would allow the opinions to be assessed on the basis of the underlying reasoning rather than only depending on the authority of the experts.

Appendix 2 Literature search methods

Search criteria and terms

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

- a) the trial includes a randomisation procedure in its design (use [Cochrane Highly Sensitive Search Strategies](#)⁶⁴)^{mm}
- b) the trial contains the proposed medicine and the relevant comparator(s)
- c) the trial recruits participants with characteristics that overlap with those of the target population (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.

Use Table A2.1 to tabulate search terms based on the search criteria above and adapted to capture direct randomised trials, randomised trials required for indirect comparisons, or nonrandomised studies. Present Table A2.1 in the main body of the submission.

Table A2.1 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] |
| Comparator | [insert description of category] | [include known proprietary and nonproprietary names, MeSH terms and developmental/provisional medicine names] |

MeSH = medical subject headings

Ensure that the search terms for population are broad; only apply them if the proposed medicine is used for multiple indications. Do not include terms for trial outcomes in the search strategy. Exclude any identified trials that do not report on an appropriate outcome in Subsection 2.2. Include the comparator search terms for all relevant comparators.

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 A2.2. Where additional databases are relevant to include (eg PsycINFO for mental health literature), add these to Table A2.2.

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.⁶⁴

^{mm} http://handbook.cochrane.org/chapter_6/6_4_11_1_the_cochrane_highly_sensitive_search_strategies_for.htm

Provide a complete electronic search strategy for PubMed in an attachment to the submission. Present Table A2.2 in the main body of the submission.

Table A2.2 Record of search strategies

| Source | Date searched | Date span of search | Details of search |
|--|---------------|---------------------|---|
| MEDLINE (via PubMed) | [insert date] | [insert dates] | 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 dates] | State any key differences from the complete search strategy provided for the PubMed search |
| Cochrane Library ^a | [insert date] | [insert dates] | State any key differences from the complete search strategy provided for the PubMed search |
| ClinicalTrials.gov | [insert date] | [insert dates] | State any key differences from the complete search strategy provided for the PubMed search |
| International Clinical Trials Registry Platform ^b | [insert date] | [insert dates] | State any key differences from the complete search strategy provided for the PubMed search |
| Australian Clinical Trials Registry | [insert date] | [insert dates] | State any key differences from the complete search strategy provided for the PubMed search |
| Internal registries | [insert date] | [insert dates] | Not applicable |
| Other (state other sources ^c) | [insert date] | [insert dates] | Not applicable |

a Includes 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/)ⁿⁿ

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.

ⁿⁿ www.who.int/ictrp/en/

Appendix 3 Identify relevant trials

Search results

From the literature searches reported in Subsection 2.1, complete a PRISMA flowchart^{1,2} (Figure A3.1) to indicate the number of papers screened at each stage of study selection.

Clearly depict the reasons for study exclusion (as discussed in Subsection 2.2.1) in the PRISMA flowchart.

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

1. on the basis of title and abstract, or when the article cannot be retrieved
2. after retrieving full-text articles
3. on the basis of clearly specified reasons other than the exclusion criteria described in Subsection 2.2.1 (justify each exclusion at this point).

Direct randomised trials

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

Indirect comparison of randomised trials

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. An acceptable approach to identifying studies for an indirect comparison of randomised trials is discussed later in this appendix.

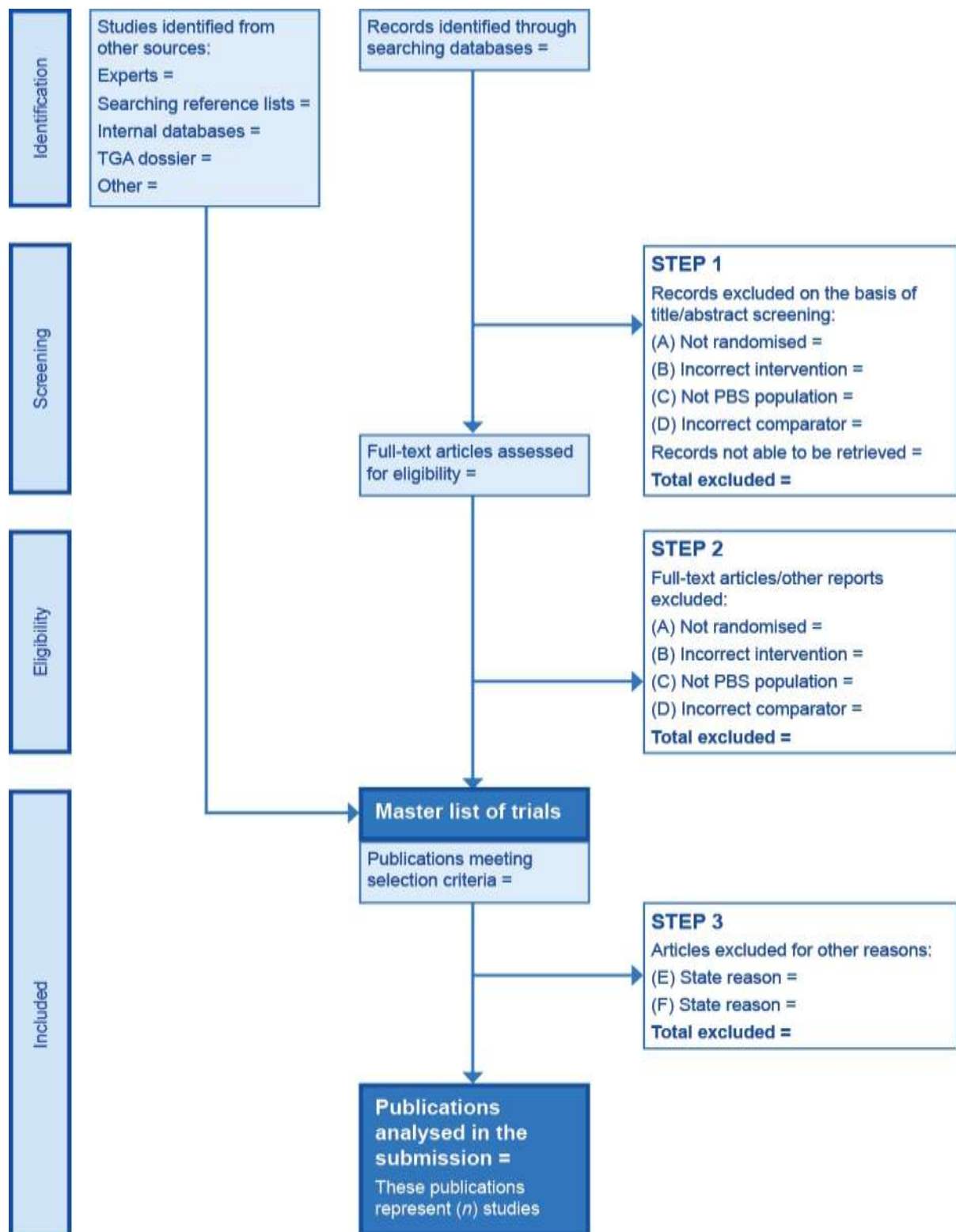
Nonrandomised studies

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 comparison^{25,65,66} or a simulated treatment comparison.^{26,66} If this approach is taken, still perform a search for nonrandomised studies and include relevant studies.

Published systematic reviews and meta-analyses

Extract individual trials from published meta-analyses and compare each trial against the study selection criteria. Exclude any trials that do not meet the criteria. Justify when this is not possible. Consider presenting the treatment effect from the published meta-analysis in a sensitivity analysis.

Figure A3.1 PRISMA flowchart for presenting initial search results



Master list of relevant trials

Prepare a master list of all the included trials and relevant systematic reviews or meta-analyses that meet the inclusion criteria from Subsection 2.2.1. Ensure that the list represents the trials remaining after step 2 of the PRISMA flowchart, and includes relevant trials identified outside database searches (eg experts, searching reference lists, TGA dossier).

Ensure that the list satisfactorily addresses 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 A3.1 provides a suggested format for presenting a master list of all the trials included in the submission.

Table A3.1 Trials (and associated reports) presented in the submission

| Category | Study identifier (ID) | Reports |
|--|---|--|
| Trials meeting the selection criteria (remaining after step 2 of PRISMA ^a) | Unique (ID) of trial used in submission | <ul style="list-style-type: none"> Internal study report title. Date. Author(s). Title. <i>Journal</i> Year; Vol(No):pages Author(s). Title. <i>Journal</i> Year; Vol(No):pages |
| | ID of trial used in submission | <ul style="list-style-type: none"> Internal study report title. Date. Author(s). Title. <i>Journal</i> Year; Vol(No):pages Author(s). Title. <i>Journal</i> Year; Vol(No):pages |
| Trials excluded from analysis (step 3 of PRISMA) | ID of trial used in submission <i>Brief reason for exclusion (justify below)</i> | <ul style="list-style-type: none"> Internal study report title. Date. Author(s). Title. <i>Journal</i> Year; Vol(No):pages Author(s). Title. <i>Journal</i> Year; Vol(No):pages |

a Includes eligible full-text publications from the database searches specified in Table 2.1.2 and additional eligible publications and study reports identified from other sources.

Do not remove trials from the master list. Include all trials throughout the submission, and exclude and justify trials using sensitivity analyses (step 3 of PRISMA).

Option to present supplementary evidence

Where data from one or more direct randomised trials are available, justify the inclusion of an indirect comparison of randomised trials or a nonrandomised study. Present the literature search and study selection for supplementary data. Indicate how supplementary evidence is used in the submission in Subsection 2.2.5. Label supplementary evidence throughout the submission when it is presented.

Appendix 6 discusses supplementary evidence that explores nonhealth outcomes to be included in Section 3.

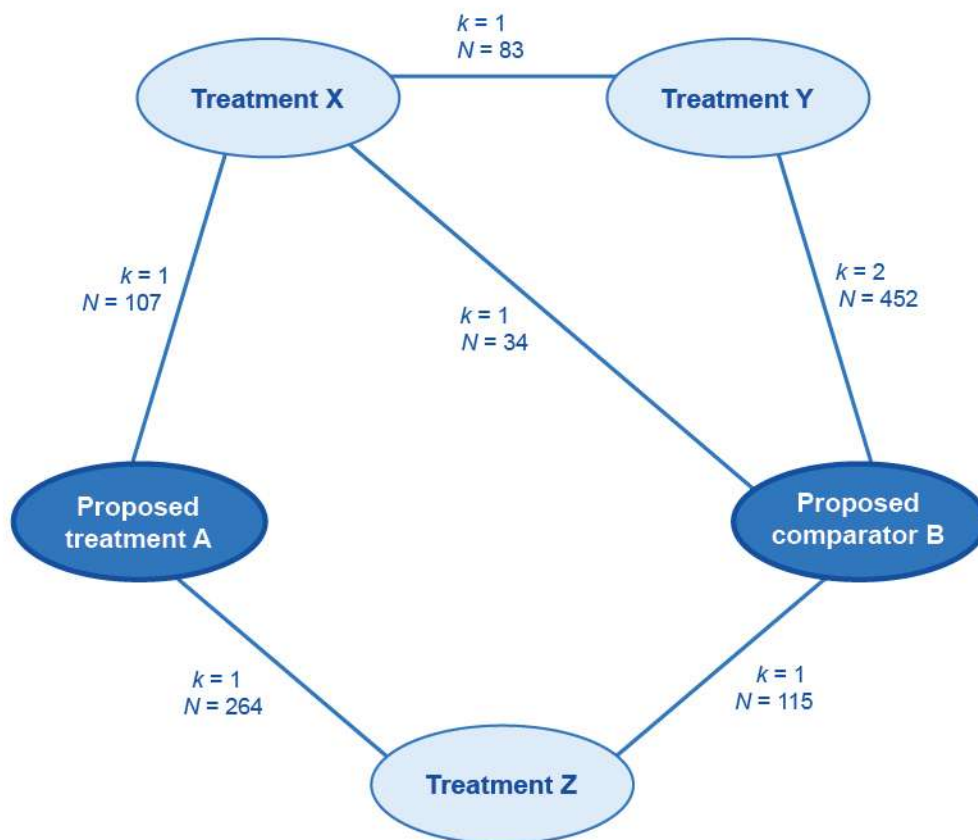
Selecting trials for an indirect comparison

If the proposed medicine and the main comparator can be compared using one or more direct randomised trials, an indirect comparison is not usually required.

When direct randomised trials are not available, conduct an indirect comparison of randomised trials. The approach for performing an indirect comparison is based on the [report of the Indirect Comparisons Working Group](#) to the PBAC.⁰⁰

List all indirect comparisons possible using the trials within the master list. If there are two or more common references, or if more than one indirect comparison is possible, present a network diagram with the trials listed against the links in the diagram (see example in Figure A3.2). In the master list of trials, identify the trials that are unable to be used within the network because no common reference is available, or because the number of steps required to include the trials in the network would substantially increase uncertainty (shorter links are preferable). Where a network meta-analysis is to be presented, describe the search strategy required to capture the complete range of trials eligible for the network and describe any limitations of the search.

Figure A3.2 Example network diagram of the trials included to inform an indirect comparison of the proposed medicine with the main comparator



k = number of trials; N = number of patients enrolled

⁰⁰ www.pbs.gov.au/info/industry/useful-resources/pbac-feedback

In an attachment, present the results (relative and absolute comparative treatment effect) for the outcome(s) on which the submission’s therapeutic claim is based, for all trials listed in the master list of relevant trials. If there are multiple trials with the same treatment comparison, use forest plots.

Excluding trials on the basis of heterogeneity

Justify the exclusion of any trials or pathways. Do not exclude trials or pathways on the basis of heterogeneous characteristics when these are unlikely to influence the treatment effect in the trial (ie unlikely to affect the assumption of transitivity).

Although trials are excluded to improve the transitivity of the trials remaining in the comparison, the possible reasons for exclusion are many, and there is a risk that this process will introduce bias. Therefore, unless there is concern about heterogeneity, and this has a demonstrable effect on the results of the indirect comparison, retain the trials and examine the effect of removing them in sensitivity analyses.

Only one intervention trial and one comparator trial that are not transitive

Where there is one trial of the proposed medicine and one trial of the main comparator with a common reference, do not exclude them because of poor transitivity. Discuss the implications of differences in trial and patient characteristics when presenting the results of the indirect comparison (Subsection 2.6.3). If patient characteristics are heterogeneous in trials, adjust for these differences with, for example, a matching-adjusted indirect comparison or simulated treatment comparison.

Two or more indirect comparison pathways

If there are multiple comparison pathways in an indirect network of trials, present longer pathways or those that do not meet the transitivity assumption as supplementary analyses, if required. To justify the choice of the pathway as the base case, reference trial characteristics that may cause heterogeneity (Appendix 4) and discuss why such characteristics affect the transitivity of trials.

Two or more intervention trials or comparator trials

If there are multiple trials of the same comparison, justify the exclusion of trials on the basis that differences in trial characteristics may affect the transitivity of the trials in an indirect comparison. Adapt the table in Appendix 4 to permit a comparison of trial and patient characteristics within and across trial sets, and a comparison of differences identified that may affect the treatment effect across the trials.

Excluding trials on the basis of differences in treatment effect in the common reference arm

Compare the event rates in the common reference groups within trial sets (Table A3.2).

Table A3.2 Example comparison of event rates

| Comparison | A vs C | A vs C | B vs C | B vs C | B vs C | B vs C |
|---|---------------|---------------|---------------|---------------|---------------|---------------|
| Common reference arm | Trial 1 | Trial 2 | Trial 3 | Trial 4 | Trial 5 | Trial 6 |
| Event rate/median survival/change from baseline | [add] | [add] | [add] | [add] | [add] | [add] |

Justify the exclusion of trials with markedly different event rates or treatment effects in the common reference arms, both within the trial sets and across the indirect comparison. Take care when excluding trials because of differences in event rates in the common reference arms when there is

evidence of a constant relative (or absolute) treatment effect across the range of these event rates. Include any excluded trials in a sensitivity analysis in Subsection 2.6.3.

Presenting trials included in the indirect comparison

Present a summary list of trials using the unique name from the master list to identify trials that are included in the indirect comparison, included in sensitivity analyses or excluded from the remainder of the submission (Table A3.3).

Table A3.3 Example summary list of trials included in the indirect comparison

| Trial identifier | Included/sensitivity analysis/excluded | Brief reason |
|-------------------------|---|--|
| Trial 1 | Included | Not applicable |
| Trial 2 | Included | Not applicable |
| Trial 3 | Sensitivity analysis | Contains some patients with earlier stage of disease or condition than trial 1 and trial 2 |
| Trial 4 | Excluded | Common reference arm uses different dosing, reducing the likelihood of transitivity |

Appendix 4 Heterogeneity of treatment effect across studies

This appendix provides possible sources of heterogeneity between trials, or when comparing one jurisdiction with another. It is a useful reference for describing potential confounders when combining trials in a meta-analysis, performing indirect comparisons of randomised trials or network meta-analyses, or comparing variables from the clinical trial setting with the population in the economic model.

Make comparisons across trials or jurisdictions on the basis of the distributions or proportions of each characteristic rather than simply identifying whether there is a representation of each characteristic in each trial or jurisdiction. For example, two trials may include patients aged 20–60 years, thus, the population may appear homogeneous. However, if one trial has a much lower mean age, or the proportion of patients younger than 40 is far higher than for the other trial, this may cause heterogeneity and violate the assumption of transitivity.

Table A4.1 provides a list of important factors to consider and may, where appropriate, be used as a template for the presentation of factors across trials or jurisdictions.

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

Table A4.1 Example factors that might cause comparative treatment effect heterogeneity

| Category | Factor | Trial 1 | Trial 2 | Trial 3 |
|--|--|----------------|----------------|----------------|
| Different quality of methods of trials | Adequate concealment of randomisation | [add] | [add] | [add] |
| | Blinding | [add] | [add] | [add] |
| | Duration of follow-up | [add] | [add] | [add] |
| | Loss to follow-up | [add] | [add] | [add] |
| | Crossover | [add] | [add] | [add] |
| Confounding factors in relation to participant populations | Age | [add] | [add] | [add] |
| | Sex | [add] | [add] | [add] |
| | Genetic variation | [add] | [add] | [add] |
| | Diagnostic workup | [add] | [add] | [add] |
| | Intensity of surveillance | [add] | [add] | [add] |
| | Severity of disease or condition | [add] | [add] | [add] |
| | Physiological reserve | [add] | [add] | [add] |
| | Stage or duration of disease or condition | [add] | [add] | [add] |
| | Previous therapy | [add] | [add] | [add] |
| | Coexisting disease or condition | [add] | [add] | [add] |
| | Background therapy of concomitant treatments/advances in standard of care | [add] | [add] | [add] |
| Confounding factors in relation to circumstances | Health systems | [add] | [add] | [add] |
| | Geography | [add] | [add] | [add] |
| | Setting in hospital or ambulatory care | [add] | [add] | [add] |
| | Date of trials | [add] | [add] | [add] |
| Different treatment | Dose | [add] | [add] | [add] |
| | Duration | [add] | [add] | [add] |
| | Timing | [add] | [add] | [add] |
| | Stopping or continuation criteria | [add] | [add] | [add] |
| Different outcome measures and methods of statistical analysis | Definition of outcome(s) | [add] | [add] | [add] |
| | Rating instrument | [add] | [add] | [add] |
| | Frequency of measurement | [add] | [add] | [add] |
| | Start point of measurement against duration or progression of disease or treatment, especially in time-to-event analyses | [add] | [add] | [add] |

Appendix 5 Translating comparative treatment effects of proposed surrogate measures to target clinical outcomes

Introduction

The PBAC prefers submissions that do not rely on proposed surrogate measures (PSMs) to inform effectiveness in terms of patient-relevant or clinically relevant outcomes. Where possible, present evidence from direct randomised trials of the treatment effect of the proposed medicine on clinically relevant outcomes.

Where no such evidence is available, establish the likely comparative treatment effect on clinically relevant outcomes by transforming the comparative treatment effect of a surrogate measure.

A surrogate measure is a biomarker that is intended to substitute for one or more target clinical outcomes (TCOs). Although a surrogate measure may or may not have clinical relevance, it is not the key purpose for treatment, which is to affect the severity of, or the transition to, future TCOs.

Relevant to the PBAC, the relationship between a PSM and a TCO is one that quantifies the change in the TCO as a consequence of a change in the PSM. Throughout this appendix, the transformation of the PSM to the TCO should be interpreted as the transformation of the comparative treatment effect on the PSM to the comparative treatment effect on the TCO.

This appendix takes the following approach:

- A5.1 – Define the PSM and the TCO.
- A5.2 – Establish the biological reasoning for the link between the PSM and the TCO, including how pivotal the PSM is to the causation pathway of the TCO, and present epidemiological evidence to support this.
- A5.3 – Present randomised trial evidence to support the nature of the PSM-TCO comparative treatment effect relationship.
- A5.4 – Translate the comparative treatment effect on the PSM from the studies included in Part A, Subsection 2.2, to an estimate of the comparative treatment effect for the TCO.

When interpreting the evidence to identify the relationship between the PSM and the TCO (Section A5.2 of this appendix), and the relationship between the comparative treatment effect on the PSM and the comparative treatment effect on the TCO (Section A5.3 of this appendix), present indications of causality. That is, the PSM (and the comparative treatment effect on the PSM) always precedes the TCO (and the comparative treatment effect on the TCO), and their associations are strong, measured with high precision, and maintained after adjustment for confounders (if there are sufficient numbers of trials with sufficient information to enable such adjustment).

Use the following types of evidence to analyse a PSM-TCO relationship (listed from strongest to weakest):

1. multitrial meta-regression

2. single trial or small number of randomised trials where individual patient data are available (including multicentre analysis where participants were randomised by centre)
3. one randomised trial – no individual patient data or not randomised by centre
4. no randomised trial data.

Given the uncertainty associated with transforming PSMs to TCOs, ensure that the treatment effect observed on the PSM is robust and unbiased. Bias may result from, for example, issues of study quality, imbalances in baseline characteristics, loss to follow-up, discontinuations, inappropriate dosing, subgroup analysis or adjustments for crossover. Where an unknown proportion of the comparative treatment effect on the PSM may be the result of bias, the estimate of the comparative treatment effect on the TCO will be uncertain. In the absence of a robust estimate of the comparative treatment effect on the PSM, transformation to a comparative treatment effect on the TCO is not informative.

The approach taken in this appendix has been informed by the [Surrogate to Final Outcomes Working Group report](#), and this remains a useful resource when additional explanation is required.^{pp}

A5.1 Definition, selection and measurement

A5.1.1 Proposed surrogate measure

Where an intervention may have multiple benefits (eg avoiding multiple strains of a virus or multiple forms of cardiovascular events), a PSM that captures the overall intended clinical outcome is more persuasive. Ensure that the PSM is responsive and able to be measured with reliability and validity.

Define and describe the PSM, with reference to the epidemiological and randomised trial evidence identified in this appendix, by including the following:

- the units of measurement
- the measurement tool(s) or criteria used
- the evidence of reliability from test to test
- the variability across observers or different measurement tools
- the measurement of the comparative treatment effect (eg odds ratio, standardised mean difference).

Ensure that the definition and method of measurement of the PSM are consistent across the evidence. Report and discuss any discrepancies when presenting evidence in this appendix.

A5.1.2 Target clinical outcome

Ensure that the choice of TCO is patient-relevant and captures the key purposes for intervening in a disease process. The goal of treatment may be to improve quality of life, or prevent or slow a medical condition in the long term. Ensure that the TCO is consistent with the health states defined in the natural history of the disease or condition. In some cases, more than one TCO may be required to capture the effects of the proposed medicine on the disease or condition process. Justify if the nominated TCO does not capture an outcome of the disease or condition, or an adverse

^{pp} www.pbs.gov.au/info/industry/useful-resources/pbac-feedback

outcome of the treatment. There may be evidence that the proposed medicine has a positive treatment effect for one TCO (eg myocardial infarction) and a negative treatment effect for another TCO (eg haemorrhagic stroke).

With reference to the epidemiological and randomised trial evidence identified in this appendix, ensure to:

- justify the choice of the TCO and justify the exclusion of other potentially relevant TCOs (particularly those for which the proposed medicine may have a negative treatment effect)
- describe how the TCO is patient-relevant and nominate, with evidence, the extent of change that would be considered meaningful (see Subsection 2.4.3)
- state whether the TCO is reversible
- state whether the TCO is itself a substitute for a more clinically relevant outcome (multistep transformation to a subsequent TCO is discouraged)
- provide the units of measurement
- list the measurement tools or criteria used
- provide evidence of reliability from test to test
- explore variability across observers or different measurement tools
- describe the measurement of the comparative treatment effect (eg odds ratio, standardised mean difference).

Ensure that the definition and method of measurement of the TCO are consistent across the evidence. Report and discuss any discrepancies when presenting evidence in this appendix.

A5.1.3 Relationship between the proposed surrogate measure and the target clinical outcome

When exploring the nature of the PSM-TCO relationship in subsequent parts of this appendix, comment on the following:

- Is the nature of the PSM-TCO relationship still current?
- Have there been changes to treatments or health care systems over time that may have affected the PSM-TCO relationship?
- Is there any evidence of resistance or tolerance to a medicine, or a waning treatment effect over time? Consider and explain any waning treatment effects, and any effects of having no long-term randomised trials that capture the PSM and the TCO.

Derive the PSM-TCO comparative treatment effect relationship from randomised trials that measure both the PSM and the TCO. If this type of evidence is unavailable, it is difficult to quantify the link between changes in the PSM and changes in the TCO. Ensure that the epidemiological evidence in Section A5.2 of this appendix is unequivocal and robust.

A5.2 Biological reasoning and epidemiological evidence

A5.2.1 Biological reasoning

The information request for biological reasoning concerns the disease pathogenesis and disease or condition pathways, and how the PSM and the TCO relate to them, independent of medicine

actions. (Mechanisms of action are presented in Section A5.4 of this appendix.) To provide confidence that altering the PSM provides clinical benefit, clearly explain the biological relationship between the PSM and the TCO.

Present and discuss the disease or condition pathway, clearly linking the PSM to the TCO. State whether the PSM is a necessary step in the development of the TCO, and discuss how close the development of the PSM is, in both temporal and pathological terms, to the development of the TCO.

A5.2.2 Epidemiological evidence

Epidemiological or observational studies support a claimed biological plausibility of the PSM-TCO relationship. Reasons for examining any association are also relevant for investigating the association between the PSM and the TCO.

Describe in detail the epidemiological evidence identified, which may include in vitro studies, animal studies, case reports, cross-sectional observational studies, ecological association studies, retrospective observational cohort studies, non–population based prospective observational cohort studies, or population-based prospective observational cohort studies.

Describe the limitations of the evidence with reference to the study design (eg individual-based associations from observational studies are more convincing than ecological associations).

Present the statistical associations, including the nature or shape of the association, the strength of the association and the precision (95% confidence interval [CI]). Report all relevant statistical outputs, such as regression coefficients and R-squared.

Describe and explain any contradictory findings, primarily where the direction of effect changes, or there is a large difference in the magnitude of effect.

A5.3 Randomised trial data for all medicines

A5.3.1 Identifying relevant trials

Review the literature systematically to find randomised trials that explore the relationship between the PSM and the TCO, irrespective of the medicine or class of medicines examined. Present the search terms, inclusion criteria and the PRISMA flowchart, clearly showing the exclusion of trials. List the excluded trials and reasons for exclusion in an attachment.

From the list of included trials, compile a list of the medicines, categorised by mechanism of action or class, that act on the PSM (see Table A5.1). Present the extension studies associated with the identified trials.

For each mechanism of action, discuss the biological reasoning for the effect of the medicine on the PSM. Discuss whether the mechanism of action of the medicine is the same as, or similar to, the pathological mechanism of the disease or condition. Rationalise any lag in onset of the treatment effect and the implications for the PSM or the TCO, or both.

Table A5.1 Biological reasoning for the effect of the medicine on the proposed surrogate measure

| Class of medicine (list of medicines) | Mechanism of action | Biological reasoning for the effect of the medicine on the proposed surrogate measure | Trials available, citations (medicines included in each trial) |
|--|----------------------------|--|---|
| [add] | [add] | [add] | [add] |
| [add] | [add] | [add] | [add] |

A5.3.2 Trial characteristics

For each of the included trials or meta-analyses, discuss the following factors that may affect the estimate of the relationship between the comparative treatment effect on the PSM and the comparative treatment effect on the TCO:

- The quality of the included trials or meta-analyses (present an assessment of the internal validity of the included trials according to the guidance provided in Part A, Subsection 2.3, in an attachment).
- Whether relevant trials have been excluded from any meta-analyses or meta-regressions.
- Whether the analysis of the PSM was designed prospectively or retrospectively.

Present the characteristics of each of the trials as per Table A5.2.

Table A5.2 Characteristics of trials included in the assessment of the relationship between the proposed surrogate measure and the target clinical outcome

| Trial and date | Patient characteristics | Disease or condition characteristics | Treatment settings | Measurement of proposed surrogate measure and target clinical outcome |
|-----------------------|--------------------------------|---|---------------------------|--|
| [add] | [add] | [add] | [add] | [add] |
| [add] | [add] | [add] | [add] | [add] |

A5.3.3 Trial results

Present the results of the randomised trials and the proposed relationship between the comparative treatment effect on the PSM and the comparative treatment effect on the TCO (Table A5.3). Where multiple trials exist for a class of medicine, clearly show the results of a meta-analysis for individual studies. Present the results of any meta-regressions, including the intercept and coefficient (and their 95% CIs), the R-squared for trials and for individuals (if individual patient data are available), and the surrogate threshold effect as determined by prediction bands. Justify where a meta-regression has not been presented.

Discuss the PSM-TCO comparative treatment effect relationship. Include details of the shape of the relationship (eg linear, exponential) and whether there is any evidence of a floor or ceiling effect, below or above which the comparative treatment effect on the PSM no longer predicts a comparative treatment effect on the TCO.

Table A5.3 Results of randomised trials

| Trials/meta-analyses (grouped and meta-analysed by class or mechanism of action) | Baseline value of PSM / final value of PSM^a | Comparative treatment effect on PSM | Comparative treatment effect on TCO^b | Proposed relationship (and measure of uncertainty) |
|---|---|--|--|---|
| [add] | [add] | [add] | [add] | [add] |
| [add] | [add] | [add] | [add] | [add] |

PSM = proposed surrogate measure; TCO = target clinical outcome

a Where the PSM is a continuous variable, present the mean baseline and mean final value for the PSM, separated by treatment arm. Where the PSM is a dichotomous variable, such as progression-free survival, this column may be adapted to show the proportion in each arm achieving the PSM.

b Where the trial has included a placebo, no treatment or best supportive care arm, report the absolute number of TCO events in that arm to give an indication of the baseline risk. A long-standing comparator may also be used as an adequate reference for baseline risk.

Where available, present results of the relationship between the comparative treatment effect for the PSM and the TCO across different trial dates, disease or condition stages, treatment settings and patient populations. State which particular subpopulations (or subpopulations are not included in the overall trial populations) do not have trial evidence available. Where these subpopulations would be treated according to the proposed listing in Part A, Subsection 1.4 of the submission, strongly justify the extrapolation of the PSM-TCO relationship to this subpopulation in Section A5.4 of this appendix.

Discuss where the relationship of the comparative treatment effect for the PSM and the TCO differs across trials, medicines or mechanisms of action. Discuss possible causes of the heterogeneity – for example:

- mechanism of action of the medicine
- population characteristics
- disease or condition characteristics, or severity
- treatment settings
- definition or measurement of the PSM
- definition or measurement of the TCO
- quality of the trial
- nature of the proposed relationship (eg linear, asymptotic, floor or ceiling effects).

A5.3.4 Multiplicity of pathways

Although unexplained heterogeneity is difficult to interpret, heterogeneity that can be linked to a characteristic will require further consideration, particularly if the cause of the difference in the relationship between the PSM and the TCO differs according to mechanism of action of a medicine, population characteristics, or disease or condition characteristics. Where differences in the relationship between the PSM and the TCO are present, it is likely that the TCO can be affected by an alternative pathological pathway that is more or less prevalent across differences in the included trials. Where the PSM-TCO comparative treatment effect relationships differ according to the:

- mechanism of action, explain why different medicines with similar effects on the PSM may result in different effects on the TCO

- patient characteristics, or disease or condition characteristics, explain why similar changes in the PSM in these subpopulations may result in different effects on the TCO.

Alternative pathological pathways that do not involve the PSM undermine the validity of the PSM. Therefore, where appropriate, exclude trials with medicines or populations in which the alternative pathway is present if:

- there is compelling evidence of the existence of the alternative pathway (such evidence may be randomised trial evidence linking an alternative PSM with the TCO)

and

- the alternative pathway is not present for the proposed medicine (and the main comparator) or the population in which listing is being sought.

Present evidence to support these claims.

Where trials are removed that have medicines of different mechanisms of action or populations that do not reflect the proposed listing, present the estimate of the PSM-TCO comparative treatment effect relationship with all trials included as the base case. Remove less-relevant trials through a sensitivity analysis.

A5.3.5 Validity of results

For each of the trials, meta-analyses and meta-regressions, compare the observed TCO comparative treatment effect with the predicted effect on the TCO if calculated according to the epidemiological evidence presented in Section A5.2 of this appendix (Table A5.4).

Table A5.4 Comparing randomised trial evidence and epidemiological evidence

| Trial, meta-analysis or meta-regression | Comparative treatment effect on PSM | Observed comparative treatment effect on TCO | Predicted comparative treatment effect on TCO after applying the relationship observed in epidemiological studies |
|---|-------------------------------------|--|---|
| [add] | [add] | [add] | [add] |
| [add] | [add] | [add] | [add] |

PSM = proposed surrogate measure; TCO = target clinical outcome

Discuss differences between the observed and predicted comparative treatment effect on the TCO.

A5.3.6 Summarising the evidence

Several parameters of the evidence presented are critical to understanding and interpreting the translation of the PSM for the proposed medicine to an estimate of the TCO (Table A5.5). These are general conditions, outside of which the translation of the PSM to the TCO becomes less certain.

Table A5.5 Summary of conditions under which the relationship has been determined

| Parameter of evidence | Results | Cross-reference |
|--|----------------|------------------------|
| Median baseline value of PSM (IQR) | [add] | [add] |
| Median final value of PSM (IQR) | [add] | [add] |
| Median change in PSM (IQR) | [add] | [add] |
| Median change in PSM for the comparator identified in Part A, Subsection 1.1 of the submission (IQR) | [add] | [add] |
| Range of disease or condition severity | [add] | [add] |
| Range of patient characteristics (eg age, sex, race) | [add] | [add] |
| Range of trial dates | [add] | [add] |
| Range of TCO event rates (from placebo arms) ^a | [add] | [add] |
| Range of estimates of the PSM-TCO comparative treatment effect relationship | [add] | [add] |

IQR = interquartile range; PSM = proposed surrogate measure; TCO = target clinical outcome
a Placebo, no treatment or best supportive care arms, or long-standing comparator

Where more than one estimate of the relationship between the comparative treatment effect on the PSM and the comparative treatment effect on the TCO has been established, justify the selection of one estimate for the base case, and present the remainder as sensitivity analyses.

A5.4 Applying the relationship between comparative treatment effects to the proposed medicine

A5.4.1 Mechanism of action

When applying the PSM-TCO comparative treatment effect relationship to the trial evidence for the proposed medicine, it is critical that both the proposed medicine and the main comparator have the same mechanism(s) of action as medicines for which the PSM-TCO comparative treatment effect has been established in Section A5.3 of this appendix. When a medicine is not of a class of medicines presented in Section A5.3 of this appendix, it is not possible to determine to what extent the TCO is affected by changes in the PSM, and to what extent it is affected by alternative pathological pathways or by negative physiological effects. Therefore, where one or both of the proposed medicine and the main comparator are not represented by the mechanism(s) of action in Section A5.3 of this appendix, the comparative treatment effect on the PSM may have a very different relationship to the comparative treatment effect on the TCO. Where this is the case, the transformation of the PSM to the TCO will be uncertain.

Explain the mechanism(s) of action and the biological reasoning for the mechanism(s) of action of the proposed medicine and the main comparator on the PSM and the TCO. Identify differences between the mechanism(s) of action of the proposed medicine, and the main comparator and the medicines identified in the trial evidence in Section A5.3 of this appendix. Clearly explain how any differences will not result in a different measurement of the PSM-TCO comparative treatment effect relationship.

Where the proposed medicine and the main comparator are within the same class of medicines identified in Section A5.3 of this appendix, it is still important to identify differences in physiological effects, and discuss whether different effects can alter the disease or condition process and, hence, the PSM-TCO comparative treatment effect relationship.

A5.4.2 Applicability of the evidence

As outlined in Section A5.3 of this appendix, the applicability of the results of the relationship between the treatment effect on the PSM and the treatment effect on the TCO to different populations and stages of disease is not guaranteed. However, evidence of consistency across different populations and stages of disease is supportive. Compare the patient population, disease or condition stages and circumstances of use for the proposed medicine and the studies identified in Section A5.3 of this appendix. If there are differences, justify why the relationship between the treatment effect on the PSM and the treatment effect on the TCO identified in Section A5.3 is applicable to the clinical trial(s) of the proposed medicine.

The PSM-TCO comparative treatment effect relationship is uncertain beyond the observed ranges for the PSM presented in Section A5.3 of this appendix. Compare the baseline values of the PSM and the comparative treatment effect on the PSM presented in Section A5.3 with that observed for the key trials of the proposed medicine, and discuss.

A5.4.3 Estimate the comparative treatment effect for the proposed medicine

Present the proposed medicine's comparative treatment effect (with CIs) on the PSM for each trial and for a pooled analysis. Translate this using the relationship proposed in Section A5.3 of this appendix. The comparative treatment effect on the PSM and the estimate of the PSM-TCO relationship will have a degree of uncertainty; thus, capture this in the statistical approach and present as a 95% CI around the estimated comparative treatment effect on the TCO. Do not simply translate the upper and lower CIs of the comparative treatment effect for the PSM observed in the key trial by the point estimate of the relationship established in Section A5.3 of this appendix, because this does not adequately capture the uncertainty in the estimate of the comparative treatment effect on the TCO.

Discuss the implications of any surrogate threshold effect identified in Section A5.3 of this appendix.

State whether there are any concerns about the duration of the treatment effect.

Appendix 6 Including nonhealth outcomes in a supplementary analysis

Presenting nonhealth outcomes

Occasionally, listing a proposed medicine may have direct patient benefits that are not health outcomes – for example, providing a more convenient form of administration to the patient.

Supplementary methods to estimate the monetary (or other) value of the nonhealth benefit may include a conjoint analysis or a discrete choice experiment that includes a monetary attribute, an attribute reflecting a range of options for each of the nonhealth outcomes of interest, and/or other attributes.

Where there are no other substantive changes in health outcomes between the proposed medicine and its main comparator, this estimate (eg willingness to pay) can be included in a supplementary cost-benefit analysis. Where this cost-benefit analysis results in a consumer surplus, nominate a suitable basis for sharing this consumer surplus between the sponsor and the taxpayer.

Production changes

In the context of health economics analyses, a production change is a change in total output value across society of productive work in the economy. Productivity is a function of output units (eg days of work) multiplied by their value (eg an appropriate daily wage as a proxy for the value of each day of work).

Health interventions may claim to result in a change in production across society associated with patients gaining or losing working time as a result of changes in their health and consequent capacity to work. Less commonly, a health intervention may claim that workers' efficiency will be affected, such that the value of their work output is changed on a per-unit basis (ie it can be represented by a higher or lower wage).

Changes in production as an outcome of therapy may be included in supplementary analyses in submissions to the PBAC, but do not include them in the base-case analysis. This separation allows the PBAC to consider the impact of including production changes on the direction and extent of change on the base case. Including production gains favours interventions that improve the health of people who are able, and choose, to return to contributing to societal production and, hence, there are equity implications of including productivity changes in the base case.

If presenting productivity claims associated with a proposed medicine, there are several difficulties in estimating the net present value of production changes. From a societal perspective, the productivity of an individual worker cannot be considered in isolation, but should be considered in the context of a workplace, a workforce and society. The following three underpinning assumptions should be incorporated into all productivity analyses:

- For short-term absence, production will be made up on return to work.
- Employers usually have excess capacity in the labour force to cover absenteeism.
- For long-term absence, production will be made up by a replacement worker who would otherwise be unemployed.

When presenting estimates of the marginal increase in society's production because of the return of healthy workers:

- provide details of the method used and its assumptions
- discount appropriately any productivity changes anticipated beyond one year
- address each of the assumptions listed above when estimating production changes from the potential working time gained or lost (reported in time units).

For example, the claim that there has been a recovery of production lost because of returning to health from an episode of illness depends on demonstrating the following three factors:

- The worker returns to work and the worker is productive.
- The production lost is not made up elsewhere by others in the company or the same worker following return to work.
- No temporary replacement has been employed.

Address each of these three factors to provide robust evidence in support of estimates.

Ensure that estimates of the proportion of people who choose to return to work account for those who would choose not to return (and instead use their time gain on other activities that will have been captured by a gain in utility weights), as well as the influence of incentives provided through sickness benefits, which may operate differently across jurisdictions.

The approach above may be adapted to other contexts, such as a medicine that prevents future episodes of illness, or a medicine that might improve production capacity in individuals who, without the proposed medicine, would otherwise stay at work, although unwell, and therefore function at less than full production capacity.

When the economic approach is a cost-utility analysis, discuss how the method of estimating productivity changes avoids double-counting the estimates of health-related quality-of-life changes. The utility weights in this analysis already capture these health-related changes because they incorporate the utility impacts of productive capacity for the individual receiving the proposed medicine. These health-related changes are therefore already appropriately included in the denominator of the cost-utility ratio.

Strongly justify any production changes that are combined with surrogate outcome indicators in an economic evaluation, because this combination is generally associated with inappropriately high levels of uncertainty.

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