Australian Government

Department of Health and Ageing

Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee
(Version 4.0)

November 2006

Pharmaceutical Benefits Advisory Committee

ISBN: 1-74186-170-5 (print version)
ISBN: 1-74186-171-3 (online)

Publications Approval Number: 3963

Address for correspondence

The Secretary
Pharmaceutical Benefits Advisory Committee
GPO Box 9848
CANBERRA ACT 2601

Submissions should be delivered to:

10th Floor
Scarborough House
Atlantic Street
PHILLIP ACT 2606

Foreword

This revision of the *Guidelines for Preparing Submissions to the Pharmaceutical Benefits Advisory Committee* is the first full revision of the guidelines since 1995 and has involved substantial changes in many areas of the document. These changes have built on experience gained since the first revision of the guidelines was published in 1995 based on the experience of making decisions relying on cost-effectiveness. The revision process has included 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.

The release of this revision coincides with an increasing international trend towards reliance on information about the costs and effectiveness of medicines by large third-party payers, including governments managing drug subsidy programs. It is anticipated that, as interest and expectations increase, this reliance may start to guide the drug development process internationally. Awareness of this trend has influenced the development of this revision.

These guidelines are structured and comprehensive. 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 minimise uncertainty where possible. However, while they represent the currently preferred approach, reflecting the experience of more than one thousand decisions, they are not prescriptive and there is flexibility in their interpretation.

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.

Lloyd Sansom
Chair
Pharmaceutical Benefits Advisory Committee

Contacts

Pharmaceutical Benefits Advisory Committee Secretariat

The Pharmaceutical Benefits Advisory Committee (PBAC) and its subcommittees have secretariats within the Australian Government Department of Health and Ageing:

PBAC Secretariat and Listings Section
Tel: (02) 6289 7099
Fax: (02) 6289 4175

Economics Sub-Committee (ESC) and Drug Utilisation Sub-Committee (DUSC)
Pharmaceutical Evaluation Section
Tel: (02) 6289 7501 (ESC Secretary)
(02) 6289 7293 (DUSC Secretary)
Fax: (02) 6289 8633

Vaccines are considered by the Australian Technical Advisory Group on Immunisation (ATAGI), which also has a secretariat within the Australian Government Department of Health and Ageing:

ATAGI: Immunisation Section
Tel: (02) 6289 8572
Fax: (02) 6289 3677

The secretariats are available for discussion about proposed submissions or related matters. They are also the first point of contact concerning the relevant committee's discussions and decisions.

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Pharmaceutical Benefits Advisory Committee
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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

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Abbreviations

the Act	*National Health Act 1953*
ACIR	Australian Childhood Immunisation Register
ACTR	Australian Clinical Trials Registry
ADEC	Australian Drug Evaluation Committee
AQoL	Assessment of Quality of Life
AR-DRG	Australian Refined Diagnosis Related Group
ARTG	Australian Register of Therapeutic Goods
ATAGI	Australian Technical Advisory Group on Immunisation
ATC	anatomical therapeutic chemical
CBA	cost-benefit analysis
CEA	cost-effectiveness analysis
CI	confidence interval
CUA	cost-utility analysis
CV	contingent valuation
DoHA	Australian Government Department of Health and Ageing
DPMQ	dispensed price for maximum quantity
DUE	drug usage evaluation
DUSC	Drug Utilisation Sub-Committee
ESC	Economics Sub-Committee
HUI	Health Utilities Index
ID	identification
ITT	intention to treat
MAUI	multi-attribute utility instrument
MBS	Medicare Benefits Scheme
NIP	National Immunisation Program
NNT	number needed to treat
NPS	National Prescribing Service
NPWP	Nutritional Products Working Party
PBAC	Pharmaceutical Benefits Advisory Committee
PBPA	Pharmaceutical Benefits Pricing Authority
PBS	Pharmaceutical Benefits Scheme
QALY	quality-adjusted life-year
QUM	quality use of medicines

RADAR	Rational Assessment of Drugs and Research
RDI	recommended dietary intake
RPBS	Repatriation Pharmaceutical Benefits Scheme
RSA	risk-sharing arrangement
SG	standard gamble
TGA	Therapeutic Goods Administration
TGP	Therapeutic Group Premium
TPN	total parenteral nutrition
TTO	time trade-off
WTP	willingness to pay

PART I

GENERAL INFORMATION

1 Role of the Pharmaceutical Benefits Advisory Committee

1.1 Overview of PBAC roles

The Pharmaceutical Benefits Advisory Committee (PBAC) is established under the *National Health Act 1953* (the Act). Its primary role is to recommend to the Minister for Health which drugs and medicinal preparations should be subsidised by the Australian Government under the Pharmaceutical Benefits Scheme (PBS). In doing this, PBAC is required by the Act to consider both the effectiveness and cost of the proposed drugs and medicinal preparations.

Since the beginning of 2006, PBAC has also been required under the Act to recommend to the Minister for Health vaccines for funding under the National Immunisation Program (NIP). The principles described here for considering PBS listing of drug products in general also apply to the funding for vaccines by the NIP. Accordingly, in the remainder of these guidelines, unless otherwise indicated, references to the PBS should be taken to include the NIP, and the term 'drugs' to include vaccines. Following due process, PBAC regularly reviews the list of PBS items, including restrictions, maximum quantities and number of repeats. It also provides advice about any other matters relating to the PBS that are referred to it by the minister.

Box 1.1 lists the main roles of PBAC. Further details are given in the remainder of this chapter.

Box 1.1   Roles of the Pharmaceutical Benefits Advisory Committee

- Recommends drugs and medicinal preparations to the Minister for Health for funding under the Pharmaceutical Benefits Scheme (PBS).

- Recommends vaccines for funding under the National Immunisation Program (since 2006).

- Advises the minister and the Pharmaceutical Benefits Pricing Authority about cost-effectiveness ('value for money').

- Recommends maximum quantities and repeats on the basis of community use, and any restrictions on the indications where PBS subsidy is available.

- Regularly reviews the list of PBS items.

- Advises the minister about any other matters relating to the PBS.

1.2   Membership of PBAC and its subcommittees

The membership of PBAC is prescribed in the Act. The members, who are appointed by the Minister for Health, include medical practitioners (specialists, general practitioners and clinical pharmacologists), pharmacists, consumers and health economists. The membership is published in the *Government Gazette* and details are available on request from the PBAC Secretariat.

Under the Act, PBAC may also establish subcommittees, comprising members with appropriate expertise, to help it perform its functions. There are currently two subcommittees:

- **Drug Utilisation Sub-Committee (DUSC)** — which monitors the patterns and trends of drug use and makes such data available publicly. DUSC evaluates use and financial forecasts of selected major submissions to PBAC. DUSC was formed by PBAC in 1988. The members have a broad range of relevant expertise and mainly come from organisations interested in the evaluation of drug utilisation.

- **Economics Sub-Committee (ESC)** — which advises on cost-effectiveness policies and evaluates cost-effectiveness aspects of major submissions to PBAC by reviewing and interpreting economic analyses and assessing their quality, validity and relevance. After a preliminary period as a working party, ESC was formed by PBAC at the beginning of 1994. The members include clinicians, clinical epidemiologists, health economists, biostatisticians and clinical pharmacologists. As part of its terms of reference, ESC is also responsible for revisions of the guidelines (see Subsection 2.1).

1.3   Assessing suitability for listing

The primary objective of the PBS is to improve health. The range of drugs and forms available under the PBS provides a formulary of drugs to meet the health needs of the majority of the Australian community. The role of a drug product in meeting the health needs of the Australian community is therefore a primary consideration. Thus, PBAC focuses on health outcomes.

PBAC may also consider nonhealth outcomes, including aspects of the delivery of a health care intervention beyond the health gain obtained; for example, greater convenience or production gains to society beyond those valued by the population benefiting with improved health. However, the valuation of nonhealth outcomes is not straightforward and those outcomes might not be as influential in decision making as health outcomes.

Similarly, PBAC mainly considers the costs of providing health care resources. These extend beyond the costs of the drug to include possible cost offsets of reduced provision of health care resources as a result of listing a drug. PBAC may also consider costs and cost offsets of nonhealth care resources, but these might not be as influential in decision making as health care resources.

1.3.1 Regulatory framework

All new pharmaceutical products must be registered on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA) before being generally marketed in Australia. Registration is based on assessment of quality, safety and efficacy, a process that usually involves the Australian Drug Evaluation Committee (ADEC). PBAC therefore accepts that products included on the ARTG have established safety and efficacy adequate to allow marketing in Australia. Products are registered for specific therapeutic indications and, in general, PBAC does not recommend a product to be listed in the PBS for indications beyond those registered.

Listed drugs are classified either as pharmaceutical benefits (drugs listed under section 85 of the Act), special pharmaceutical products (drugs listed under section 100 of the Act as requiring special distribution arrangements, such as highly specialised drugs; see Subsection 1.3.6), or vaccines (listed in the NIP schedule under section 9C of the Act). However, the requirements of the PBAC under the Act, and thus the considerations for listing and submission requirements, are the same for each type of listing.

1.3.2 Quality use of medicines

PBAC encourages the quality use of medicines (QUM) through the inclusion of cautions and notes in the PBS Schedule, the wording of PBS restrictions and the provision and publication of Australian drug utilisation data. It supports the educational activities promoting the appropriate use of pharmaceutical benefits by the National Prescribing Service (NPS), particularly its Rational Assessment of Drugs and Research (RADAR) program. In making a submission, sponsors should be aware of the possibility that PBAC could refer matters for inclusion in this program alongside a recommendation to list a proposed drug. Further information on QUM is provided in Part II, Subsection F.1.

1.3.3 General guidelines followed by PBAC

Under the Act, PBAC is required to consider the effectiveness and cost of a proposed PBS listing compared with other therapies. Therefore, when recommending listings to the Minister for Health, the committee also advises the Pharmaceutical Benefits Pricing Authority (PBPA) about how the new listing compares with alternative drugs and/or current standard care in terms of cost-effectiveness ('value for money'). The general guidelines followed by PBAC are shown in Box 1.2.

To assess value for money, PBAC considers the clinical place, overall effectiveness, cost and cost-effectiveness of a proposed drug compared with other drugs already listed in the PBS for the same, or similar, indications. Where there is no listed alternative, PBAC considers the clinical place, overall effectiveness, cost and cost-effectiveness of the proposed drug compared with standard medical care. On the basis of its community usage, PBAC recommends maximum quantities and repeats and may also recommend restrictions as to the indications where PBS subsidy is available.

Box 1.2   General guidelines followed by PBAC

A new drug may be recommended for listing if:

- it is needed for the prevention or treatment of significant medical conditions not already covered, or inadequately covered, by drugs in the existing list and is of acceptable cost-effectiveness

- it is more effective or less toxic (or both) than a drug already listed for the same indications and is of acceptable cost-effectiveness

- it is at least as effective and safe as a drug already listed for the same indications and is of similar or better cost-effectiveness.

A new drug that is less effective and/or more toxic than a drug already listed for the same indications might be considered for listing. In such a circumstance, other supportive factors would be needed to justify a recommendation, for example, if the new drug would decrease the overall costs of therapy and/or if it were restricted to a subsequent line of therapy after the more effective or less toxic therapy.

Recommendation to list a new drug is unlikely if:

- its use might increase problems of abuse or dependence

- its sole use would be to treat an individual patient whose response to, or need for, a drug is unique.

Removal of a drug from the list may occur if:

- a more effective or equally effective but less toxic drug becomes available

- evidence becomes available that the effectiveness of the drug is unsatisfactory

- evidence becomes available that the toxicity or abuse potential of the drug outweighs its therapeutic value

- the drug has fallen into disuse or is no longer available

- treatment with a drug is no longer deemed cost-effective compared with other therapies.

PBAC follows due process in considering the removal of a drug, including consulting with affected stakeholders.

At the direction of the Minister for Health, PBAC:

- takes into account the community need or benefit, particularly for additional forms of an already-listed drug where proliferation of products might cause confusion

- gives a lower priority for listing to a drug intended specifically for in-hospital use, since the PBS is primarily for community-based patients

- gives a low priority for listing to a drug for the treatment of clinically minor or trivial conditions.

1.3.4 Setting conditions of use

PBAC makes recommendations about the maximum quantity and the number of repeat prescriptions that should be available for each form of a drug. For acute medical conditions, the maximum quantity is usually sufficient for a normal single course of treatment (bearing in mind the size of the manufacturer's pack). For chronic medical conditions, the maximum quantity and repeats usually provide up to six months' therapy, depending on the need for clinical review of the condition to be treated. For patients requiring higher than average doses, increases in the listed maximum quantities and repeats are generally available through the authority system (see Subsection 1.3.5).

1.3.5 Restricted benefit and authority required listings

Drugs and medicinal products can be listed on the PBS as:

- unrestricted benefits, which have no restrictions on their therapeutic uses for the purposes of subsidy
- restricted benefits, which can only be prescribed for specific therapeutic uses
- authority required benefits, which are restricted and can only be prescribed with previous approval from Medicare Australia or the Australian Government Department of Veterans' Affairs.

A drug or drug form is considered for restricted benefit or authority required listing for the following reasons:

- to limit PBS usage so that this is in accordance with the approval and registration granted by the TGA
- to allow the controlled introduction of a drug in a new therapeutic class
- to limit PBS usage to the indications, conditions or settings seen as being appropriate for clinical, cost-effectiveness, or other reasons
- to alleviate concerns about adverse reactions, possible misuse, overuse or abuse.

1.3.6 Highly specialised drugs

Following an agreement between federal and state and territory health ministers, the Highly Specialised Drugs Working Party was established in 1991. The Highly Specialised Drug Program operates under section 100 of the Act and subsidises the use of highly specialised drugs through hospital outpatient departments for community patients whose treatment is not appropriate for a community medical practice setting.

1.4 Processing submissions

PBAC considers submissions from industry sponsors of drug products, medical bodies, health professionals, 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.

PBAC is conscious of the need to be as open as possible in its proceedings, consistent with the secrecy provisions of the Act. It therefore provides to sponsors all relevant documents and evaluations considered by the committee. It also allows up to two sets of written pre-PBAC consultation documents from each sponsor in relation to its submission for a product, as well as a hearing before the committee when it is considering advice from its subcommittees.

Although marketing approval and registration on the ARTG are prerequisites for PBS listing (see Subsection 1.3.1), PBAC accepts submissions before finalisation of marketing approval, provided that the TGA delegate has recommended the drug for registration in his or her overview (advice to ADEC).

1.4.1 Sources of advice

In formulating its conclusions, PBAC may seek expert opinion from relevant professional bodies and/or appropriate specialists, and may meet with representatives of relevant medical professional organisations and colleges. PBAC may also seek input from appropriate consumer bodies. As a routine, PBAC seeks advice from the Australian Technical Advisory Group on Immunisation in relation to vaccines, the Nutritional Products Working Party in relation to nutritional products and the Expert Advisory Group on Antibiotic Resistance in relation to the development of resistance to new antimicrobial agents. Where advice is obtained, due process is followed, in which the relevant sponsor is informed and given an opportunity to reply.

1.4.2 Timing of PBAC procedures

PBAC is conscious of the need to avoid unnecessary delays between marketing approval and subsidised listing where the latter is appropriate. To this end, all submissions received by a reasonable cut-off date are considered at the next PBAC meeting. These cut-off dates are provided to the pharmaceutical industry well in advance of meetings.

The meeting dates for the following year, and the associated cut-off dates, are advised to industry following each July PBAC meeting and are posted on the PBAC area of the Australian Government Department of Health and Ageing (DoHA) website.[1] The cut-off date for major submissions is generally 17 weeks before the PBAC meeting (18 weeks over the Christmas to New Year period). Minor submissions may be accepted up to 6 weeks later (11 weeks before the PBAC meeting). Contact should be made with the PBAC secretariat before presenting a submission. Further information on major and minor submissions is given in Section 3.

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[1] http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-listing-dates.htm

Submissions should be presented on time and should be complete. No guarantee can be given that material supplied late will be incorporated into the submission or included in the agenda papers. Advice of committee decisions is provided to sponsors in writing within 15 working days of a meeting, and PBAC and PBPA meetings are coordinated to minimise processing time.

Box 1.3 shows a timeline for major actions and events in PBAC procedures, relative to PBAC meetings. PBAC public output in relation to a submission includes a brief summary of the outcome[2] followed by a more extensive public summary document.[3]

Box 1.3   Timeline of PBAC procedures

Action or event	Time relative to PBAC meeting
• TGA delegate's overview/advice to ADEC and/or ADEC resolution and/or TGA registration granted	
• Cut-off date for major submissions to department	17 weeks before
• Cut-off date for minor submissions to department	11 weeks before
• Departmental papers to sponsors	6 weeks before
• Sponsor's pre-subcommittee response to department	5 weeks before
• Meeting of subcommittees	4 weeks before
• Subcommittee papers to sponsors	2 weeks before
• Sponsor's pre-PBAC response to department	1 week before
• PBAC meeting	
• Verbal advice to sponsor	half a week after
• Written advice to sponsor	3 weeks after
• Publication of PBAC outcomes on departmental website	6 weeks after
• PBAC ratified minutes to sponsor	10 weeks after
• Publication of public summary document on departmental website	16 weeks after
• Publication of public summary document (first time rejections)	18 weeks after

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[2] See http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-outcomes
[3] See http://www.health.gov.au/internet/wcms/publishing.nsf/Content/public-summary-documents

2   Introduction to the guidelines

These *Guidelines for Preparing Submissions to the Pharmaceutical Benefits Advisory Committee* (referred to in this document as the 'PBAC Guidelines') provide practical information for the pharmaceutical industry for making a submission to PBAC.

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

2.1   Development of the guidelines

2.1.1   History of the guidelines

The PBAC Guidelines were first released in draft form in August 1990. Initially, their use was optional, and this period provided valuable experience and feedback. Constructive and detailed criticisms of the draft guidelines were received from pharmaceutical companies, the Australian Pharmaceutical Manufacturers Association and independent experts. This feedback was reviewed in detail to produce the first revision in August 1992.

In January 1993, it became mandatory for companies making submissions to PBAC to follow these guidelines. The experience base has expanded greatly, and this revision draws on the lessons of more than 1200 submissions containing economic evaluations. The pool of experienced evaluators has also expanded beyond the Pharmaceutical Evaluation Section within DoHA and now includes four independent groups working under contract. The ESC, which was formed by PBAC at the beginning of 1994 (see Subsection 1.2) is responsible for revisions of the guidelines.

In 1995, PBAC endorsed the first experience-based revision, by any decision maker in the world, of guidelines on presenting economic analyses of medicines. Two years later, PBAC released a glossary to accompany the guidelines, with the objective of working with a common set of terminology and definitions (see Subsection 2.1.3).

In 2002, PBAC endorsed a revision of the guidelines that consolidated a number of changes that had been announced over the years since 1995. That revision identified a wide number of topics requiring more substantive consideration in a subsequent revision.

2.1.2   This revision

Overall, the PBAC Guidelines continue to stand the test of time. In developing this current revision, PBAC has reviewed all the existing material and addressed many new topics that have been identified since 2002. At the start of the review, a list of topics was agreed with representatives of the groups that prepare submissions to PBAC. This process was coordinated by Medicines Australia, which is the peak group representing multinational pharmaceutical companies in Australia. Proposals in relation to each section and to new appendixes were then discussed over a series of meetings involving Medicines Australia representatives, ESC members (and DUSC members for drug utilisation

matters) and relevant departmental officers. These discussions were informed by the emergence and revision of similar guidelines overseas.

The outcome of these meetings was the development of a draft of the revised guidelines. This consultation draft was published on DoHA's website, with a wide invitation seeking comments from any interested party. Subsequently, a professional medical writer was contracted to improve the presentation, layout and clarity of the document. Following a careful review of feedback received, a further meeting with Medicines Australia and many subsequent changes made to improve the document, ESC and PBAC are pleased to endorse this substantive revision for use by preparers, evaluators and users of submissions to PBAC.

This revision primarily seeks to maximise the confidence of PBAC in accepting the many inferences necessarily made in major submissions. New sections help improve the translation of the best available comparative clinical data to the PBS listing as a prelude to the economic evaluation; request that the budget impact analysis is aligned with a standardised Excel workbook that facilitates the presentation of these analyses in a consistent way across submissions; and encourage the provision of other relevant information.

Additional sections in Part III also provide guidance on presenting information from less preferred sources, including indirect comparisons based on randomised trials or nonrandomised studies and an economic evaluation based on a conclusion of noninferiority. Some additional information to support these and other aspects of the submission are included in appendixes (see Subsection 2.2 for further details of the structure of the guidelines).

2.1.3   Associated documents

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

- the *Manual of Resource Items and their Associated Costs for use in Submissions to the Pharmaceutical Benefits Advisory Committee Involving Economic Evaluation* (PBAC Manual; DoHA 2002)[4]

- the Glossary to the PBAC Guidelines (DoHA 1997)[5]

- *Sources of Epidemiological Data for Use in Generating Utilisation Estimates* (DoHA 2006)[6]

- Highly Specialised Drug Program criteria[7]

- Utilisation and cost model spreadsheets for PBAC submissions (DoHA 2006)[8]

- *Applications for Additional Brands of Existing Pharmaceutical Benefit Items* (DoHA 2005).[9]

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[4] http://www.carers.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pubs-manual-section3.htm

[5] http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pubs-pharmpac-glossary-glossary.htm-copy3

[6] November 2006: this document temporarily unavailable while being updated

[7] http://www.pbs.gov.au/html/healthpro/browseby/section100?subbook=HS

[8] http://www.health.gov.au/internet/wcms/publishing.nsf/Content/PBAC_Submission_Proforma

The PBAC Manual is revised periodically in the same way as the PBAC Guidelines. The Glossary will be revised alongside this revision of the PBAC Guidelines (see Subsection 2.4).

2.2 Structure of the guidelines

The guidelines are organised into four parts, as follows:

- **Part I (General information)**
  Part I provides background on the purpose and development of the guidelines, including the importance of including an economic evaluation, layout and style conventions, different types of submissions, and a checklist of the information that is to be contained in a submission.

- **Part II (Guidelines for preparing a major submission using preferred data and more common analyses)**
  Part II provides information on the preferred content and presentation for the majority of major submissions (see Subsection 5.2 for an overview). The content of a major submission is based on direct randomised trials and presentation of a cost-effectiveness or cost-utility analysis based on a conclusion of therapeutic superiority for the proposed drug over the main comparator. The order of the sections in Part II follows the order in which information should be presented as submission sections A–F (see Subsection 5.2.1).

- **Part III (Guidelines for preparing a major submission using other data or less common analyses)**
  Part III provides requests for further and/or alternative information that is relevant for a minority of major submissions where:
  – direct randomised trial evidence is not available for submission section B
  – a cost analysis or a cost-minimisation analysis is presented in submission section D
  – a budget impact analysis is presented using a market-share approach.

- **Part IV (Additional information requests for specific types of products)**
  Part IV provides further requests for information for major submissions for the following types of products:
  – fixed combination products
  – nutritional products
  – vaccine products.

Appendixes include additional information on various aspects of the submission.

Subsection 5.2 includes further information on the designation of sections and subsections of these guidelines and cross-referencing between parts and sections of the document.

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[9] http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-listing-guidelines.htm+-+copy1

2.3 Writing and style conventions used in these guidelines

Several conventions have informed the revision of the guidelines to assist users of the document to navigate their way to the information needed when preparing their submissions.

The PBAC Guidelines include a series of requests for specific types of information. The aim is to provide an ordered series of reference points (requests for information) 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 **should** be done. This allows requests for information that is known to be more persuasive or influential to be communicated as simply as possible in these guidelines. Following these requests helps to improve the comparability of submissions considered by PBAC and hence the consistency of decision making.

Within each section, the main requests for information expected to be addressed by each major submission are highlighted as '**Information requests**' in boxes. Other subsidiary requests and background information are provided in normal text.

In two instances, the request includes the word '**must**'. These only relate to the physical presentation of the main body of the submission and the requirement to provide all relevant direct randomised trials when these are available. In each case, the requirement is included in the 'Information requests' box under the separate heading of '**Information requirements**'. Failure to comply with these requests is sufficient to render the submission unacceptable, and for the submission to be returned to the sponsor.

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

> **Key points — writing style used in these guidelines**
>
> **Default (imperative)**
>
> Requests for information that are expressed as imperatives **should** be followed wherever possible. However, such requests allow submitters to select the specific information they include in the submission to meet the request, and to provide justification when providing alternative information to that requested.
>
> Major requests for information are shown in the boxes at the start of each section of text ('**Information requests**'); subsidiary requests and further information are included in the text of each section.
>
> **Must**
>
> Submissions **must** follow requests for information that contain the term, 'must', for the submission to be acceptable.
>
> Such requirements are shown in the boxes at the start of the relevant section with the heading '**Information requirements**'. Failure to follow such requirements will result in an unsuccessful submission.
>
> **Could**
>
> Requests for information that contain the term, '**could**', allow the submitter to choose what type of information to present, based on the options provided. Submissions should explain the reasons for selecting the information presented.

2.4 The future

These PBAC Guidelines will remain a living document that will be open to regular review and improvement. The revision process will continue to be managed by the ESC in consultation with those who prepare submissions to PBAC. Future revisions will be on smaller scale and disseminated through the website of DoHA on a more frequent basis. A summary of each change will be recorded at the front of the electronic version published on the DoHA website, and those involved in preparing submissions will be notified.

Further feedback on these guidelines is welcome and should be forwarded to:

The Director
Pharmaceutical Evaluation Section
MDP 83
Department of Health and Ageing
GPO Box 9848
Canberra ACT 2601
AUSTRALIA

Particular topics identified for attention following the publication of this 2006 version of the PBAC Guidelines include:

- updating the Glossary (see Subsection 2.1.3)
- providing more background information on the various 'section 100' programs, including the Highly Specialised Drugs Program

- reviewing the primary perspective to be adopted (societal or health care system) and any differential weighting of inputs in an economic evaluation with consequential implications for:

  – the valuation and incorporation of production changes in an economic evaluation
  – broader impacts beyond the health of the individual receiving the medicine (eg including carers)
  – the place of cost-benefit analysis in routine PBAC decision making

- considering further guidance in relation to other technical policy issues:

  – selecting the main comparator
  – indirect comparisons in relation to direct randomised trials
  – nonrandomised studies (observational data) in relation to randomised trials
  – other statistical techniques, such as Bayesian analyses
  – transforming surrogate outcomes for clinical and economic evaluation
  – sensitivity analysis in economic evaluation
  – postmarketing surveillance
  – PBAC's contribution to risk-sharing arrangements
  – influence of QUM on PBAC considerations
  – 'biosimilar' drugs.

3 Types of submissions

This chapter identifies three broad categories of requests for either new PBS listings or amendments to existing listings and indicates the types of submissions that are required. The remainder of these guidelines is concerned only with major submissions, which include the presentation of an economic evaluation.

Depending on the type of request, a submission can be assessed at three levels:

- evaluation by the Pharmaceutical Evaluation Section
- review by subcommittee members
- review by PBAC members.

3.1 Submissions to list generic equivalents

Listing a generic equivalent (or new brand) of the same form of an already-listed drug does not usually require a submission to PBAC. However, a submission should still be sent to the PBAC Secretary for consideration within the Pharmaceutical Evaluation Branch (but it is not forwarded to PBAC). Further information can be obtained from the PBAC Secretariat and Listings Section (see page iv) and from the *Applications for Additional Brands of Existing Pharmaceutical Benefit Items* (see Subsection 2.1.3).

3.2 Minor submissions

Some submissions relate to new forms of previously listed products or changes to the conditions of use. Such submissions are considered to be minor submissions and include requests for the following additions or changes to the Schedule of Pharmaceutical Benefits:

- listing a new form (or strength) of a currently listed drug for which a price advantage is not requested, or for which the likely volume and proportion of use is expected to be small (in which case the main aspect of the submission is to justify the clinical need for the product on the PBS)
- changing the maximum quantity per prescription of a currently listed drug
- changing the number of repeats per prescription of a currently listed drug
- clarifying the wording of a restriction (while not altering the intended use).

The above list is not necessarily exhaustive, as there may be other types of minor submissions. If in doubt about the status of a submission, sponsors should seek the advice of the PBAC Secretariat (see page iv).

Minor submissions do not usually require the presentation of an economic evaluation (see also Subsection 3.4.3). They are not evaluated by the Pharmaceutical Evaluation Section before consideration by PBAC. Table 3.1 shows a checklist of information that is required for a minor submission. Information on cut-off dates for presentation of minor submissions is given in Subsection 1.4.2.

Table 3.1   Checklist of information to be included in a minor submission

Component	Included?
• Two copies of the full submission (which may just be a simple letter explaining or justifying the change and detailing the timing involved)	Y/N
• One copy of the current TGA-approved product information with approval date (if and when available, with the latest draft product information in the meantime)	Y/N
• An electronic version of the submission, such as on a computer disk or a compact disk	Y/N
If the submission is for a new form or strength of a currently listed drug:	
• One copy of the PB11 (the official application form)	Y/N
• One copy of the letter of registration with details of marketing approval and registration (if and when available)	Y/N
If applicable, one copy (bound as a set) of:	
– the full TGA clinical evaluator's report	Y/N
– the TGA delegate's overview (advice to ADEC)	Y/N
– the ADEC resolution (if and when available)	Y/N
– the relevant extract of the ADEC minutes (if and when available)	Y/N
• If the relevant registration application was not considered by ADEC, then provide the summary from TGA identifying evidence for the decision to register the new form or strength	Y/N

3.3   Major submissions

Submissions to list new drugs on the Schedule of Pharmaceutical Benefits or to make substantial changes to current listings are classified as major submissions. Examples include the following requests for additions or changes to the schedule:

- list a new drug (including a new fixed combination product, a new nutritional product, a new vaccine or a new orphan drug)

- substantially change the listing of a currently restricted drug (including a new indication or a derestriction)

- enable a review of the comparative cost-effectiveness of a currently listed drug in order to change a PBAC recommendation to the PBPA on its therapeutic relativity or price advantage

- list a new form (or strength) of a currently listed drug for which a price advantage is requested.

Major submissions require presentation of an economic evaluation. They are evaluated by the Pharmaceutical Evaluation Section and presented to ESC before consideration by PBAC. Information on cut-off dates for presentation of major submissions is given in Subsection 1.4.2.

The remainder of these guidelines provides detailed information for the preparation of major submissions.

3.3.1   Orphan drugs

When a drug is used to treat a rare disease or disorder (defined as having a prevalence of ≤2000 individuals in Australia), it can be identified by the TGA as an 'orphan drug'.

PBAC is aware of, and sympathetic to, the difficulties faced by sponsors of orphan drugs. Furthermore, the committee does not set a minimum standard for the type and level of evidence or other information that can be included in a submission to PBAC. However, it would be unlawful for PBAC not to consider comparative costs and effectiveness. See Part II, Subsection F.3 for further guidance on identifying information that might be relevant to a submission for an orphan drug, such as whether the 'rule of rescue' might apply.

3.4 Resubmissions

Resubmissions ask PBAC to reconsider matters from relevant previous submissions. Even if such a submission is based entirely on new data, modifies the previously requested restriction or changes the comparator, it will be regarded as a resubmission. This is because the information in the resubmission will have to provide the basis for any change to PBAC's earlier decision.

3.4.1 Aspects to be highlighted in a resubmission

The following matters should be highlighted in a resubmission:

- the main matters of concern to PBAC and/or the matters that PBAC has requested to be addressed

- the matters in dispute if the sponsor disagrees with the reasons for the previous decision

- how the resubmission addresses each of these matters, including:

  – identification of all new circumstances, new data, new arguments or new approaches included in the resubmission

  – comparison of the resubmission and the previous submission

  – a commentary on how the new material changes the previous basis of PBAC's considerations.

It is particularly important to highlight any changes to the structure and/or the variables in a modelled economic evaluation. Compare the structures and/or variables across the revised model and the previous model so that the implications for the changes in the results of these models can be made clear. Provide an electronic version of the revised model as part of the resubmission, together with an electronic version of the previous model if necessary.

Any new randomised trial relevant to the clinical evaluation should be presented separately and incorporated into the systematic overview presented in Part II, Subsection B.6. Unless there is a substantial change to the requested restriction, or the new trial changes the basis of the previous submission (eg enables a direct randomised comparison in preference to an indirect comparison), new randomised trial data augments rather than replaces the previous overview.

3.4.2 Presentation of a resubmission

There are three interrelated issues that are helpful to have in mind when preparing the materials of a resubmission:

- A resubmission should stand alone by containing all supporting documentation relied on by the resubmission as necessary for PBAC to reach a decision. Do not assume that those evaluating or considering the resubmission will have any aspect of a previous related submission on hand. However, previous information clearly not in dispute (eg pharmacology, actions and uses, marketing status, approved indications) need not be included in a resubmission.

- A resubmission should refer to previous considerations and thus should be seen as part of a continuum of considerations. Inevitably, conclusions would have been drawn about the drug (or the model or any other aspect of a submission that may be in dispute) during the previous considerations. An essential aim of a resubmission is to change at least some of those conclusions in order to change the overall decision (eg from rejection to recommendation).

  However, a resubmission should not be based on the assumption that any comment made in a previous pre-subcommittee or pre-PBAC response document has been accepted, unless the matter is specifically accepted in the subcommittee advice or in the PBAC minutes. This is because these response documents are not formally reviewed by the areas or subcommittees responsible for preparing the documents on which the responses are based. If the matter is relevant to the resubmission, then it should be re-presented as having been provided following the lodgment of the previous submission, together with any comment from the relevant subcommittee or PBAC as appropriate.

- A resubmission should thus integrate all the extra materials submitted into the flow of the claims, together with their supporting evidence in the main body of the resubmission. Cross-referencing is particularly important, because there is usually a large amount of material in any submission.

3.4.3 Minor resubmissions

On exceptional occasions, a sponsor may seek to lodge a resubmission that would not qualify for any of the circumstances for minor submissions in Subsection 3.2, but that contains new aspects that could be argued to be straightforward (eg reducing the price and re-running an otherwise accepted economic evaluation without other changes to show the impact of this reduction). Such a circumstance may be identified by PBAC in deciding not deciding to recommend on the basis of the previous submission. Otherwise, sponsors are encouraged to seek the advice of the PBAC Secretariat (see page iv). As a minor resubmission, it is expected that it would not introduce substantive changes, such as a different population identified by a modification to the requested restriction, a different nomination for the main comparator, new data or substantive new analyses. Such changes might result in a PBAC request for a major resubmission to examine the implications of the substantive change.

Minor resubmissions are not evaluated by the Pharmaceutical Evaluation Section.

Key points — types of submissions

- *Submissions to list generic equivalents*:
  – are usually considered only by the Pharmaceutical Evaluation Branch.
- *Minor submissions to list new forms of previously listed products or changes to the conditions of use*:
  – do not require an economic evaluation
  – are not evaluated by the Pharmaceutical Evaluation Section or presented to the ESC before consideration by PBAC.
- *Major submissions to list new listings, including orphan drugs and significant changes to existing listings*:
  – require an economic evaluation
  – are evaluated by the Pharmaceutical Evaluation Section and presented to the ESC before consideration by PBAC.
- *Resubmissions*:
  – are usually considered to be major submissions
  – might be considered to be minor submissions under exceptional circumstances.

4 Rationale and basis for the economic evaluation

Australia, like other countries, is faced with a steady increase in the total cost of pharmaceuticals. Although the drug budget is not 'capped' in Australia, choices must be made as to which drugs will have their use subsidised by the Australian Government. Economic evaluation is one factor to be considered when making choices between competing therapeutic modalities. Other important factors which are considered include uncertainty, equity, extent of use and total costs (see Subsection 4.5).

4.1 Analysis of cost-effectiveness

Since January 1993, PBAC has considered the results of economic analyses in its decision making to assess the degree to which new drugs represent 'value for money' for the Australian community. To achieve this, an economic evaluation is required with all major submissions; that is, a submission for a new drug, a submission to substantially change the restricted listing of an already-listed drug, or a resubmission in these circumstances (see Section 3 for further details about different types of submissions). These submissions must also be evaluated by the Pharmaceutical Evaluation Section and be presented to the ESC before they are considered by PBAC.

The primary focus of an economic evaluation for PBAC decision making is on how much it would cost to achieve additional health outcomes with the new therapy ('proposed drug') compared with existing therapies that would be replaced ('incremental cost-effectiveness'). Therefore, in the first instance, the costs associated with altered uses of drugs, medical and other related health care resources all need to be taken into account and outcomes valued in terms of overall quality and length of life; for example, 'quality-adjusted life-years gained' (cost-utility analysis). This evaluation is referred to as the 'base case'.

Supplementary economic evaluations may take account of a broader array of consequences in terms of costs and outcomes (such as changes in production and impacts on carers). In this case, outcomes may be valued in monetary terms (cost-benefit analyses). However, only the outcomes and costs associated with the disease identified by the main indication generally need to be included in these analyses (and not other, unrelated health problems that patients might develop in the fullness of time if they receive effective therapy for their current medical condition).

The scope of evidence should include expected adverse as well as beneficial effects and the associated provision of resources (to estimate costs). The length of follow-up in the analysis should, in principle, cover the period of expected incremental effects and/or costs.

4.2 Interpretation of clinical and economic evidence

Clinical studies to support a general marketing application often have not collected the necessary array of information, particularly relating to the provision of resources, and are seldom of sufficient duration to predict all the possible outcomes of therapy. It is possible

that, with increasing attention being given to the information needs of third-party payers, research practice will change and that, in the future, more of the extra data necessary for economic evaluation will be collected in relevant randomised trials as a routine part of the research and development of new drugs.

Within this constraint, the best study design to provide reliable results that can be used to estimate the relative treatment effect of the compared therapies or strategies is a direct randomised trial — that is, a trial in which participants are randomly allocated to groups to receive either the proposed drug or the therapy that prescribers would most replace in practice (sometimes called a 'head-to-head' randomised trial).

However, even with such trials, the trial protocol might differ from the proposed clinical practice setting for the main indication in one of the following ways:

- The participants and circumstances of use in the trial are not the same as the proposed population for treatment (and might therefore have a different expected risk). Results generated in this way need to be ***applied*** to the proposed population and expected risk.

- The length of follow-up of participants in the trial might be less than the expected duration of treatment or expected duration of health impacts overall. Results generated in this way need to be ***extrapolated*** to the proposed duration of treatment or expected health impacts.

- The outcomes measured in the trial might not be the patient-relevant final outcomes of treatment. Results generated in this way need to be ***transformed*** to take account of the patient-relevant final outcomes (in terms of quality-adjusted life-years gained).

Therefore, the results of the trials need to be applied, extrapolated and transformed (collectively referred to as '***translated***') into a decision analysis appropriate for the proposed clinical use of the proposed drug on the PBS in Australia, taking into account the above issues.

If direct randomised trials are not available, then an indirect comparison of randomised trials, each including a common reference, or nonrandomised studies could be used to assess the comparative effectiveness of the proposed drug. The results of these studies should form a basis for translation into a decision analysis to generate an economic evaluation.

4.3   Australian context

While the results of overseas randomised trials of sufficient scientific rigour are a reasonable basis for economic evaluations relevant to the Australian health care system, an economic evaluation performed overseas will often not be relevant in Australia. This is because of major differences in unit costs, the patterns of resource provision and the way in which health care is funded overseas. Sponsors are therefore encouraged to submit an economic evaluation that is relevant to the Australian context in Australian dollars.

4.4   Uncertainty

Clearly, there is uncertainty in the above analyses. The sources of uncertainty in the 'base case' are broad, extending beyond statistical uncertainty (which arises from the need to

use samples to generate evidence) to include a wide range of nonstatistical uncertainties that cannot be reduced by increasing sample size. These include the implications of specifying the decision analysis to reflect Australian populations, practices, prices and preferences for changes in health status. They also include biases and limitations in the evidence itself, or in translating the trial evidence to generate the ultimate impacts of the proposed drug in an economic evaluation, and in the selection and aggregation of multiple sources of other contributing evidence in the construction of the decision analysis.

Although the extent of uncertainty will vary across circumstances and submissions, a general principle of these guidelines is to indicate preferred ways for a submission to minimise uncertainty. Similarly, the more a submission can identify the existence and extent of uncertainty, the more helpful it will be for PBAC.

4.5   Relevant factors influencing PBAC decision making

In making decisions as to whether to recommend that a proposed drug be listed on the PBS, PBAC considers many factors. Each of these factors might have a separate influence on the decision to list the proposed drug on the PBS and, depending on the circumstances of each consideration, might influence PBAC in favour of, or against, a recommendation to list. More than one factor might be relevant to each consideration.

Tables A1.1 and A1.2 in Appendix 1 list relevant factors, which are divided into two groups: quantitative and qualitative. The qualitative factors (Table A1.2) include some of the underlying assumptions implicit in such concepts as quality-adjusted life-years and discounting. To enable consistency across submissions regarding these factors, a particular position has been adopted (which is specified in these guidelines in the sections indicated by the cross-references in the tables). However, in certain circumstances, it might be reasonable to argue that a different position should be considered.

Individual factors are not weighted equally by PBAC in its decision-making process, and different factors might be more or less important in different situations. In other words, the importance of any particular factor cannot be quantified. The descriptions provided in Appendix 1 represent PBAC's understanding at the present time. PBAC continues to reflect on its processes and to further develop its understanding of these matters.

4.6   Flexibility in interpretation of the guidelines

Despite the differences in data available and uncertainties that might exist in the base case, it is in the interests of the community, industry and PBAC that uniformity be maintained in the way that economic analyses are conducted and evaluated. However, the practical aspects of the economic evaluation of the performance of pharmaceuticals are challenging for members of the pharmaceutical industry, PBAC and the administrative arm of government. For this reason, there will continue to be flexibility in the interpretation of these guidelines, to help industry and government to further increase their experience of, and expertise in, the techniques of economic evaluation.

Key points — approach to economic evaluation

- PBAC is required to assess the degree to which new drugs represent 'value for money' for the Australian community.

- Major submissions to PBAC (new drugs, substantial changes to restrictions of existing drugs, and resubmissions in these circumstances) therefore need to include economic evaluations.

- Major submissions are evaluated by the Pharmaceutical Evaluation Section and presented to the ESC before they are considered by PBAC.

- Before economic evaluation, the clinical data should be translated (ie applied, extrapolated and/or transformed) to the specific context of the proposed listing.

- The economic evaluation should focus on the effectiveness of the proposed drug compared with other treatments, its cost and the likely changes in the provision of health care resources after its introduction (including changes in the provision of other health care resources not subsidised through the PBS).

- Economic evaluations should be relevant to the Australian context.

- As the practical aspects of the economic evaluation of the performance of pharmaceuticals are challenging, there will continue to be flexibility in the interpretation of these guidelines.

5   Organisation of a major submission

These PBAC Guidelines are designed to assist sponsors to identify and present the basic information needed by PBAC and the ESC and to provide guidance on the most appropriate form of economic evaluation for specific submissions.

This section outlines the information that should be presented in a major submission. A flowchart showing PBAC's key decisions in evaluating major submissions is also included, along with advice on presenting alternative information and submissions that rely on new methods or techniques.

5.1   Choice of information

A wide array of information should be presented in a major submission to PBAC. Some information is requested for all submissions, whereas some requests only apply to some submissions, according to the claims made. In addition, a large number of requests provide guidance on presenting the 'next best' option when it is not possible to provide the preferred information.

Wherever possible, the choice of information to be presented is based on currently established best methodological practice. Where best methodological practice is not yet established, the choice of information may be guided by PBAC's preference for comparability across submissions; for example, a cost-utility analysis is requested in preference to a cost-benefit analysis (see Subsection 4.1). The choice of information may also be guided by PBAC's experience in addressing situations when best practice from one methodological discipline needs to be moderated by best practice from another; for example, it might not always be helpful to present a cost-utility analysis in all instances, particularly where the transformation of health outcomes to quality-adjusted life-years gained adds more uncertainty than comparability and it might not be justifiable to substitute the results of a subgroup analysis for the results of the full intention-to-treat population.

Each submission should be as succinct and informative as possible. PBAC and the ESC are most likely to be influenced by arguments based on scientifically rigorous data rather than opinions. Submissions should use suitable scientific language but avoid jargon.

5.2   Overview of a major submission

5.2.1   Sections of a major submission

To achieve a 'base case' estimate and decision analysis with uncertainty identified, a major submission needs to include the following sections (presented in this order):

- Submission executive summary
    - Clearly set out the key aspects and issues presented in the main body of the submission.

- Submission section A

  – Establish the context for the submission. Describe the proposed drug, its intended use on the PBS, and the therapies that would be co-administered or substituted (the therapy likely to be most replaced by prescribers in practice is the 'main comparator').

- Submission section B

  – Provide the best available evidence comparing the clinical performance of the proposed drug with that of the main comparator, preferably from direct randomised trials. Provide details about the trials, including the scientific rigour of the methods, and the size, statistical precision, clinical importance and patient relevance of the results. Conclude with a comparative therapeutic assessment of the proposed drug.

- Submission section C

  – Describe the methods used in premodelling studies to translate (apply, extrapolate and transform) the results of the evaluation of the clinical studies to the context of the requested listing. Include a description of the analytical plan and research questions, the data used (with reasons for any exclusions) and analyses. Provide a table with the results of the analyses (ie the variables for incorporation into any modelled economic evaluation).

- Submission section D

  – Provide an economic evaluation that focuses on changes in health outcomes and in the provision of health care resources due to the proposed drug. Present the structure and variables of any modelled economic evaluation, with the results in a disaggregated form, before aggregating them and applying extensive sensitivity analyses.

- Submission section E

  – Include financial analyses for the PBS/Repatriation Pharmaceutical Benefits Scheme (RPBS) and government health budgets.

- Submission section F (optional)

  – Present any additional information of relevance to the major submission.

The information requests for the preferred flow of information (from direct randomised trials) are described in detail in Part II of these guidelines. Alternative requirements, such as for when there are no direct randomised trials, or when noninferiority is claimed, are described in Part III using the same main submission section designations (B, C, D, etc) to show where the information will be placed in a completed submission but with modified subsection headings, as required. The requests in Parts II and III refer to all drugs and medicinal products. Additional information requests for three specified product types (fixed combination products, nutritional products and vaccines) are presented in Part IV of the guidelines.

Figure 5.1 illustrates the flow of decision making relating to major submissions and how these decisions relate to the sections of the submission, as set out in Parts II and III of these guidelines. The order of the information requests in Part II and/or Part III indicates the preferred order for the information that should be presented to optimise its evaluation by PBAC. Arranging the same information in another order has generally been found to be unhelpful.

PART II

Section A

PART III

Section B

Section B(i)

Section B(ii)

Section C

Section C(i)

Section D(i)

Section D

Section E

Section E(i)

Section F

Pharmacological class and action

Requested restrictions compared to (draft) TGA-approved version

Proposed drug | **Appropriate main comparator**

Yes

Direct randomised trials

No

Systematic summary of trials

Indirect randomised trials

NO

YES

Compare harms

Systematic summary of trials

Nonrandomised studies

Systematic summary of studies

Compare harms

Compare harms

Therapeutic conclusion

Superior

Noninferior

Identify issues to translate direct randomised trial data to:
– apply to PBS listing
– extrapolate time frame
– transform outcome

If another evidentiary basis, construct economic evaluation using best available data

Determine equi-effective doses

Pre-modelling studies

No translation issues

Cost-minimisation analysis

Stepped economic evaluation needed

Trial-based economic evaluation

Modelled economic evaluation

Base case incremental ratio of economic evaluation (stepped where needed) + Appropriate sensitivity analyses

Utilisation and financial implications

Epidemiological approach

Market approach

Optional matters (QUM, RSA, other relevant factors)

Figure 5.1   Key decisions and stages in preparing a major submission to PBAC (bold boxes show steps for the majority of submissions and are described in Part II of these guidelines; alternative steps for a minority of submissions are described in Part III)

5.2.2 Section designations and cross-references within these guidelines

Subsection 2.2 describes how the information requests for the majority of submissions, alternative requests for some submissions and additional requests for specific product types are presented in Parts II, III and IV of these guidelines, respectively.

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

- Within Part I of the guidelines, main sections are numbered 1, 2, 3, etc with subsections as 1.1, 1.2, etc.

- Within Parts II and III, the sections are labelled according to the submission section to which they refer (ie A–F). In Part II, which will apply to the majority of submissions, the designations are simply Section A, Section B, etc, with subsections given as Subsection A.1, A.2 and so on.

- Within Part III, the designations are Section B(i), Section C(i), etc, with subsections as Subsection B(i).1, B(i).2, as required.

- Within Part IV, the three product types are labelled PT1, 2, 3, with subsections as Subsection PT1.1, PT1.2, etc.

- Appendixes are labelled Appendix 1, 2, 3 etc, with subsections as A1.1, A1.2 etc (but only as required for cross-referencing).

- Within each part of the guidelines, cross-references to other sections and subsections *within the same part* are given as 'see Section 3', or 'Subsection B.6', etc. However, cross-references *across parts* are given as 'see Part II, Section B' or 'Part III, Subsection B(ii).3', etc.

- Figures are labelled consecutively within each main section of the guidelines; for example, Figure 5.1 (in Part I, Section 5); Figure A.1 (in Part II, Section A).

- Tables are labelled consecutively within each main section of Part I and the appendixes: for example, Table 1.1 (in Part I, Section 1); Table A1.1 (in Appendix 1). In Parts II, III and IV, tables are numbered consecutively in each subsection; for example, Tables B.1.1, B.1.2 etc in Part II, Subsection B.1).

Throughout the guidelines, generic references to sections A–E of a submission (see Subsection 5.2.1) are presented in the form 'submission section A'.

5.3 Presentation of the submission

The main body of the submission **must** be a separate bound document including key reports of the relevant trials. Other information may be provided as attachments or technical documents. This other, supplementary material is evaluated primarily by the Pharmaceutical Evaluation Section (which also checks the extraction of data and the detailed calculations in the supplementary material and in electronic format, such as on a computer disk or a compact disk), but is also available to committee members on request.

The executive summary is the document from the submission that is included in the ESC and PBAC agenda papers. It is therefore vital that the submission includes frequent and

accurate cross-references between the executive summary and the main body of the submission, and between the main body of the submission and reports of the key trials, attachments, technical documents and material in electronic formats. This will assist those who have to evaluate and consider the submission.

5.4   Provision of alternative information

The PBAC Guidelines provide guidance on the preferred information for inclusion in a submission. Where there is more than one way to present information, the preferences indicated in the guidelines are based on currently established best practice and supported by experience (see Subsection 5.1).

As an overall guide, submissions should follow each major (boxed) request in these guidelines as well as the subsidiary requests included in the main text. However, given the large number of requests and the wide variation in the information available when submissions are being prepared, judgment is needed in preparing submissions, as well as in evaluating and considering them. If there is a specific reason not to follow a request, alternative information can be provided, together with the justification for doing so. However, not all justifications may be accepted, and sponsors are advised to consult with the PBAC Secretariat and/or the Pharmaceutical Evaluation Section before varying the format of their submission.

If possible, the information requested should be provided alongside the alternative information for which the justification is provided. This allows PBAC to judge the importance of accepting the alternative information for the overall conclusions of the committee. In a few instances (for example, presenting hospital costs that are not calculated on a per episode basis, or a new technique for analysing data), the guidelines specifically request the dual presentation of information (see Subsection 5.5).

5.5   Submissions relying on new methods or techniques

If a major submission relies on one or more new methods or techniques that are not requested in the PBAC Guidelines, the submission should provide the relevant results according to both the approach requested in the guidelines and the alternative new approach. An explanation and justification for the new approach should also be supplied.

Each set of results should be used to generate a separate base case, and the two associated sets of sensitivity analyses should also be presented. This approach both supports the 'reference points' approach generated by following the requested approach in these guidelines (and thus the consistency of decision making), and allows new approaches to be examined in an informed way, including justified variations from the 'reference points' in appropriate circumstances.

This principle does not necessarily apply to circumstances where a request in the guidelines cannot be met due to the lack of available information. For example, Part II, Subsection B.5 requests the presentation of any multi-attribute utility instrument used in a trial, and clearly this request cannot be met in reporting those trials that did not use such an instrument.

Key points — organisation of a major submission

- Submissions consist of an executive summary, the main text of the submission, and additional information (attachments and technical documents).

- Part II (for the majority of submissions) and Part III (for supplementary and alternative information in a minority of submissions) of these guidelines provide the preferred order for the presentation of information in the main text of major submissions.

- The preferred order for the presentation of information consists of six sections (A–F). If possible, do not present information in any other order, as this will reduce 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).

- Provide justification for any variations to the requested information.

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

6   Lodging a major submission

6.1   Submission checklist

Information requirements

- Each copy of the main body of a major submission **must** be suitably bound, identified, indexed, paginated, divided with labelled tabs, and have all economic calculations in Australian dollars.

- The investigator's summary of each sponsor's trial report, the main published paper, and an adequate account of the methods and results for each trial or study **must** be included as attachments within the main body of the submission.

- All submitted information **must** be legible and in English.

Information requests

- Before lodging a major submission with the PBAC Secretary, complete the checklist provided (Table 6.1) to ensure that the submission is complete.

- Provide all ancillary information identified in the checklist.

- Provide three copies each of the executive summary, product information, registration details and any additional material as identified in the checklist.

- Provide 12 copies of the main body of a major submission and an electronic version in a suitable format (as indicated in the checklist).

- If the submission is for funding a vaccine under the National Immunisation Program (NIP), provide an additional copy (total of 13 copies).

- If the submission is to be sent to the PBAC Secretariat in multiple boxes, identify which box contains the covering letter for the submission on the outside of that box.

A major submission consists of the following components:

- executive summary
- main body of text
- attachments
- index.

The main body of a major submission **must** be bound, paginated, labelled and indexed in such a way that information can be easily located and the document withstands regular use. In particular, it is important for the bindings to be both robust and the correct size for the number of pages contained (neither too big nor too small). All pages **must** also be clearly legible, in English and with all cost calculations presented in Australian dollars (A$).

The attachments to be provided within the main body of the submission **must** incorporate the investigator's summary of each sponsor's trial report (usually the synopsis from the front of the sponsor's internal clinical trial report) and the main published paper (where available), together with adequate details of the trial methods, analysis and all trial results presented in the submission for use in the economic evaluation; OR the main published

paper alone if the sponsor has no access to any more detailed report. These materials **must** be legible and in English (or be accompanied by a reputable translation).

Ancillary papers and materials that accompany the submission are:

- covering letter and application forms
- TGA evaluation and Australian Drug Evaluation Committee (ADEC) papers
- TGA-approved product information, marketing approval and registration details
- samples of the pharmaceutical presentation.

Additional documents that are not part of the main body of the submission, such as technical documents, other attachments (including more complete details of internal trial reports of published and unpublished trials relied on in the submission) and other references should be presented in separate bound volumes, with the contents identified on the cover of each such volume.

Table 6.1 shows a checklist of items to be included when lodging a major submission with the PBAC Secretary. The checklist is designed to ensure that each submission lodged is sufficient for a complete assessment while not unnecessarily wasting paper.

6.2 Provision of information to allow independent verification of computer analyses

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Information requests

- Provide sufficient information to permit independent verification of computer-based analyses to generate information for submission sections C or D (eg input data, methods of analysis, outputs).

- Provide an electronic copy of all computer-based analyses (including the economic evaluation) in the form in which it was conducted, together with any associated data files and a technical document or an attachment with clear cross-references to the submission.

- Use a software package that can be readily evaluated by the Pharmaceutical Evaluation Section, or before lodging the submission, discuss the arrangements to ensure the acceptability for evaluation of any software that is not on the maintained list of software packages.

6.2.1 Electronic copies of all computer-based analyses

Whenever a submission includes an analysis requiring use of a computer program to generate information for submission sections C or D, provide sufficient information (input data, description of methods used to conduct the analysis, outputs and electronic copy) to permit independent verification of the results of the analysis and to permit an assessment of the validity of the methods of analysis. Provide more information to support each analysis (eg justification for the approach adopted) if nonrequested methods are used to conduct the analysis and/or if the results of the analysis are important to the conclusions about the comparative effectiveness, safety or cost-effectiveness of the proposed drug versus the main comparator(s). Part II, Section C of these guidelines describes several situations where additional substantial analyses might be presented.

In general terms, providing the analysis in the form in which it was conducted is preferable to merely describing the methods used to conduct the analysis and its results. If the analysis was prepared for the submission using specific computer software, then provide a copy of all relevant electronic files of the statistical analyses and economic evaluation presented in submission sections C and D and a technical document or an attachment to the submission to give details of calculations. Ensure that clear cross-references are provided as appropriate between the technical document or attachment and the relevant item in the main body of the submission and for the extraction of data from each source (to the level of the page, table or figure number of the source document).

The following guidance most specifically relates to the provision of information in relation to a statistical analysis of clinical data, such as an analysis relying on individual patient data. Adapt this guidance for other types of analyses or models, whether for the clinical evaluation or the economic evaluation.

Typically, the analysed dataset should be supplied in such a form that it is available for the analysis. This might be as Excel files (file extension either xls or csv), or flat files (ie relatively unformatted ASCII files; typically with file extension txt or dat) with little or no formatting beyond comma or tab separation of values (which are accessible by most widely used statistical programs), or possibly SAS datasets (file extension sas7bdat).

If any intermediate file processing, reformatting and/or file concatenation is required for the preparation of the input data for the actual statistical analysis, provide the computer code(s) required to carry this out.

If full details of the variable names, order and format (eg whether a data value is a date or time in a certain format, a string, or a numerical value with a particular precision) are not clearly apparent from the data input section of the analysis code, this should also be provided.

6.2.2   Software packages

Provide the complete computer code implementing the statistical analysis and full details of the version of the software package or system used. A list of statistical software packages that can be readily evaluated by the Pharmaceutical Evaluation Section currently includes:

- SAS®
- STATA®.

Similarly, specify the name and version of any software package that is used to conduct the economic evaluation. A list of software packages that can be readily evaluated by the Pharmaceutical Evaluation Section currently includes:

- TreeAge Pro Suite®
- Excel 2003®, including @RISK®, but not necessarily including all advanced features and plug-ins (eg Crystal Ball® or customised macros developed using Visual Basic).

Statistical analyses and economic evaluations constructed using any of these packages may be submitted without earlier arrangement with the Pharmaceutical Evaluation Section (see page iv).

Advances in software available for statistical analyses and economic evaluations are expected over time. Such advances are welcomed; however, their acceptance should be balanced by an approach that ensures their competent introduction.

The Pharmaceutical Evaluation Section maintains an expert level of competency in the use of the most commonly used software programs for statistical analysis and economic evaluation; however, it is not feasible for expert-level skills to be developed for every software program available. Therefore, discuss with the Pharmaceutical Evaluation Section (see page iv) the arrangements to ensure the acceptability for evaluation of any submission relying on software that is not on the maintained list of software packages before it is lodged.

If the evaluation of the submission is hindered because the software cannot be accessed during the evaluation, or because learning to operate the software substantially detracts from evaluating the statistical analysis or economic evaluation, the Pharmaceutical Evaluation Section might be forced to advise PBAC that the model could not be independently verified in the time available to do so.

Table 6.1   Checklist of information to be included in a major submission

Component	Included?
One (1) each of the following:	
• The original, signed covering letter for the submission (with an attachment containing the complete index to the submission).	Y/N
• The original, signed PB11 form (the official application form for a new drug, form or strength, which also specifies the requested price).	Y/N
• A comprehensive index attached to the covering letter, which serves as a checklist for all documentation and other materials comprising the submission and confirming:	Y/N
– the numbers of copies of the main body of the submission and details of its contents	Y/N
– the numbers of copies of other parts of the submissions and details of their contents.	Y/N
Two (2) each of the following:	
• Samples of the pharmaceutical presentation if it is novel; for example, a 'compliance' pack or a type of form not currently listed. (In such a case, the submission should also explain how this pharmaceutical presentation impacts on the clinical and economic performance of the drug.)	Y/N
• Copies of the covering letter for the submission (each copied single-sided and stapled).	Y/N
• Copies of the PB11 (each copied single-sided and stapled).	Y/N
• Sets of copies of:	
– the full TGA clinical evaluator's report	Y/N
– the TGA delegate's overview (advice to ADEC)	Y/N
– the ADEC resolution (if and when available)	Y/N
– the relevant extract of the ADEC minutes (if and when available).	Y/N
• If the relevant registration application has been considered more than once by ADEC, or has been the subject of one or more registration appeal processes, then also provide two sets of copies of all documents originating from the TGA that contain the deliberations of the additional considerations and appeals (including all additional documents corresponding to the TGA clinical evaluator's report, the TGA delegate's overview, the ADEC resolution and the relevant extract of ADEC minutes).	Y/N
• If the relevant TGA application was not considered or is not scheduled for consideration by ADEC, provide any TGA clinical evaluation report that is available and any summary from TGA identifying the evidentiary basis for the decision to register the proposed drug or approve the relevant new indication.	Y/N
Three (3) each of the following:	
• The executive summary of the submission (each copied single-sided and stapled).	Y/N
• The current TGA-approved product information with approval date (if and when available, with the latest draft product information in the meantime; each copied single-sided and stapled).	Y/N
• The letter of registration with details of marketing approval and registration (if and when available; each copied single-sided and stapled).	Y/N
• Any additional technical documents, attachments and references provided separately to the main body of the submission, which should:	Y/N
– be suitably bound (ie each folder is robust enough to withstand regular use, with the width of its spine matching the number of pages it contains)	Y/N
– have the contents identified on the cover	Y/N
– be legible and in English (or accompanied by a reputable translation).	Y/N
Twelve (12) of the following:	
• Bound copies of the main body of the submission, which **must**:	Y/N

Component	Included?
– be suitably bound (ie each folder is robust enough to withstand regular use, with the width of its spine matching the number of pages it contains)	Y/N
– have the contents identified on the cover	Y/N
– have a clear and adequate index (which encompasses both the main body of the submission and the contents of all other documentation contained in separate volumes and also identifies all other materials supplied as part of the submission, and that is also attached to the covering letter of the submission)	Y/N
– have consistent pagination throughout	Y/N
– include dividers between each section, attachments and references, with an appropriately labelled tab extending beyond the page width	Y/N
– have all cost calculations in Australian dollars (A$)	Y/N
– incorporate attachments containing reports of each of the relevant randomised trials (or each of the relevant nonrandomised studies if necessary), which **must** be: (i) the investigator's summary of each sponsor's trial report and the main published paper (where available), together with adequate details of the trial methods, analysis and all trial results presented in the submission for use in the economic evaluation; OR the main published paper alone if the sponsor has no access to any more detailed report (ii) legible and in English (or be accompanied by a reputable translation).	Y/N
• NOTE: If the submission is for funding a vaccine under the National Immunisation Program, provide an additional copy for a total of 13 copies.	Y/N
One (1) electronic version of the submission	
• Supply the whole submission and any accompanying calculations and models in electronic format, such as on one or more computer disks or compact disks (with any spreadsheet compatible with Microsoft Excel 2003, any word-processed document compatible with Word 2003, and any other software package consistent with Subsection 6.2). Ensure that all components of these electronic documents, spreadsheets and analyses are fully accessible (eg do not have password protection) and fully enabled to allow all document text, tables and figures to be accessed for copying and fully executable to allow all spreadsheet cells and all statistical or decision analysis input variables to be changed.	Y/N

6.3   Provision of information after lodgment of the submission

6.3.1   Postsubmission communication with PBAC

As outlined in Box 1.3, PBAC procedures provide for three postsubmission opportunities for sponsors to communicate with PBAC:

- a pre-subcommittee response to the departmental papers for a major submission

- a pre-PBAC response to the subcommittee papers for a major submission or to the departmental papers for a minor submission

- an option for a hearing before PBAC for a major submission.

As responses, it is expected that these will address issues raised in the relevant papers rather than introduce substantive changes, such as a different population identified by a modification to the requested restriction, a different nomination for the main comparator, new data or new analyses. Such changes might result in a PBAC request for a major resubmission to examine the implications of the substantive change.

Before the departmental papers are finalised, sponsors may be approached by the department for further information or clarification of aspects of their submissions. Sponsors are expected to deal with these requests expeditiously.

6.3.2 Provision of information sourced from the TGA after lodgment of the submission

If any of the documents requested in the checklist in Table 6.1 are not available at the time the submission is lodged, provide them to the PBAC Secretariat as soon as they become available. In particular, upon receipt of notification of TGA registration approval, advise the PBAC Secretariat immediately in writing of any aspect of a submission that is not consistent with the final TGA registration. At this time, also provide to the PBAC Secretariat a copy of the TGA-approved product information, accompanied by a document highlighting any variation between the most recent draft provided with the submission and the subsequent TGA-approved product information that would have any bearing on the consideration of the submission or on the consideration of any subsequent PBAC recommendation to list.

PART II

GUIDELINES FOR PREPARING THE MAIN BODY OF A MAJOR SUBMISSION

Submission executive summary

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

Checklist for the executive summary of a major submission

Component	Included?
The Australian approved name, brand name and marketing status of the proposed drug.	Y/N
The principal pharmacological action of the proposed drug.	Y/N
The form(s), strength(s), pack size(s), maximum quantity(ies), number(s) of repeats and dispensed price(s) requested for PBS listing.	Y/N
The main indication(s) and any requested restriction(s) for PBS listing, with a brief rationale.	Y/N
The inclusion of a diagnostic requirement in a requested restriction if relevant.	Y/N
The recommended course of treatment.	Y/N
The main comparator(s) and the main expected changes in the clinical management algorithm.	Y/N
Whether the key clinical evidence in the submission comes from direct randomised trials, or from an analysis of two sets of randomised trials involving a common reference (eg placebo or other active therapy), or from nonrandomised studies.	Y/N
The main results of the clinical evaluation in terms of comparative effectiveness and comparative toxicity.	Y/N
The therapeutic conclusion that best describes the proposed drug and therefore the type(s) of economic evaluation presented.	Y/N
The reasons for and results of any premodelling studies presented in Section C to generate variables for incorporation into a modelled economic evaluation.	Y/N
The cost per patient per course (for acute therapy) or the cost per patient per year (for chronic therapy).	Y/N
The other types of resources affected by the listing of the proposed drug and the net present value of the overall incremental costs in the base case of the economic evaluation.	Y/N
The net present value of the overall incremental effectiveness in the base case of the economic evaluation.	Y/N
The base case results of the economic evaluation, together with the results of the three steps outlined in Section D, where presented.	Y/N
The main sources of uncertainty in the structure and variables in the economic evaluation and the results of associated sensitivity analyses.	Y/N
The numbers of patients treated, the numbers of packs dispensed and the net costs to the PBS/RPBS of the proposed drug in each year over five years.	Y/N

Section A
Details of the proposed drug and its intended use on the PBS

Introduction

Submission section A establishes the context for the submission. It requests a description of the proposed drug (including its pharmacological class and action, indications, and treatment details); information on its intended use (indications and restrictions) on the PBS; the therapies that will be co-administered or substituted; and a description of the main comparator (and how it differs from the proposed drug).
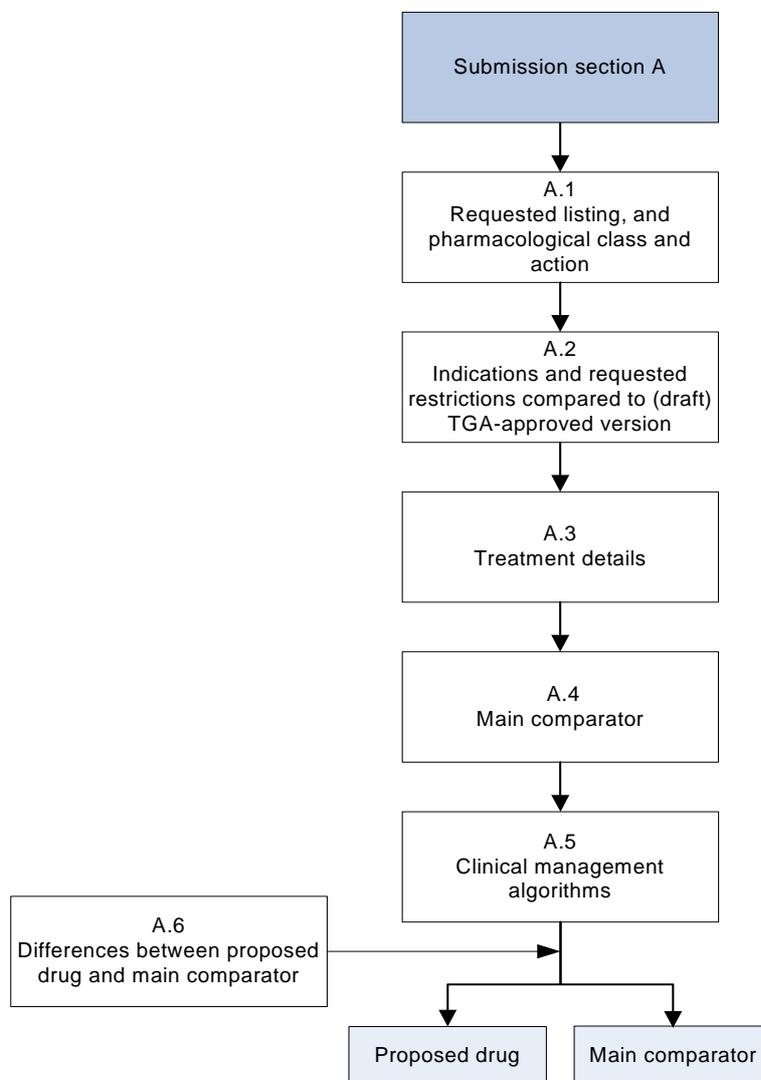
Figure A.1   Key information requests for submission section A of a major submissions to PBAC

A.1   Requested PBS listing and pharmacological class and action

> **Information requests**
> - Present the essential elements of the requested listing using the standard format of the Schedule of Pharmaceutical Benefits.
> - Summarise the proposed drug's principal pharmacological action and define its therapeutic class.
> - State the anatomical therapeutic chemical (ATC) classification of the proposed drug, if one has been assigned.

Essential elements

The essential elements of the requested PBS listing for the proposed drug include the following information:

- the Australian approved name
- the brand name
- the pharmaceutical form(s) (eg ampoule, vial, sustained-release tablet)
- the strength(s)
- the pack size(s)
- the maximum quantity for each strength
- the number of repeats for each strength (if any)
- the dispensed price of each strength.

Maximum quantities

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

- For an acute-use therapy, demonstrate that the requested maximum quantity is consistent with the likely use of the proposed drug for a normal course of therapy.
- For a chronic-use therapy, demonstrate that the maximum quantity is consistent with the likely use of the proposed drug for one month of therapy between each dispensing by the pharmacist and six months of therapy between each prescription by the prescriber.

Justify proposed deviations from this general approach; for example, to minimise wastage or to facilitate intermittent therapy as appropriate in particular circumstances (see also Subsection A.3).[10]

Number of repeats

Demonstrate that the requested maximum quantities and the requested numbers of any repeats are consistent with the TGA-approved dosage recommendations (see also Subsection A.3).

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[10] See Subsection 5.2.2 for information on section and subsection numbering and cross-referencing within this document.

Proposed drug's principal pharmacological action and therapeutic class

Provide sufficient information about the pharmacological action and therapeutic class to inform an assessment of the existence of alternative pharmacological analogues listed on the PBS as possible nominations for the main comparator (see also Subsection A.4).

ATC classification

The anatomical therapeutic chemical (ATC) classification is updated on an annual basis by the Collaborating Centre for Drug Statistics Methodology of the World Health Organization.[11] Further information on the classification is available from the Drug Utilisation Sub-Committee Secretariat (see page iv).

A.2   Indications and requested restrictions

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Information requests

- State whether the proposed drug has been approved by the TGA for the proposed indication(s).

- Specify the meeting at which ADEC recommended or is scheduled to consider the proposed drug for the proposed indication(s).

- State the indication(s) approved by the TGA (or recommended by ADEC, the TGA delegate or, if none is specifically mentioned in the TGA delegate's overview, the indication(s) as contained in the draft product information supplied).

- If an unrestricted listing is requested, identify the main indication(s).

Additional information requests if one or more restrictions are requested

- State the type of restriction and suggest wording for the requested restriction.

- Summarise the intent of the requested restriction and justify the type and wording of the requested restriction from among the main options considered.

- If continuation criteria are proposed, justify their inclusion and present the economic evaluation both with and without the application of these criteria.

- If the requested restriction requires a diagnostic test, indicate whether the test is available and subsidised for the intended purpose of the restriction and, if not, suggest a practical solution to ensure its accessibility.

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Details of TGA consideration

To minimise delays in processing, a submission can be lodged for PBAC consideration once the TGA delegate has recommended in writing (in the TGA delegate's overview) that the proposed drug be registered or that the relevant new indication be approved. In these circumstances, preparation for PBAC consideration overlaps with finalisation of TGA consideration and so it is helpful to have details of the TGA consideration.

Base the submission on the relevant TGA-approved product information. If the relevant registration application to the TGA has not been finalised, base the submission on the

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[11] http://www.whocc.no/atcddd/

most recent written recommendation(s) of the TGA delegate or ADEC, together with the most recent draft product information.

Indications proposed or approved by the TGA

The indications for use of a drug approved by the TGA are identified in the 'Indications' section of the product information and in the Australian Register of Therapeutic Goods (ARTG).

Main indication if unrestricted listing is requested

The main indication is defined as the indication likely to account for the largest proportion of patients treated with the proposed drug. This proportion should be identified from the estimates of the numbers of patients provided in answer to Subsection E.2. Usually, the submission need only include information relating to this main indication. However, where there are two or three major indications, none of which is likely to dominate use of the drug, the submission should repeat submission sections A to E for each indication. If a sponsor is in doubt, the advice of the PBAC Secretariat or the Pharmaceutical Evaluation Section should be sought (see page iv).

The default listing on the PBS is as an unrestricted benefit, defined in the Schedule of Pharmaceutical Benefits as being those that 'have no restrictions on their therapeutic uses'. In such cases, no measures are applied to limit PBS-subsidised usage of the drug, such as limiting usage to the TGA-approved indications. Thus, although it would be expected that the main indication(s) would be in accordance with the drug's TGA-approved indications, the PBS would not be separately endorsing or reinforcing this consistency.

For an unrestricted listing, the emphasis in defining the main indication(s) is on identifying the most likely use that *would* eventuate without any influence by the PBS.

Type and suggested wording of any requested restriction

Types of restrictions include 'restricted benefit', 'authority required' or a section 100 arrangement that provides for different distribution arrangements, such as distribution of highly specialised drugs from hospital outpatient departments (see Part I, Subsection 1.3).

In contrast to a submission requesting an unrestricted listing, a submission requesting a restricted listing is specifically seeking PBAC endorsement of use within the requested restriction and to exclude use beyond that restriction. The emphasis in determining the wording (and type) of the restriction is therefore on identifying what use *should* eventuate and the extent of influence that might be required through the PBS and through any other complementary activities proposed to reinforce that use.

In recent times, most new drugs have been listed with a restriction, although there is no requirement that new drugs must be restricted; nor is there a limitation that a PBS-restricted drug cannot subsequently be listed without restriction. However, wherever a restriction is to apply, PBAC is mindful of the consistency between the TGA-approved indication and the PBS restriction (see Appendix 2, which outlines the position of PBAC on relating a PBS restriction to the associated TGA-approved indication). However, the need for consistency does not mean that the wording needs to be identical; it is frequently

the case that the PBS restriction excludes some patients who would fall within the TGA-approved indication. Further, as the emphasis of the restriction is on identifying eligible patients, wording about the intended therapeutic effect is frequently omitted from the wording of the PBS restriction.

Submissions therefore need to ensure that any restriction requested for PBS listing is within the TGA-approved indications (it may be narrower, for example to identify the patient group likely to benefit most from the use of the proposed drug). Without limiting the option of being narrower, the restriction(s) requested should also generally be consistent with other sections of the product information, such as any eligibility criteria in the clinical trials section.

PBAC is mindful not only of the TGA-approved indications (as coming from within the same Australian Government department), but also of other authoritative sources and guidance as to what constitutes good clinical practice. The closer these other sources are to the Australian setting and to the decision-making criteria of PBAC (especially the requirement to consider cost-effectiveness), the more likely they are to influence PBAC.

Elements that may be included in a restriction

Patient characteristics
Examples of patient characteristics that could be considered for definition in the wording of a restriction include:

- age
- sex
- ethnicity
- medical condition
- severity of medical condition
- previous therapies (see 'Complex restrictions', below)
- any specific initiation or continuation criteria that eligible patients would be required to meet.

Circumstances of use
Examples of types of circumstances of use that could be considered for definition in the wording of a restriction include:

- the position of the proposed drug in the overall algorithm for managing the medical condition (eg prevention, first-line treatment, second-line treatment)

- the doses of the proposed drug (including any limitations on dose or quantity of the drug delivered to the patient)

- the frequencies and durations of use of the proposed drug (including any limitations on the duration or frequency of delivery of the drug)

- the modes of administration of the proposed drug (including specification of any facilities that are required)

- any required co-administered interventions with the proposed drug (including any specific diagnostic tests required and required co-administered drugs)

- any contraindicated interventions with the proposed drug (including any contraindicated drugs)

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

- any unique characteristics of the prescriber (eg specific qualifications or training) in using the proposed drug.

Complex restrictions

A common example of a more complex restriction is the limitation of a proposed drug to patients as second- or subsequent-line therapy. This usually involves identifying those patients for whom one or more previous therapies cannot be used to manage the indication; in turn, this usually involves demonstrating that one or more of the following circumstances apply:

- that the patient has responded inadequately to previous therapy

- that the patient has developed an intolerance of a severity necessitating the permanent withdrawal of previous therapy

- that previous therapy is contraindicated according to the relevant TGA-approved product information document.

Definition of elements

For each element defined in the wording of a restriction:

- identify the element unambiguously; examples include:
  - risk factors of the medical condition
  - markers of severity or progression of the medical condition
  - drug, dosage and duration criteria for previous therapy as appropriate (for each of the three circumstances listed above if a subsequent line of therapy is requested)
- specify objective criteria in preference to subjective criteria in identifying the element
- justify any threshold within these criteria (these thresholds and justifications should be consistent with trial eligibility criteria and subgroup stratification criteria as appropriate)
- resolve copyright issues over any particular proposed instrument to be used within the restriction before proposing its use as part of a restriction.

Attention to these elements will help minimise usage beyond the intention of the requested restriction (see Subsection E.6).

Other issues

An 'authority required' restriction might need to include so-called 'grandfathering' provisions in order to provide for individuals who would have started therapy before implementation of a requested PBS listing and for whom it would not be advisable, on clinical or other grounds, to have a break in therapy in order to demonstrate eligibility for PBS subsidy. Appendix 3 provides further information on grandfathering provisions.

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

If a restricted listing is sought for more than one indication, submit separate submission sections A to E for each indication, or consider lodging separate submissions.

If the members of the ESC or PBAC are unlikely to be familiar with the medical condition(s) identified in the requested restriction(s), it may be helpful to include a succinct summary of the medical condition suitable for an informed layperson.

Justification for restriction

Justify a requested restriction as follows:

- indicate the intention of the requested restriction

- identify the main options for restrictions considered by the sponsor, both in terms of type of restriction and reinforcement (eg 'restricted benefit', 'authority required') and in terms of the wording of the restriction

- state whether any other options would be acceptable to the sponsor

- address the trade-offs between the clinical preference for simple, unambiguous listings versus increasingly complex restrictions to limit new drugs to those relatively few patients for whom the proposed drug might be justified as being acceptably cost-effective at the price requested.

The further the eligibility criteria specified in a requested restriction shift prescribing away from otherwise uninfluenced practice, the more incentive there is for prescribers and patients to seek subsidy despite the restriction. The approach listed above (identifying and justifying any restrictions and any other options that might be accepted) is intended to help a submission justify the restriction requested from the alternative options that might apply. This approach becomes more important as the requested restriction becomes more complex or more expensive for Medicare Australia to administer. Further, if it is appropriate for the submission to include one or more of these options as alternative listing scenarios for PBAC consideration, this approach also provides a basis for comparing the issues involved with these multiple scenarios.

As noted above, a common circumstance in which many options are available for consideration is where a requested restriction seeks to limit a proposed drug to patients as second- or subsequent-line therapy.

Continuation criteria

The general intention of a restriction is to identify those individuals who would be eligible for PBS-subsidised access to the proposed drug. The specific intention of a restriction containing continuation criteria is to identify, from among all individuals who were eligible to initiate use of the proposed drug, those individuals who would be eligible to continue PBS-subsidised access to the drug.

There are substantial problems with continuation criteria. Their use should therefore be considered an option of last resort when eligibility criteria alone cannot adequately identify patients for whom use of the proposed drug would be acceptably cost-effective at the price requested. The need for them is questionable if they merely identify those individuals for whom, from a clinical viewpoint alone, it would be good practice to cease therapy. The more they exclude patients who are perceived to benefit clinically, but for

whom the cost-effectiveness is not deemed acceptable by PBAC, the more they need to be justified — to patients, to prescribers, to government and to PBAC.

Once again, the further the continuation criteria take prescribing away from otherwise uninfluenced practice, the more incentive there is for prescribers and patients to seek to maintain subsidy despite the continuation rules. Continuation criteria are also unlikely to be suitable if there is evidence that breaks in therapy are likely to cause rebound, increase risks of toxicity associated with subsequent recommencement, or reduce the likelihood of benefit from subsequent recommencement.

Thus, for each element in any continuation criteria:

- justify its inclusion
- use unambiguous terminology (this includes dosage and duration criteria for the proposed drug before assessment for continuation)
- specify objective criteria in preference to subjective criteria to determine eligibility for continued PBS subsidy
- assess the proposed continuation criteria's ability to identify the extent of long-term health outcomes if the criteria rely on surrogate outcomes measured in trials
- justify the basis for defining any proposed threshold of the outcomes to be assessed as part of the continuation criteria (these thresholds and justifications should be consistent with trial eligibility criteria and subgroup stratification criteria, as appropriate).

The understanding of the evidence base for continuation rules is at an early stage of development and is frequently problematic, particularly in relation to identifying the extent of long-term health outcomes and other consequences when conditioned by selection for ongoing treatment according to an earlier extent of effect, whether on a physiological or a symptomatic measure. However, given that continuation criteria are considered to be an option of last resort, present the economic evaluation both with and without the application of continuation criteria in submission section D. This helps support the acceptance of the criteria as being necessary to a decision to recommend listing. A reasonable exception to this approach would be if listing of the proposed drug is being sought on a cost-minimisation basis compared with a drug already listed with a restriction that contains continuation criteria.

Assessments and monitoring requirements for a restriction

Indicate whether any assessments or monitoring are required to demonstrate eligibility for the requested restriction. If so, determine whether any identified diagnostic test is available on the market and whether it is subsidised via the Medicare Benefits Schedule (MBS) or through some other ongoing subsidised arrangement. If available on the MBS, supply the details of the relevant MBS item. If such a test is not readily accessible, discuss the practicalities of requesting a restriction that relies on it.

A requirement for specific assessments or monitoring by a requested restriction has the following implications for other parts of the submission:

- The implications of misclassification arising from both false positive and false negative assessments should be considered, because both types of assessments can

reduce the extent to which the diagnostic criteria can help make the incremental cost-effectiveness more favourable (see Subsection D.4) and can influence the numbers of treated patients (see Subsection E.2). Relevant information on the diagnostic performance should be provided in submission section C.

- If provision of resources for assessments (eg a diagnostic test or the time to conduct a diagnostic questionnaire) would be expected to change as a result of implementing the requested restriction, the costs associated with those changes should be included in the economic evaluation presented in submission section D. For example, the resources might not be provided routinely under current practice, but would need to be provided to demonstrate eligibility for a requested restriction (see Subsection D.4).

- If increased use of a resource for assessment involves any risk of harm to individuals examined (for example, by requiring a biopsy), the associated health impairments and the associated provision of any further resources to manage those circumstances should also be included in the economic evaluation.

A.3   Treatment details

> **Information requests**
> - Describe the proposed course of treatment with the proposed drug.
> - Identify any co-administered therapies, defined as other therapies that are likely to be prescribed:
>   - with the proposed drug as part of a course of treatment, or
>   - to manage adverse reactions of the proposed drug.
> - Identify any therapies that are likely to be prescribed less frequently, defined as other therapies that:
>   - are substituted by the proposed drug for the main indication, or
>   - are prescribed to manage adverse reactions of substituted therapies.
> - Describe the course of treatment for each drug included in the economic evaluation.

Course of treatment

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

- dose
- dosing frequency per day or other appropriate time interval
- duration of course
- anticipated frequency of repeat courses of treatment.

Confirm that these details are consistent with those recommended in the relevant TGA-approved product information (or, if this is not available for the proposed drug at the time of finalising the submission, in the most recent draft product information together with the most recent written recommendation(s) of the TGA delegate or ADEC).

Other relevant therapies

Other relevant therapies include drugs and other health care interventions that would be less prescribed or more prescribed should the proposed drug be listed as requested.

Justify any exclusion of therapies identified in submission section A but excluded from the economic evaluation in submission section D or from the financial analyses in submission section E.

Provide details of the course of treatment as requested above for each drug, particularly each existing PBS drug, included in the economic evaluation.

A.4   Main comparator

Information requests
- Of the substituted therapies, identify the main comparator(s) and justify the selection.
- Identify any other factors that may affect the identification of the main comparator either now or in the future.

The main comparator

The main comparator is defined as the therapy that prescribers would most replace with the proposed drug in practice if the PBS subsidises the proposed drug as requested. PBAC does not and has no power to recommend that prescribers substitute the proposed drug for any particular comparator. Therefore, 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 definition of the main comparator.

In practice, however, the main comparator can be difficult to identify. The following general hierarchy is intended to assist in selecting the appropriate main comparator. If a sponsor is in any doubt, the advice of the PBAC Secretariat or the Pharmaceutical Evaluation Section should be sought (see page iv).

(a)   **Existing pharmacological analogues** — If the proposed drug 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.

A reasonable exception would be if there is an important difference between the requested restrictions for the proposed drug and the PBS restrictions that apply to its listed analogues. If there is such a difference, the main comparator would usually be the drug that is prescribed on the PBS to treat the indication defined by the requested restriction for the largest number of patients.

This exception would not usually be considered to be reasonable if these analogues were listed without a PBS restriction. Reference to the TGA-approved indications, to trial evidence, or to any other authority that might identify 'appropriate' usage would not usually constitute reasonable grounds to exclude an unrestricted pharmacological analogue as a main comparator. This is because, for

an unrestricted listing, arguments based on appropriateness of use are not relevant to the definition above for determining the main comparator.

(b)   **New therapeutic class** — If the proposed drug is in a new therapeutic class but would be used for an indication for which there are other, widely used, listed drugs, the main comparator would usually be the drug that is prescribed on the PBS to treat that indication for the largest number of patients.

(c)   **No currently listed drug** — If no currently PBS-listed drug is available, the main comparator would usually be standard medical management (this could include a nonlisted drug, a surgical procedure or conservative management). When this situation arises, the main comparator should be clearly and consistently defined both in the submission and in the direct randomised trials.

If the proposed drug is supplied in a special form (eg sustained-release tablets or oral pressurised inhalation), the main comparator selected according to the above criteria should be in a similar form, if available.

If an expert panel or survey has been used to help identify the main comparator, see Appendix 4 for further advice on presenting the necessary background information.

In some cases, comparisons with more than one main comparator will be necessary.

Selecting a current PBS-listed drug as the main comparator according to step (b) above can raise difficulties if the current drug is widely perceived as having a substantial disadvantage compared with the proposed drug. This perceived disadvantage might arise because the current drug has a less favourable toxicity profile, is available in a less acceptable form, has greater potential for abuse or misuse, or is much less effective.

In some instances, this perceived disadvantage will have limited the extent of use of the identified comparator to a proportion of all eligible patients. If this is the case, the proposed drug is likely to be used in much larger numbers of patients than is currently the case for the main comparator. In this situation, it is helpful to provide both the following comparisons:

- Compare the proposed drug with the actions that most prescribers are likely to replace in practice, which would usually be no active intervention or watchful waiting.

- Compare the proposed drug with the identified comparator, given that it is already established as being worth subsidising on the PBS. This second comparison is particularly useful if the incremental cost-effectiveness ratio for the first comparison relies on a disease-specific outcome (see Subsection D.5).

In other instances, despite the perceived disadvantage of the identified comparator, there might be evidence of its widespread continued use in the absence of any alternative, such that the proposed drug is unlikely to be used in much larger numbers of patients than is currently the case for the main comparator. In these instances, only one comparison is necessary, despite any potential arguments that the main comparator is not being used appropriately. This comparison of the proposed drug and the main comparator allows the advantages of the proposed drug over the main comparator, including cost-effectiveness, to be identified and quantified. The comparison should also help explain any expected rapid substitution.

Other factors affecting the identification of the main comparator

Prescribing practice can change rapidly, and a drug chosen on reasonable grounds at the outset as the main comparator might not always remain so. This is particularly likely given the long lead times necessary to obtain primary data as part of Phase III or Phase IIIb trials. Allowance will be made for this during the consideration of submissions. If a sponsor is designing such a trial with a view to eventual submission to PBAC, the advice of the PBAC Secretariat or the Pharmaceutical Evaluation Section may be sought (see page iv).

Other matters that have affected the acceptability of the main comparator following lodgment of a submission include:

- a TGA-approved indication for the proposed drug different from that originally anticipated by the sponsor

- the consideration by the previous PBAC meeting or the same PBAC meeting of another potentially competing drug that is a closer pharmacological analogue or is proposed to be listed for a similar therapeutic indication.

If there is an expectation that the latter circumstance might apply, it would be helpful to include a comparison against the potentially competing drug(s) as a supplement to the submission. As this situation usually requires an indirect comparison of two or more sets of randomised trials involving the superseded comparator as a common reference, it is helpful to confirm the comparative therapeutic effect of the proposed drug against the common reference as a step towards comparing the proposed drug with its main comparator.

A.5   Clinical management algorithms

Information requests
- Present the clinical management algorithm that depicts the context of the intended use of the proposed drug following a listing on the PBS.

- Present the corresponding algorithm depicting the current context.

- Highlight the differences between the two algorithms to summarise the changes in the patterns of resource provision, both those required by any requested restriction and those that would be expected to follow as consequences of the requested listing.

- Indicate whether multiple listing scenarios are presented.

Algorithms for intended and current contexts

These requests for clinical management algorithms are most relevant to a submission presenting a modelled economic evaluation (see Subsection D.1). These information requests are also helpful for Subsection E.3. A submission not presenting a modelled economic evaluation might only need to present straightforward algorithms.

The objective of these clinical management algorithms is to help clarify the comparison addressed in the submission through the following three steps:

- Define the eligible patients and the circumstances of use if the listing were implemented as requested (algorithm 1).

- Identify the current situation in terms of the expected substitution of therapy options for these patients and their circumstances of use, both at the time of substitution and subsequently (algorithm 2).

- Identify the full nature of the comparison(s) being made in the submission and limit the comparison to these contexts (highlight the differences between algorithms 1 and 2).

The algorithms are expected to be of varying complexity, depending on the particular contexts to be described in each submission. Overall, ensure that the algorithms identify the nature of any and all differences across the full streams of resource provision consequences, both before and after the point(s) in the algorithm at which the proposed drug is introduced. This ensures greater clarity about the context of the intended use of the proposed drug in terms of patients and circumstances, from which the comparative health outcomes, the comparative costs, the comparative cost-effectiveness and the financial implications can all be estimated.

In each algorithm, summarise any and all relevant diagnostic and treatment steps, including any required previous therapies, any diagnostic criteria and/or tests (including those demonstrating that one or more previous therapies cannot be used to manage the indication and including those required to support any continuation criteria in the requested restriction), any required co-administered therapies, and any consequences for subsequent therapy options. Specify any other important characteristics of patients and types of circumstances of use. Examples include specifying the characteristics of the medical condition in the eligible patients (eg in terms of risk factors) and the aspects of the spectrum of the medical condition (eg in terms of severity of disease or remaining treatment options). Subsection D.2 gives further examples.

Justify the basis for the selection of the algorithm with reference to a literature review of relevant published clinical management guidelines. Provide a copy of those clinical management guidelines in an attachment or technical document. If an expert panel or survey has been used to help specify the clinical management algorithms, see Appendix 4 for further advice on presenting the necessary background information.

A number of issues complicate the construction of algorithms that identify the comparison(s) for a drug that is already listed, but for which the submission is requesting that the current restriction be varied, particularly when more than one of the following circumstances applies at the same time:

(a)   The instance of a submission requesting a completely different indication is the most straightforward because it is similar to the normal circumstance of a submission requesting the listing of a new drug.

(b)   In the instance of a submission requesting that one or more current restriction criteria be relaxed to enable previously ineligible patients to become eligible, limit the comparison to only those patients. Examples include modifying eligibility criteria in relation to risk factors and/or co-morbidities. If the submission requests that risk factor criteria be relaxed to thresholds predicting a reduced risk of adverse major clinical outcomes compared with the current restriction, refer to the discussion of treatment effect variation in Section C for additional guidance when seeking to justify the relaxed thresholds.

As the current restriction is usually the result of seeking to limit subsidy to those patients within the overall process of the medical condition for whom the proposed drug is likely to benefit most and so for whom the drug is most cost-effective, compare the new incremental cost-effectiveness ratios for the patients who would become newly eligible with the ratio relevant to the current restriction. This is particularly helpful if these incremental cost-effectiveness ratios do not have a common outcome, such as extra quality-adjusted life-years gained (see Subsection D.6).

(c)   In the instance of a submission requesting relaxation or removal of one or more continuation criteria that had previously been established to limit ongoing PBS subsidy to those patients with some evidence of more favourable cost-effectiveness, no new patients would become eligible. The relevant comparison in this case is the increment of the extent of costs and health outcomes of the requested restriction (continuing the proposed drug) over the current restriction (ceasing the proposed drug), limited to those patients who would become newly eligible for continuing treatment should the requested change be implemented.

(d)   In the instance of a submission requesting that the proposed drug be used earlier rather than later in the progression of a medical condition, there would likely be an increase in the number of eligible patients overall and in the severity spectrum of the medical condition for which the proposed drug would be subsidised. This might arise because the current restriction limits eligibility to patients with more severe and/or more advanced disease, on the grounds that, if the treatment effect is constant across the spectrum of severity, the most severe patients would benefit most. Examples include primary prevention rather than secondary prevention; chemotherapy for early cancer rather than chemotherapy for advanced cancer; and removing a requirement to restrict the proposed drug to second- or subsequent-line therapy.

A further complication for a submission in this instance is that the current restriction means that the proposed drug would be on both sides of the comparison for at least some patients. The relevant comparison is the increment of the extent of costs and health outcomes of the requested restriction (treating more patients earlier and possibly longer, depending on the consequences for continuing therapy with the proposed drug as the medical condition progresses for some patients to the point that they would become eligible under the current restriction) over the current restriction (treating fewer patients later).

Option to present multiple listing scenarios

The clinical management algorithm for the requested restriction specifies the preferred listing scenario for the proposed drug. However, as part of justifying the requested restriction in response to Subsection A.2, more than one listing scenario might have been canvassed as being appropriate for PBAC consideration. In some circumstances, it might be worth developing an option for the modelled economic evaluation presented in submission section D and the budget impact analyses in submission section E to analyse more than one listing scenario. This approach has the advantage of more fully informing PBAC of the comparative merits of recommending different listing scenarios and thus potentially of reducing the number of submissions required, each requesting a different listing scenario.

If multiple scenarios are to be presented in a submission, pay particular attention to the following matters when presenting the alternative scenarios throughout the submission:

(a)   Consider the incremental aspects of the scenarios in relation to each other: the scenario generating the most favourable incremental cost-effectiveness ratio over the main comparator might become the appropriate clinical management algorithm for the other, less favourable scenarios (eg for different continuation rules, or for varying the eligibility criteria to allow access for the same patients to treatment at different points in the progression of the medical condition or its management).

(b)   In submission sections D and E, consider specifying the implications of any substantial expected usage beyond the intention of the requested restriction as a separate scenario.

(c)   In submission sections D and E, consider constructing a single but broader model capable of presenting the multiple scenarios rather than a separate model for each scenario, particularly where this would generate efficiencies in validating and interpreting the model and the scenarios that it is informing.

A.6   Differences between the proposed drug and the main comparator

> **Information request**
> * Describe the main differences in the indications, contraindications, precautions (cautions and warnings) and adverse reactions between the proposed drug and the main comparator.

The differences between the proposed drug and the main comparator can usually be determined by comparing their respective current TGA-approved product information. This information should be supplemented if the TGA-approved product information for the main comparator is out of date or if the main comparator does not have TGA-approved product information.

Further information on an extended assessment of comparative harms is requested in Subsection B.7.

Section B
Clinical evaluation for the main indication

Introduction

The purpose of submission section B is to identify and present the best available clinical evidence for the main indication.

Subsection B.1 sets out the requested search strategy to identify all trials that can be used to compare the proposed drug with its main comparator. PBAC has a strong preference for clinical and economic evaluations that are based on direct randomised trials; that is, trials that directly compare the proposed drug with the main comparator. However, PBAC recognises that direct randomised trials are not always available. If this is the case, alternatives might be (in order of priority):

- an indirect comparison across two or more sets of randomised trials involving one or more common reference

- nonrandomised studies (including comparisons involving single arms extracted from randomised trials).

The clear preference for evidence from the most scientifically rigorous sources does not imply that a minimum standard must be met. PBAC has considered and will continue to consider all levels of evidence. However, PBAC will be most influenced by the results of direct randomised trials as the most rigorous source of data.

Therefore, the remainder of Section B relates to the assessment of the characteristics of direct randomised trials and the interpretation of the results. Part III, Section B(i) and Section B(ii) of the guidelines provide guidance for the presentation of submission section B of a submission based on other types of studies. Figure B.1 shows a flowchart of these options.
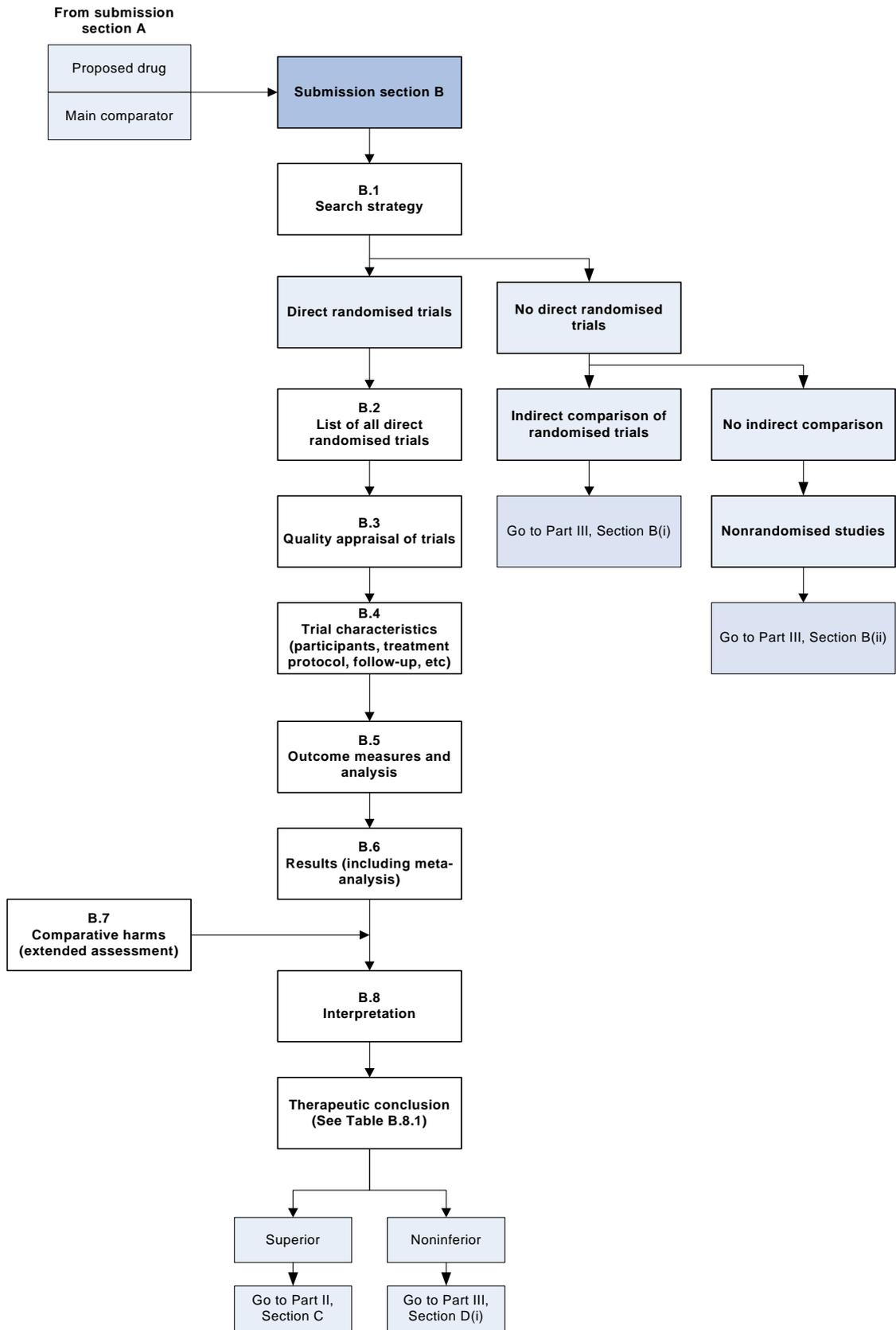
Figure B.1   Key information requests for submission section B of a major submission to PBAC

B.1 Description of search strategies

> **Information request**
> - Describe the search strategies and characteristics used to locate reports of potentially relevant trials from the published literature, registers of randomised trials and unpublished sources held by the sponsor.

Search strategies

The primary objective of the search strategies is to locate *all* randomised trials that, for the main indication, compare the proposed drug directly with the main comparator for participants with characteristics that overlap with patients who would be eligible for use of the proposed drug.

The search should involve at least four approaches:

(a)   a search of the published literature

(b)   a search of registers of randomised trials

(c)   an examination of the dossier seeking marketing approval submitted to the TGA, supplemented by checks with the sponsor's head office and subsidiaries of the company (and any other original sponsor or co-licensed companies) for any further randomised trials (which may be unpublished)

(d)   manual checking of reference lists of all relevant articles that are obtained by other means.

When describing the search strategies and characteristics for (a), (b) and (d), sufficient detail should be provided so that an independent replication of the search would yield the same results.

The methods used to search the published literature are pivotal to assessing the completeness of the overall search. Therefore, specify the following characteristics of the search strategy:

- The specific databases and registers of clinical trials searched, including at least MEDLINE[12], EMBASE[13], The Cochrane Library (including the Cochrane Database of Systematic Reviews,and the Cochrane Central Register of Controlled Trials)[14], the National Institutes of Health[15] and the Australian Clinical Trials Registry (ACTR[16]). The search should also include databases internal to the company and any other known registers of randomised trials relevant to the therapeutic area.
- The date the search was conducted.
- The date span of the search (which should include the most recent update of each database searched).

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[12] http://medline.cos.com/
[13] http://www.embase.com/
[14] http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME
[15] http://clinicaltrials.gov/
[16] http://www.actr.org.au/

- The complete search strategies used, including the search terms (key or MeSH words) and the relationship (sets and Boolean) between the search terms.

- Any supplementary searches, especially manual checking of references in the retrieved papers from the database searches.

B.2   Listing of all direct randomised trials

Information requirements

- The submission **must** identify and list all relevant direct randomised trials.

- If no relevant direct randomised trials are found in the searches, a 'nil return' **must** be included in the submission.

Information requests

- Present tables listing all citations of the direct randomised trials identified from the search of the published literature, marketing dossier and other sources. Show the inclusion and exclusion criteria for identifying relevant trials and state which trials have been published.

- On the hard-copy of each of the search printouts supplied as technical documents with the submission, annotate each citation to indicate excluded citations with the reason for the exclusion.

- Collocate all reports of each direct randomised trial to create a master list and indicate the preferred identification (ID) for each trial to be used throughout the submission for consistency.

- Justify the exclusion of any relevant direct randomised trials. Tabulate a summary highlighting key aspects of the identified trials, presenting included and then excluded trials.

- Separately identify any meta-analysis of randomised trials and assess their exclusion or inclusion using the same criteria as above. Include any relevant systematic reviews from the Cochrane Database of Systematic Reviews.

- Identify any direct randomised trial that was designed prospectively as a noninferiority trial and/or whether the therapeutic conclusion presented in Subsection B.8 is one of noninferiority or equivalence.

- Include copies (or sufficient details) of the included trials as attachments in the main body of the submission and ensure that the location of each item is clearly shown in the submission index.

The listing of relevant direct randomised trials **must** be complete in order to satisfactorily address publication bias, duplication bias and outcomes reporting bias. The Pharmaceutical Evaluation Section 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.

If no relevant direct randomised trials are found in the searches, the submission **must** include a statement to this effect with the results of the searches.

Search results

Assess all citations retrieved by the searches (see Subsection B.1) to extract all trials that meet each of the following inclusion criteria for direct randomised trials:

(a)   the trial included a randomisation procedure in its design

(b)   the trial compared the proposed drug and the main comparator in separate arms

(c)   the trial recruited participants with characteristics that overlap with those of patients who would be eligible for the main indication.

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

Tables B.2.1 and B.2.2 provide a suggested format for presenting the search results to summarise the inclusion and exclusion of citations from the results of searches reported in Subsection B.1.

Table B.2.1   Summary of identification of direct randomised trials from the search of the published literature

	MEDLINE	EMBASE	Trial registries	Other database
• Number of citations retrieved by search				
• Number of citations excluded after title/abstract review: – not a randomised trial – randomised trial does not include the proposed drug and the main comparator in separate arms – characteristics of the recruited participants do not overlap with the main indication • TOTAL				
• Number of citations excluded after full text review: – not a randomised trial – randomised trial does not include the proposed drug and the main comparator in separate arms – characteristics of the recruited participants do not overlap with the main indication • TOTAL				
• Number of citations of direct randomised trials included from each database				
• Consolidated number of citations of direct randomised trials (removing exact duplicates across different databases)				
• Number of multiple (additional) citations of direct randomised trials identified				
• Number of published direct randomised trials included				

Note: Present columns that correspond with submitted printouts (eg if the printouts combine MEDLINE and EMBASE, these results can be combined in the table)

Table B.2.2 Summary of identification of sponsor's[a] direct randomised trials and information from the manual search of retrieved citations

	TGA dossier	Other 'in-house' trials	Manual search	Total
• Number of reports or citations of randomised trials retrieved				
• Number of randomised trials excluded: – randomised trial does not include the proposed drug and the main comparator in separate arms – characteristics of the recruited participants do not overlap with the main indication • TOTAL	b			
• Number of direct randomised trials included from these searches	b			
• Number of these direct randomised trials identified in Table B.2.1	b			
• Number of other direct randomised trials identified in Table B.2.1				
• Total direct randomised trials included				

TGA = Therapeutic Goods Administration
a For the purposes of the search for relevant randomised trials, 'sponsor' includes any original sponsor (including head office and all subsidiaries) and/or any co-licensing sponsor of the proposed drug in addition to the sponsor lodging the submission.
b Separately list and identify each of these trials using the identifying nomenclature used for the trials in the TGA evaluation reports to enable a cross-check against the trials considered by the TGA.
Note: If the only source of a direct randomised trial relevant to the submission is located by a manual search within an independently conducted meta-analysis (preferably published in a peer-reviewed journal and incorporating all important trials listed in this Section B), count the trial here and list the trial with the master list as shown in Table B.2.3.

Annotated search printouts

On the hard copy of each of the search printouts supplied as technical documents with the submission, annotate each citation as appropriate with the letter (a), (b) or (c) to indicate which of the above criteria was invoked to exclude that citation. Each citation without an annotation should thus be a report of a direct randomised trial included in the submission.

Master list of trials

Table B.2.3 provides a suggested format for presentation of a master list of all the direct randomised trials identified in the search.

Table B.2.3 Trials (and associated reports) presented in the submission

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

If there are no direct trials, see Figure B.1 for the next step in the clinical evaluation.

Option to present supplementary randomised trial data

Where data from one or more direct randomised trials are available, the presentation of an indirect comparison is generally not encouraged. However, in certain circumstances, it may be reasonable to justify the inclusion of supplementary randomised trial data. The following list shows possible situations where this may apply:

- a supplementary indirect comparison of two or more sets of trials involving one or more common references that is based on much larger participant numbers (particularly if the direct randomised trials available are underpowered overall); see also Part III, Section B(i) for further guidance on presenting an indirect comparison

- a meta-analysis comparing all trials of the proposed drug against several drugs widely accepted as equivalent to the main comparator in terms of effectiveness and safety, as well as the direct randomised trials

- a meta-analysis comparing all trials of the main comparator against several drugs widely accepted as equivalent to the proposed drug in terms of effectiveness and safety, as well as the direct randomised trials

- dose–response data, which are needed to establish better the equi-effective doses in the context of a cost-minimisation analysis (see Part III, Section D(i) and Appendix 5).

Separately identify and list the supplementary randomised trials as part of the response to Subsection B.2 and include reports of these trials with other references to the submission. Present these supplementary trials in Subsections B.3–B.6. Clearly label this supplementary information to distinguish it from the information from the relevant direct randomised trial(s).

Meta-analyses

Separately identify any meta-analysis of randomised trials from the suite of searches above and assess their exclusion or inclusion using the criteria above. This should include any relevant systematic reviews from the Cochrane Database of Systematic Reviews.

If a published meta-analysis of direct randomised trials is the principal source of the presented clinical evaluation, provide a copy of the publication as an attachment in the main body of the submission. Assess whether the published meta-analysis has a well-defined clinical question relevant to the intended listing of the proposed drug, a reproducible literature search strategy and appropriate criteria for any exclusions of

identified direct randomised trials. Assess the meta-analysis using the framework of this Subsection B (see below) alongside the presentation of the individual trials. Where there is more than one such meta-analysis, tabulate these assessments.

Exclusion of trials

Justify the exclusion of any direct randomised trial included in the master list in Table B.2.3 from further detailed assessment in the submission. The grounds for exclusion might include any aspect reported in Subsections B.3–B.5 (ie the quality of the trials, the patient characteristics and circumstances of use, and the outcomes reported in the trials). This might minimise observable differences across the randomised trials, or examine and explain where possible their contribution to heterogeneity across all the trials.

It is not possible to give unequivocal guidance on the exclusion of direct randomised trials at this stage. If a decision to exclude or include one or more randomised trials is likely to be controversial, it is usually wiser to also present a sensitivity analysis examining whether that decision makes a difference to the conclusions from the overall clinical evaluation.

If one or more trials are to be excluded, identify those aspects of each trial that cause the exclusion (see Table B.2.4). Indicate whether each reason relates to the quality of the trials, the patient characteristics and circumstances of use, and/or the outcomes reported in the trials. Present greater detail of each aspect (as a minimum, to the extent requested in the relevant text below in Subsections B.3–B.5). If there is more than one type of reason for exclusion, arrange the excluded trials in Table B.2.4 by the reason for exclusion.

Table B.2.4 Reasons to exclude each trial from further detailed assessment

Trial ID	Ground(s) for seeking exclusion	Details[a]
Quality of the trial		
Trial A		
Etc		
Patient characteristics and circumstances of use in the trial		
Trial B		
Etc		
Outcomes reported in the trial		
Etc		

a Cross-reference each set of details to the source of information (specifying the trial report with page, table, figure number).

Tabulate a brief summary highlighting key aspects of the identified trials, presenting included and then excluded trials (see Tables B.2.5 and B.2.6).

Table B.2.5 Comparative summary of characteristics of direct randomised trials

Trial ID	Design characteristics [a]	Compared interventions (*N*, drug, dose, frequency, duration)	Summary of main population characteristics	Main outcomes	
				Primary	Secondary
Included trials					
Trial 1					
Etc					
Excluded trials					
Trial A					
Etc					

a C-O = cross-over; DB = double-blind; ITT = intention to treat; PG = parallel group; SB = single-blind

Table B.2.6 Comparative summary of results of direct randomised trials

Trial ID	Primary outcome (95% CI)	Secondary outcomes (95% CI)	Major adverse events
Included trials			
Trial 1			
Etc			
Excluded trials			
Trial A			
Etc			

CI = confidence interval

Presentation of noninferiority (equivalence) trials

Most randomised trials are designed to show a difference between the compared therapies. If any direct randomised trial was designed prospectively as a noninferiority trial, and/or the therapeutic conclusion presented in Subsection B.8 is noninferiority or equivalence, refer to the additional guidance on presenting the direct randomised trial in Appendix 5.

Noninferiority means that, in terms of effectiveness, the proposed drug is no worse than its main comparator. It is used to support a claim of equivalence because it is not adequate to demonstrate the *absence* of a statistically significant difference between the treatments to claim equivalence; such a lack of a significant difference might occur when the trials are too small to demonstrate a real difference in the effects of the interventions. The appropriate comparison to present is the point estimate of the difference with its 95% confidence interval. This allows PBAC to assess whether the confidence interval contains the minimal clinically important difference (see Figure B.2 in Subsection B.8).

Trial details

Include sufficient details of the relevant randomised trials as attachments in the main body of the submission. Where there is more than one report of a randomised trial (eg one or more published papers and one or more trial reports internal to the sponsor), provide both the published paper(s) and key extracts from the sponsor's internal trial report (see checklist in Part I, Table 6.1 for details on how to do this). The results might vary between reports of the same randomised trial. If so, justify and cross-reference the

selection of the source of results extracted for the submission. Provide a copy of each other publication reporting data from a listed randomised trial. Ensure that the submission index shows the location of all submitted papers, both in the main body of the submission and in the attachments.

For any relevant trial identified from a meta-analysis, include the individual trial report or publication(s) as above. If no separate report is available, indicate the efforts made to retrieve them and to obtain any missing information from the authors of the published meta-analysis.

Provide reputable translations of trial reports printed in other languages.

B.3 Assessment of the measures taken by investigators to minimise bias in the direct randomised trials

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Information requests

- For each direct randomised trial listed, provide information on the measures taken to minimise bias, using the checklist provided.

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

Assessment of measures to minimise bias

The purpose of assessments of measures to minimise bias is to provide the sponsor and PBAC with a clear idea of which trials are of greater scientific rigour. There is no minimum standard, but PBAC is most likely to be persuaded by the data of the highest scientific rigour.

The checklist in Box B.3.1 includes three sets of methodological topics that help to assess the methodological quality of each trial. Table B.3.1 shows a suggested approach to presenting the information in a summary format. This is a useful guide to help PBAC and the sponsor review the scientific rigour of the evidence by assessing the measures taken by the investigators to minimise bias. It is not intended to discourage the presentation of data.

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┌─────────────────────────────────────────────────────────────────────────────┐
│ Box B.3.1      Checklist for assessing the quality (internal validity) of randomised trials │
│ Methodological topic       Quality issue                                        │
│ (a) Randomisation      (i)    How was the randomisation sequence concealed during the allocation │
│                               process?                                          │
│ (b) Blinding           (i)    Were the following groups blinded to the treatment allocation? │
│                               1.   Trial participants                           │
│                               2.   Investigators                                │
│                               3.   Personnel assessing the outcomes             │
│                        (ii)   If any of the groups in (b)(i) were blinded to treatment allocation, how was │
│                               blinding achieved?                                │
│                        (iii)  If any of the groups in (b)(i) were not blinded to treatment allocation, why was │
│                               blinding not possible?                            │
│ (c) Follow-up          (i)    What was the basis of the analysis?               │
│                        (ii)   How many participants were randomised to each arm of the trial? │
│                        (iii)  How many participants in each arm of the trial did not receive the allocated │
│                               intervention?                                     │
│                        (iv)   How many participants in each arm of the trial were lost to follow-up? │
│                        (v)    How many participants in each arm of the trial discontinued the intervention? │
│                        (vi)   How many participants in each arm of the trial contributed data to the primary │
│                               analysis?                                         │
└─────────────────────────────────────────────────────────────────────────────┘
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Notes for trial quality checklist

(a) Randomisation distributes both known and unknown confounders by the play of chance, providing a good basis for comparison between randomised groups in a treatment trial because the groups differ only by the treatment allocation and the play of chance. Statistical methods then help determine whether observed differences can credibly be attributed to the treatment(s) under investigation rather than to chance. Secure randomisation minimises selection bias. To ensure that randomisation remains secure, it is important that personnel responsible for enrolling participants into a trial are unable to predict which treatment a participant would receive before a final decision is made regarding entry to the trial. Provide details of the methods of concealing the randomisation sequence, such as decentralised or 'third party' assignment, or sequentially numbered envelopes or containers.

(b) Blinding of participants, investigators or those responsible for assessing the outcomes helps prevent several important biases in randomised trials. Blinding of participants and investigators might influence several aspects of the trial, including the response to treatments, the use of co-interventions, and withdrawal rates from the trial. Blinding of outcome assessors might also influence the reported response to treatment. The influence of blinding is most important where the outcome is subjective, such as the evaluation of pain or preference of treatment.

If blinding of treatment allocation was used, describe the methods used, such as identical tablets or capsules. Blinding of treatment allocation might not always be possible, for example in a comparison between a liquid preparation that is cloudy and one that is clear. Where the comparator is distinguishable by visual inspection or taste, or where there is a high chance of 'unblinding' (eg oestrogen or beta-blocker treatment), it is important that the observer responsible for measuring the trial outcomes remains unaware of the treatment assignment. State the reasons for not blinding the participants, investigator(s) or

outcome assessors. Discuss the effect, if any, that the absence of blinding might have had on the measurement of the primary and secondary outcomes of the trial.

(c) Follow-up is important, and it is also important that an attempt is made to summarise the trial outcomes for all participants. A full 'intention-to-treat' (ITT) analysis is preferred for trials designed to demonstrate a therapeutic difference (and related incremental cost-effectiveness analysis) to minimise bias in the follow-up of participants. Specify how the ITT analysis dealt with missing data.

Tabulate responses

If there is more than one trial, tabulate the responses in the main body of the submission, with the detailed responses to the above questions in an accompanying attachment or technical document. In this detailed presentation, also provide adequate cross-references to the trial report (including page, table or figure numbers of the source document) from which each aspect of the information was extracted.

Tables B.3.1 and B.3.2 provide a suggested format for the presentation of the summary in the main body of the submission.

Table B.3.1   Summary of the measures undertaken to minimise bias in the direct randomised trials

Trial ID	Concealment of randomisation[a]	Blinding			Basis of analysis[b]
		Participants	Investigators	Outcomes assessors	
Trial 1	A/B/C/None	Yes/No	Yes/No	Yes/No	D/E/F/G
Trial 2	A/B/C/None	Yes/No	Yes/No	Yes/No	D/E/F/G
Etc					

a A = central telephone randomisation service; B = third-party randomisation service (eg pharmacy, pharmaceutical company); C = sequentially labelled, fully opaque, sealed envelopes
b D = intention-to-treat (all randomised participants: specify how the analysis dealt with missing data); E = all treated participants (specify how the analysis dealt with missing data); F = per protocol participants; G = other (specified)

Table B.3.2   Flow of participants through the direct randomised trials

Trial ID • Intervention arm	No. randomised	Did not receive intervention	Lost to follow-up	Dis-continued	Analysed	Source of information
Trial 1 • Proposed drug • Main comparator	N N	n (%) n (%)	n (%) n (%)	n (%) n (%)	n (%) n (%)	(Add this column to tables and submit in a separate technical attachment)
Trial 2 • Proposed drug (high dose) • Proposed drug (low dose) • Main comparator	N N N	n (%) n (%) n (%)	n (%) n (%) n (%)	n (%) n (%) n (%)	n (%) n (%) n (%)	
Etc						

Source documents

For each of the responses provided in Tables B.3.1 and B.3.2 above, specify the source document in the reports or papers accompanying the main body of the submission. Provide adequate detail of cross-referencing to page, table or figure number of the relevant trial report(s) in a way that does not detract from the presentation of the requested results.

For the presentation of a complex systematic overview, consider re-presenting the tables from the main body of the submission in a technical document or attachment and add an additional column to each table to provide adequate detail of cross-referencing (as illustrated by the shaded column in Table B.3.2). Alternatively, if it is clearer for some tables, identify the source of information cell by cell, using footnotes.

B.4 Characteristics of the direct randomised trials

Information requests

- For each direct randomised trial, provide the following details of the trial protocols and participants:

    – the eligibility criteria for participants considered for recruitment into the trial

    – the baseline demographic and clinical characteristics of each randomised group

    – the duration of follow-up (median and range) and whether the trial has been completed or is ongoing

    – precise details of the interventions administered to each randomised group, including form, dose, method of dose administration, dose timing and frequency, dose titration, dose titration criteria and treatment duration.

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

Details of trials

If there is more than one direct randomised trial, tabulate the responses in the main body of the submission. Tables B.4.1–B.4.3 provide a suggested format.

Table B.4.1 Eligibility criteria in the direct randomised trials

Trial ID	Inclusion criteria	Exclusion criteria
Trial 1	Typical inclusion criteria may relate to age, sex and clinical diagnosis.	Exclusion criteria are often used to ensure participant safety.
Trial 2		
Etc		

Indicate any significant differences in the baseline characteristics of randomised groups across the trials and discuss any impact this might have on the interpretation of the trial results, including those to be examined in Subsection C.1). Table B.4.2 provides a suggested format for this information.

Table B.4.2   Characteristics of participants in the direct randomised trials varying across randomised groups

Trial ID • Baseline characteristic	First randomised group	Second randomised group	Third randomised group	Etc
Trial 1				
Age				
Sex (etc)				
Trial 2				
Age				
Sex (etc)				
Etc				

Table B.4.3   Interventions compared by the direct randomised trials

Trial ID	Treatment	Dosage regimen	Duration of treatment	Duration of follow-up
Trial 1	Proposed drug		Median (range)	Median (range)
	Main comparator		Median (range)	Median (range)
Trial 2	Proposed drug (high dose)		Median (range)	Median (range)
	Proposed drug (low dose)		Median (range)	Median (range)
	Main comparator		Median (range)	Median (range)
Etc				

Present a separate table for any cross-over randomised trials (to report such additional details as period of wash-out between treatment periods) and indicate how the results of the cross-over have been included in the systematic overview (see Subsection B.6).

Provide any additional information about the trial or participant characteristics that is not requested elsewhere in Subsections B.3 to B.5, but is relied on in assessing the applicability of the direct randomised trial evidence to the listing requested (see Subsection C.1). For example, if it is considered that the settings and locations where the interventions were provided modify the treatment effect, summarise the details of this characteristic across all the trials and cross-reference to Subsection C.1.

If the requested restriction seeks to limit use to a last line of therapy so that placebo for standard medical management is the nominated main comparator, identify whether the participants in the direct randomised trials reflected a similar positioning in the clinical management algorithm. If the trials recruited participants earlier in the clinical management algorithm, discuss the implications for the submission.

Source documents

For each of the responses provided above, provide adequate cross-referencing to page, table or figure numbers of the relevant trial report(s), if necessary in a separate technical document or attachment, as described for Subsection B.3.

B.5   Outcome measures and analysis of the direct randomised trials

> **Information requests**
>
> - For each direct randomised trial, describe the primary outcome and how it was analysed.
>
> - For each direct randomised trial, describe the patient-relevant secondary outcomes (including any quality-of-life outcomes) and how they were analysed.
>
> - Discuss the clinical importance of the primary outcome and secondary outcomes listed in response to the requests above.
>
> - Assess each instrument used to measure quality of life.
>
> - For each direct randomised trial, indicate whether a multi-attribute utility instrument (MAUI) was used and, if so, how it was used and how its results were analysed.
>
> - For each response, specify the source document in the reports or papers accompanying the main body of the submission, together with the page or table from which the information was extracted.

Primary outcomes

List and clearly define the primary outcome measure for each direct randomised trial, including its units of measurement. Specify enough details of the outcome measurement for PBAC to assess its clinical importance (eg supine/erect blood pressure). State the difference specified as worth detecting in any power calculation. For each primary outcome, describe the statistical methods used in the primary analysis to compare across the randomised groups. State whether the primary outcome was assessed at several time points after randomisation. If so, indicate the prespecified time point of the primary analysis and describe the methods of adjusting for multiple interim analyses.

Table B.5.1 provides a suggested format for presenting and comparing primary outcomes from several trials.

Table B.5.1   Primary outcomes and statistical analyses of the direct randomised trials

Trial ID	Definition of primary outcome	Method of primary statistical analysis
Trial 1		
Trial 2		
Etc		

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

Secondary outcomes

For each direct randomised trial, list and define each secondary outcome and analysis that is patient-relevant, including the units of measurement. This may include secondary analyses of the primary outcome. Include any data collected for resources provided (economic outcomes) as well as health outcomes gained, because they are relevant both to

patients and the economic evaluation. For each patient-relevant secondary outcome, describe the statistical methods used to compare across randomised groups. State the number of prespecified secondary outcomes and any methods used to address the multiplicity of analyses across outcomes. Increasing the number of multiple comparisons increases the odds that, through chance alone, a statistically significant difference will emerge in one of these comparisons, assuming the null hypothesis is true.

Patient-relevant outcomes are those outcomes that are perceptible to the patient; the more important the outcome is to the patient, the more relevant it becomes. Examples of patient-relevant outcomes include quality-of-life measures, preference weights (see Appendix 6), and economic inputs and outcomes (see Subsection D.4).

Table B.5.2 provides a suggested format for presenting and comparing patient-relevant secondary outcomes and analyses when more than one trial is included in the submission.

Table B.5.2 Patient-relevant secondary outcomes and analyses in the direct randomised trials

Trial ID	Definition of secondary outcome	Method of statistical analysis
Trial 1		
Trial 2		
Etc		

Note: As for the primary outcomes, ensure that each outcome is reported as being truly independent, or that the statistical analysis appropriately adjusts for clustering.

Clinical importance

Discuss the clinical importance of the primary outcome and secondary outcomes listed in Tables B.5.1 and B.5.2. For primary outcomes, this might be informed by the basis given in the trial protocol for the minimal clinically important difference used in the power calculation. Discuss clinical importance in terms of both relative and absolute changes.

Composite outcomes

If one or more of the reported outcomes is a composite outcome, discuss and compare the clinical importance of each of its component outcomes. Report whether the definition of the composite outcome was prespecified explicitly. Explain the justification for the inclusion of the components in the composite outcome and for the exclusion of any components that were considered but rejected as components in the composite outcome. Disaggregate the composite outcome in order to present the results (eg comparative rates) of each component as a secondary outcome in Subsection B.6. To avoid double-counting, a composite outcome is usually defined as having been experienced when the trial participant experiences the first component outcome in the composite (such as disease progression), even though other component outcomes in the composite (such as death) might be subsequently experienced. This needs to be appropriately handled in disaggregating the composite outcome so that, where possible, all subsequent first experiences of any other component outcome in the composite are also included.

Quality-of-life instruments

Where a change in quality of life is the principal intended final outcome (see Subsection D.4), a quality-of-life measure should be considered. This is true for some indications (eg relief of pain, treatment of depression, treatment of some cancers) in which improved quality of life is the principal aim of therapy. Alternatively, quality of life might actually be impaired by the proposed drug or by its main comparator (or other intervention). Quality-of-life measures may supplement other clinical measures.

Quality-of-life instruments include generic ('global') health-related quality-of-life scales and disease-specific rating scales (eg for pain, disability or depression), which might themselves be the primary measure of outcome in the trials. Increasingly, trials are collecting data using both types of quality-of-life instruments.

Where a quality-of-life instrument is used, details should be provided on the instrument. Controversy remains over which quality-of-life instruments are most acceptable, so special attention should be paid to the following parameters:

- the validity of the instrument

- the reliability of the instrument

- the responsiveness of the instrument to differences in health states between individuals and to changes in health states over time experienced by any one individual

- the clinical importance of any differences detected by the instrument.

Where possible, provide any supportive data and references assessing these parameters of the instrument in a technical document or an attachment to the submission (provide clear cross-references between these data and the main body of the submission).

For drugs that cure or prevent short-term illnesses (eg infections), outcomes might not always be measurable on a quality-of-life instrument. It might also be reasonable to assume that certain events that may themselves be serious do not greatly impair quality of life in survivors (eg pneumonia).

Use of a MAUI (multi-attribute utility instrument)

Appendix 6 describes the use of health-related quality-adjusted life-years (QALYs) gained as a measure of health outcomes that is comparable across health states. It also provides background information on the generally preferred method of measuring QALYs, which is via the repeated application of a valid, reliable and responsive multi-attribute utility instrument (MAUI) questionnaire to participants in a randomised double-blind trial, together with the application of an appropriate scoring algorithm (see Subsection B.6).

The MAUI should be used to collect information from trial participants at baseline and at one or more time points during the trial follow-up (see advantages (h) in Appendix 6).

As health-related quality of life is inherently subjective, its assessment in a randomised trial as a basis for then estimating utility weights using a MAUI algorithm is more persuasive if the trial design blinded the observers of the outcome being measured in response to the treatment assigned (see Subsection B.3 and advantage (c) in Appendix 6).

Acceptable MAUIs are the Health Utilities Index (HUI2 or HUI3), the EQ5D ('EuroQol'), the SF-6D (a subset of the Short Form 36, or SF-36) or the Assessment of Quality of Life (AQoL) instrument. Currently, there is insufficient basis for a preference to be expressed between these MAUIs. All are based on acceptable scaling techniques of the standard gamble (SG) or time trade-off (TTO), and some have different scoring algorithms for different countries. Studies directly comparing these MAUIs suggest that each MAUI yields different results for the same health state, so their utility weight results cannot be compared with complete confidence. The MAUIs listed above vary in their coverage of important health domains, but they all cover the main areas of health-related quality of life that patients would be willing to trade for increased survival. HUI2 is designed for use in childhood conditions.

All the MAUIs have strengths and weaknesses. For example, as a general observation, the EQ5D has fewer possible health states, which means that it has been perceived as relatively unresponsive or insensitive compared with the other MAUIs listed above. Another feature of the EQ5D is that when a difference is detected, the numerical value can appear disproportionately large compared with the more gradual increments of the other MAUIs listed above.

The use of any other possible preference-based instrument, such as the Quality of Well-Being Scale (QWB) or the 15D (15 Dimensions), needs to be particularly justified, including with reference to the above criteria of comparability, acceptable scaling techniques and responsiveness.

If a MAUI has been used in a relevant randomised trial for the purposes of reporting utility weights, provide details of the selected MAUI. Justify the selection of any MAUI used in the trial but not listed above as acceptable by assessing:

- the validity of the instrument

- the reliability of the instrument

- the responsiveness or sensitivity of the instrument to differences in health states between individuals who are likely to be affected by the proposed drug and its main comparator

- the responsiveness or sensitivity of the instrument to changes in health states over time experienced by any one individual

- the duration of the period assessed when responding to the MAUI questionnaire compared with the duration of the condition of interest

- the applicability to the general Australian population of the scoring algorithm applied to the responses reported with the MAUI questionnaire to calculate utility weights.

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

Source documents

For each of the responses provided above, provide adequate cross-referencing to page, table or figure numbers of the relevant trial report(s), if necessary in a separate technical document or attachment, as described for Subsection B.3.

B.6   Systematic overview of the results of the direct randomised trials

> **Information requests**
>
> - For each direct randomised trial, present the results of the primary analysis for that trial.
>
> - Present an analysis of the results for each type of patient-relevant outcome in terms of its natural units in tables with graphed forest plots. Include results reporting quality-of-life outcomes.
>
> - Where there is more than one randomised trial reporting a particular outcome, statistically combine (meta-analyse) the results.
>
> - For each meta-analysis of each outcome, assess the potential for outcomes reporting bias by reporting in a footnote to the presentation of the forest plot for each outcome:
>
>   – the number of trials contributing to the forest plot
>
>   – the proportion of these trials over the total number of trials included in Table B.2.3.
>
> - Present the results of any multi-attribute utility instrument used in any of the direct randomised trials.
>
> - For each response, specify the source document in the reports or papers accompanying the main body of the submission, together with the page or table from which the information was extracted.

The presentation of the trial results in Subsection B.6 serves two purposes:

- First, the presentation of the results of the primary analyses as established for each direct randomised trial is part of the assessment of the scientific rigour of the trial dataset and becomes a reference point for interpreting other patient-relevant outcomes for that trial.

- Second, the presentation of the results of common outcomes across more than one trial enables an assessment to be made of the comparative effectiveness of the proposed drug and the main comparator under the circumstances of the trials as designed and conducted.

Subsection B.6 is not directly concerned with the application of the available trial evidence to the listing requested. Section C addresses this important issue.

Primary analysis

For each direct randomised trial listed in Subsection B.2, present the results for the primary outcome according to the design of the prespecified primary analysis for that trial. Justify and discuss any early stopping of a trial or reliance on any interim analysis in the interpretation of the primary outcome.

Analysis (including meta-analysis) of all patient-relevant outcomes

Present a meta-analysis for each patient-relevant outcome listed in Subsection B.5 (which may include one or more primary outcomes). First, present the results (preferably analysed on an intention-to-treat basis) for each randomised group of each randomised trial listed in Subsection B.2 reporting that particular outcome. Then present the measured

direction and the magnitude of the treatment effect across groups of each trial (also preferably analysed on an intention-to-treat basis).

Guidance is provided below on the preferred method of reporting results, depending on the way the data are reported (see also Tables B.6.1 to B.6.5).

Where there is more than one randomised trial reporting a particular outcome, the presentation of a meta-analysis, which statistically combines (pools) results across trials, is generally preferred where appropriate. Collate the results of each trial reporting the outcome into a meta-analysis and present the results of each meta-analysis in a table and as a graphed forest plot, including the pooled results across the trials. 'Revman', the software from the Cochrane Collaboration, quickly and succinctly conveys the requested array of meta-analysed information in a format suitable for including in the main body of the submission.

Where a meta-analysis is based on a subset of all available direct randomised trials, identify the trials in the subset. Report the number of trials in the subset and the proportion that this number represents of the total number of trials listed in Subsection B.2. This includes situations where there is only one randomised trial reporting a particular patient-relevant outcome, in which case the number of trials in the subset is one and there is no basis to meta-analyse the data any further. Examine whether there are any differences between the results of the subset and the total set of trials using group-level data, and assess the impact of any bias (such as outcomes reporting bias) across any differences detected.

Meta-analysis is useful because it might increase the precision of the estimates of differences between the proposed drug and the main comparator. It is also useful when there are conflicting results from trials of similar scientific rigour. Meta-analysis can also highlight advantages of a proposed drug that are too small to be detected reliably in individual randomised trials, but might be clinically important. Justify any decision *not* to present a meta-analysis whenever there is more than one direct randomised trial reporting a common, patient-relevant outcome.

Explain and justify the methods used for statistically combining cross-over trials in a meta-analysis of parallel group trials. Clearly document and reference the methods used to make them independently reproducible and verifiable.

Where a meta-analysis of group-level data is supplemented by individual patient data, provide an appropriate summary of these data for each trial and for the pooled results overall. Where individual patient data are used in a pooled analysis, ensure that the trial in which each individual was randomised is included as a covariate in the analysis.

Explain and justify any other method used for statistically combining the results of the direct randomised trials and any additional statistical tests used. Clearly document and reference the methods used to make them independently reproducible and verifiable. Provide adequate detail of all sources of information relied on for these other analyses (see Part I, Subsection 6.2), then present their results.

Dichotomous data

For each outcome measured as dichotomous data (eg with or without the event), present for each group in each trial:

- the number with the event

- the number in the group

- the percentage with the event

- the period of time after randomisation at which these data were collected in the trial (which is usually the median duration of follow-up).

Then present the relative risk, risk difference and number-needed-to-treat (NNT) with their associated 95% confidence intervals for each trial reporting the outcome.

Where there is more than one randomised trial reporting a particular dichotomous outcome, tabulate the results (point estimates and 95% confidence intervals) of the individual trials as the relative risk and the risk difference. Also present these results for the individual trials on a graphed forest plot.

Statistically combine the results for the relative risk and risk difference using the DerSimonian–Laird random effects model and include the pooled results in each table and graphed forest plot, together with their associated 95% confidence intervals.

Report results for statistical heterogeneity as the Cochran Q with a chi-square test for heterogeneity and the I^2 statistic with its 95% uncertainty interval. If heterogeneity is present, consider examining it in Section C.

Tables B.6.1 and B.6.2 provide a suggested format that reflects the Revman format for presenting and comparing dichotomous outcome data from several trials.

Table B.6.1 Results of [patient-relevant outcome] (available as dichotomous data) across the direct randomised trials (relative risk)

Trial ID	Proposed drug	Main comparator	Forest plot here	Relative risk (95% CI)
Trial 1	n with event/N (%)	n with event/N (%)		
Trial 2				
Etc				
Pooled result from random effects model				
Chi-square (Q) for heterogeneity: P = I^2 statistic with 95% uncertainty interval =				

CI = confidence interval; n = number of participants with event; N = total participants in group
Note: Provide number and % of the identified relevant direct randomised trials that contributed data to this meta-analysis.

Table B.6.2 Results of [patient-relevant outcome] (available as dichotomous data) across the direct randomised trials (risk difference)

Trial ID	Proposed drug	Main comparator	Forest plot here	Risk difference (95% CI)
Trial 1	n with event/N (%)	n with event/N (%)		
Trial 2				
Etc				
Pooled result from random effects model				
Chi-square (Q) for heterogeneity: P = I^2 statistic with 95% uncertainty interval =				

CI = confidence interval; n = number of participants with event; N = total participants in group
Note: Provide number and % of the identified relevant direct randomised trials that contributed data to this meta-analysis.

Continuous data

For each outcome measured as continuous data, present for each group in each trial the mean at baseline, the mean at end point (or other justified time point) and the mean change, each with its standard deviation. Then present, for each trial reporting the outcome, the mean difference at end point and the mean difference of the change, each with its 95% confidence interval. Report the number of participants in each randomised group of the trial contributing data to each analysis of a continuous outcome.

Where there is more than one trial, tabulate the results (point estimates and 95% confidence intervals) of the individual trials. On a graphed forest plot, plot the results (point estimates and 95% confidence intervals) of the individual trials as the weighted mean difference at end point and the weighted mean difference of the change.

Statistically combine the results for the weighted mean difference using the DerSimonian–Laird random effects model and include the pooled result in each table and graphed forest plot, together with its associated 95% confidence interval.

Report results for statistical heterogeneity as the Cochran Q with a chi-square test for heterogeneity and the I^2 statistic with its 95% uncertainty interval. If heterogeneity is present, consider examining it in Section C.

Tables B.6.3 and B.6.4 provide a suggested format that reflects the Revman format for presenting and comparing continuous outcomes data from several trials.

Table B.6.3   Results of [patient-relevant outcome] (available as continuous data) across the direct randomised trials (end point))

Trial ID	Proposed drug		Main comparator		Forest plot here	Mean difference (95% CI)
Trial 1	n reporting data/N (%)	End point[a] mean (SD)	n reporting data/N (%)	End point[a] mean (SD)		End point[a]
Trial 2						
Etc						
Pooled result from random effects model						
Chi-square (Q) for heterogeneity: $P =$ I^2 statistic with 95% uncertainty interval =						

CI = confidence interval; SD = standard deviation; ; n = number of participants reporting data; N = total participants in group
a Or other justified time point
Note: Provide number and % of the identified relevant direct randomised trials that contributed data to this meta-analysis.

Table B.6.4 Results of [patient-relevant outcome] (available as continuous data) across the direct randomised trials (change)

Trial ID	Proposed drug (mean values)			Main comparator (mean values)			Forest plot here	Mean difference (95% CI)
Trial 1	Base-line (SD)	End point[a] (SD)	Change (SD)	Base-line (SD)	End point[a] (SD)	Change (SD)		Change
Trial 2								
Etc								
Pooled result from random effects model								
Chi-square (Q) for heterogeneity: $P =$ I^2 statistic with 95% uncertainty interval =								

CI = confidence interval; SD = standard deviation
a Or other justified time point
Note: Provide number and % of the identified relevant direct randomised trials that contributed data to this meta-analysis.

Ordinal or categorical data

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

Time-to-event data

Whenever time-to-event data are reported for the overall population in a direct randomised trial, present a graphical plot of the relevant Kaplan–Meier curves (if necessary, because these data are only reported in a published citation, reproduce the graphical plot directly from the cited work).

Present a separate graphical plot for each such trial and for each time-to-event outcome, displaying a separate curve for each randomised group, preferably on an intention-to-treat basis. On each graphical plot, also display the median duration of follow-up and the remaining sample size for each curve at each of a series of time points along the x-axis. Analyse differences between event curves using the log rank test. If the Wilcoxon test is also presented, justify why it is appropriate, for example because of its emphasis on early event times.

Where the analysis is based on a Cox proportional hazards model, present the hazard ratios, together with their 95% confidence intervals. Discuss whether the results are consistent with the assumption of constant proportional hazards.

In the analysis of time-to-event data from the direct randomised trials, censoring usually precludes the estimation of a mean time-to-event. Thus, for any trial reporting time-to-event data where the trial follow-up is insufficient to record all events, the result is a restricted or truncated time-to-event analysis. If the integrals between the two truncated Kaplan–Meier curves are compared, the result is a difference in the truncated means. Therefore, present differences in times-to-event as comparisons of medians (where possible) and of truncated means (with their 95% confidence intervals), with the latter preferably calculated both:

- from commencement of the trial to the end of the most recent available follow-up of the trial

and

- for the median duration of follow-up across the trial population, where follow-up for each individual is defined to be the duration of time from the date of randomisation to the date of the clinical cut-off (for a completed trial) or to the date of the most recent data snapshot (for an ongoing trial). Assuming a constant rate of accrual into the trial, a similar duration can be estimated as being from the start of the trial to time t, where t occurs at a point in time equivalent to half the accrual period before the most recent available follow-up of the trial.

Where there is more than one randomised trial reporting a particular time-to-event outcome, present the pooled results across the trials, together with the number of trials contributing to the forest plot and the proportion of those trials over the total number of trials included in the submission. Data from multiple trials involving a particular time-to-event outcome may be statistically combined in a number of ways. Justify and reference the method(s) selected for pooling time-to-event data. Specify and describe this method in a short technical document or attachment to the submission and provide sufficient data to allow the results to be reproduced and verified independently (see Part I, Subsection 6.2).

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

Table B.6.5 provides a suggested format for presenting and comparing time-to-event outcomes from several trials.

Table B.6.5 Results of [patient-relevant outcome] across the direct randomised trials (available as time-to-event data)

Trial ID	Hazard ratio (95% CI)	Log rank *P*-value
Trial 1		
Trial 2		
Etc		
Pooled		Not applicable

CI = confidence interval
Note: Provide number and % of the identified relevant direct randomised trials that contributed data to this meta-analysis.

Adverse event data

As a minimum, report important adverse events as the number of participants reporting:

- any adverse event
- any adverse event resulting in discontinuation of the randomised treatment
- any adverse event resulting in hospitalisation
- any adverse event resulting in death
- each and every other type of adverse event where the frequency or severity differs substantially across randomised groups, for each randomised trial listed in Subsection B.2, preferably on an intention-to-treat basis.

For each important adverse event, present these results based on proportions of participants reporting each type of adverse event (ie as for dichotomous data above), therefore also presenting relative risks and risk differences with their 95% confidence intervals across the randomised groups for each trial separately. In addition, where appropriate, pool these results across all trials using the random effects model. Where the average period at risk per participant varies substantially between treatment groups, the relative adverse event rates (events/period-at-risk) should also be analysed using Poisson regression, with pooling across trials as necessary using the random effects model. See Subsection B.7 for further discussion of adverse reactions reported from other sources.

Present the results of a MAUI

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

Ideally, the scoring algorithm of the acceptable MAUIs listed in Subsection B.5 would be derived from the general population in Australia (see advantage (e) in Appendix 6), because this would assist in generating Australia-specific utility weights from responses to the MAUI questionnaires generated in international trials. However, there are few Australian-based scoring algorithms for MAUIs generated from an appropriately defined population sample and, in the absence of these, it might be justifiable to use scoring algorithms from other countries with similar cultural or political backgrounds and economic circumstances (eg Canada and England). Where more than one scoring algorithm exists for a MAUI questionnaire but no Australian scoring algorithm, consider presenting an analysis to examine the sensitivity of the trial results to using different scoring algorithms. Similarly, if more than one MAUI questionnaire is used in a trial, present an analysis to examine the sensitivity of the trial results to changing the MAUI. The available evidence suggests that differences in preferences as measured using different country scoring algorithms may be smaller than those measured by different MAUIs.

Discuss the interpretation of these QALY results. Assess the results against other outcomes measured in the trial. This could include reference to the consistency or inconsistency with any concomitantly assessed disease-specific quality-of-life and/or generic quality-of-life measure. This comparison across outcomes could help address questions of the sensitivity or responsiveness of the MAUI and the plausibility of any argument that the evidence from the measure should be ignored as not being sensitive enough (rather than that the measure is correctly reflecting low strength of preference for the difference across the interventions and/or trade-offs due to adverse reactions).

Also assess:

- whether the technique of measurement at baseline and during the trial is valid and likely to be free from bias (eg whether the results correlate with clinical or other measures of health outcomes in the trial)

- whether the results of the exercise are reliable (eg whether there is a high variance in results or inconsistencies in responses, or a high number of missing observations)

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

Source documents

For each of the responses provided above, provide adequate cross-referencing to page, table or figure numbers of the relevant trial report(s), as for Subsection B.3. For a complex systematic overview, consider re-presenting the tables from the main body of the submission in a technical document or attachment, as described Subsection B.3, including additional columns or footnotes for each table to indicate the source of the data in each row or cell, as appropriate.

B.7 Extended assessment of comparative harms

> **Information requests**
> - State whether there is any evidence beyond the direct randomised trials of delayed or rare adverse reactions reported for the proposed drug, or whether there is any pharmacological, biological or clinical basis to suspect that such delayed or rare adverse reactions may be anticipated.
> - State whether there is any evidence of dependence or abuse potential developing for the proposed drug.
> - Specify and justify the search strategy used to identify suitable sources of evidence.
> - Succinctly present any such evidence identified, with appropriate cross-referencing to any source documents provided in a technical document or attachment to the submission.
> - Provide appropriate cross-referencing to any source documents provided in a technical document or attachment to the submission.
> - Indicate how this extended toxicity or dependence profile compares with that of the main comparator.

Direct randomised trials are often an inadequate source of data on comparative harms. Thus, a wider basis of assessment of comparative harms (ie beyond the results of the direct randomised trials presented in response to Subsection B.6) is encouraged. This wide assessment is especially important for serious adverse reactions that might occur in the long term or rarely, or when the proposed drug is from a new pharmacological class. Specify and justify the search strategy used to identify suitable sources of information about any such reactions. Extend the scope of this strategy beyond that presented in Subsection B.1. The most recently available Periodic Safety Update Report for the proposed drug might serve as a useful starting point for summarising such data and identifying information sources. Similarly, a wider assessment of evidence to support claims of differential potential for abuse or dependence is also encouraged.

If the therapeutic conclusion in the submission is that the proposed drug is no worse than the main comparator in terms of effectiveness but is significantly less toxic, or there is an expectation that selection bias might have an influence, it is preferred that the toxicity (or dependence) advantage is demonstrated as a prespecified outcome in the context of the direct randomised trials.

B.8 Interpretation of the clinical evidence

> **Information requests**
> - Provide a summary assessment of the overall trial evidence presented.
> - Use this assessment to state the category from Table B.8.1 that (in terms of comparative effectiveness and comparative safety) best reflects the therapeutic conclusion of the proposed drug over its main comparator, supported by the evidence presented.

Include in this assessment of the evidence a consideration of:

- the level of the evidence (Subsection B.2)

- the quality of the evidence (Subsection B.3)

- the statistical precision of the evidence (Subsections B.6 and B.7)

- the size of the effect (Subsections B.6 and B.7)

- the clinical importance and patient relevance of the effectiveness and safety outcomes (Subsection B.5)

- the consistency of the results over the trials presented (Subsections B.6 and B.7).

The interpretation of the clinical data presented in submission section B is crucial in determining the success of the submission. It is important to classify the therapeutic profile of the proposed drug in relation to its main comparator (ie whether it is therapeutically superior, inferior or equivalent to the comparator). Table B.8.1 sets out a framework for this classification.

Table B.8.1 Classification of the therapeutic relativity of the proposed drug over its main comparator and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA = cost-effectiveness analysis; CUA = cost-utility analysis; CMA = cost-minimisation analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations (eg where the toxicity profiles of the compared drugs differ, with some aspects worse for the proposed drug and some aspects better for the proposed drug).
b An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence.

The essential difference between assessing whether the proposed drug is superior or noninferior to the main comparator is that the 95% confidence interval for superiority excludes the possibility that there is no difference between the therapies, whereas the 95%

confidence interval for noninferiority excludes the possibility that the proposed drug is inferior to a clinically important extent. Discuss any results to support a conclusion for noninferiority in the context of the similarity or otherwise of the mechanism of action(s) of the proposed drug and the main comparator in order to assess whether this conclusion is supported by a 'class effects' argument (see also Appendixes 2 and 5).

Figure B.2 provides a simplified illustration of how a statistical assessment of noninferiority relates to the more usual assessment of superiority. In each case, the interpretation of the point estimate and its 95% confidence interval is compared to the null hypothesis of the assessment. In the case of a superiority assessment, the null hypothesis is that there is no difference between the compared alternatives. In the case of a noninferiority assessment, the null hypothesis is that the difference between the compared alternatives is no worse than the minimal clinically important difference.

MCID = minimal clinically important difference
Key to trials:
Trial A = possibly superior
Trial B = superior
Trial C = possibly noninferior
Trial D = noninferior
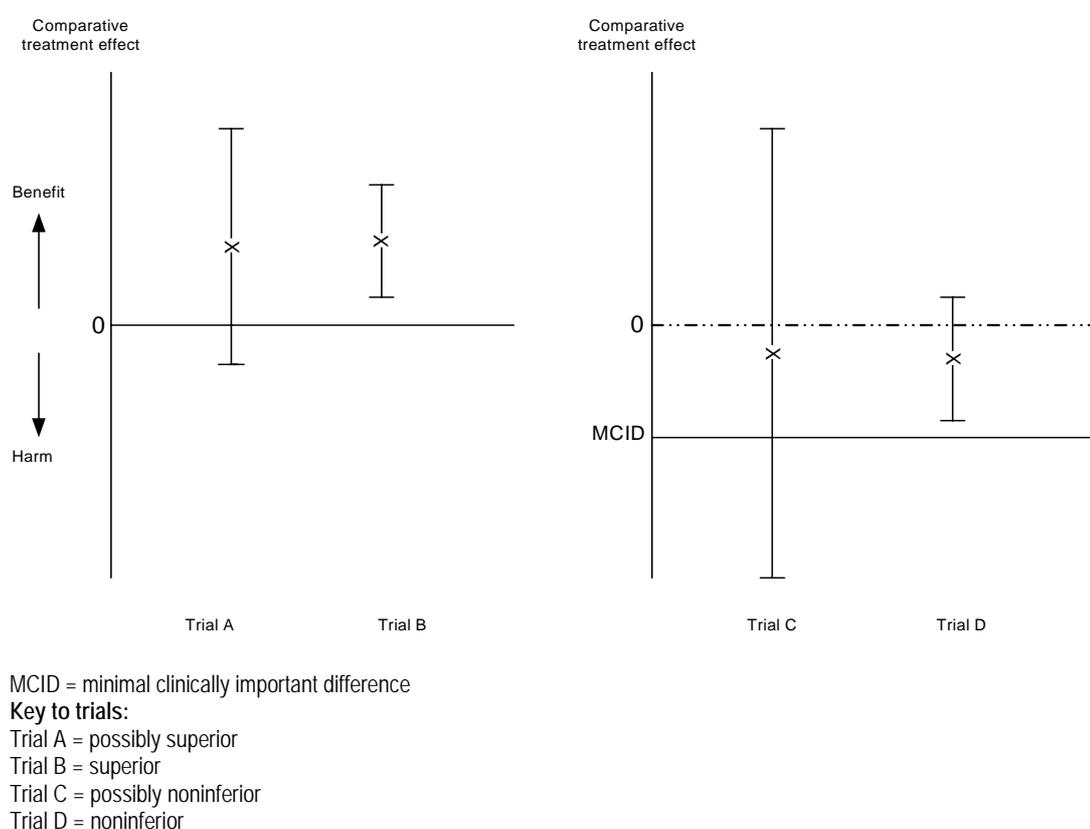
Figure B.2   Assessment of statistical significance of superiority and noninferiority

Categorising the proposed drug helps guide the selection of the more suitable options for the type of economic evaluation (see Subsection D.1). This includes the unusual circumstance of a submission for a proposed drug that is therapeutically inferior to its main comparator. It is theoretically possible to construct an economic evaluation if its overall cost of therapy is cheaper than that of its main comparator.

If the proposed drug is no worse than (or noninferior or equivalent to) the main comparator, there is no basis in terms of health outcomes to justify a higher price (unless there are cost offsets due to a different method of administering the proposed drug). A cost-minimisation analysis is therefore appropriate.

If the drug is superior to the main comparator, a cost-effectiveness analysis or cost-utility analysis is appropriate to determine whether the increase in health outcomes (and any cost offsets) justifies the increase in drug costs (and hence increased price) in terms of being acceptably cost-effective. If there are uncertainties and/or trade-offs across health outcomes (eg both increased effectiveness and reduced safety or differing safety profiles), a cost-consequence analysis is appropriate to present these results in a disaggregated way against the costs and, if it helps to reduce the uncertainty and/or quantify the trade-offs, a cost-utility analysis would also be appropriate.

Section C
Translating the clinical evaluation to the listing requested for inclusion in the economic evaluation

Introduction

The primary purpose of submission section C is to guide the presentation of analyses conducted to translate the systematic overview of the results of direct randomised trial evidence to the listing requested, and thus to the framework of the economic evaluation (submission section D). This is particularly important when one or more variables incorporated into the economic evaluation are derived from, but not directly based on, the clinical evaluation presented in submission section B. These variables may be derived using a number of analyses that modify the results of the clinical evaluation to help construct a modelled economic evaluation. Such analyses are referred to in these guidelines as 'premodelling studies'. Figure C.1 shows the steps set out in Section C to complete these studies.

The need for premodelling studies arises because the study protocols for the trials used for the clinical evaluation might differ from the proposed clinical practice setting for the main indication in one of the following ways.

- The participants and circumstances of use in the trial might not be the same as the intended population for treatment in Australia (and might therefore have a different profile of risks of future events and circumstances of use). In this case, the clinical evaluation would need to be **applied** from the baseline risk of the sample of trial participants and their circumstances of use to the expected absolute risks of future events of the intended Australian population and their circumstances of use. Examples of premodelling studies of applicability include subgroup analyses and surveys of the patterns of health care resource provision in Australia corresponding to one or more health states included in a modelled economic evaluation.

- The length of follow-up (time horizon) of participants in the trial might be less than the expected duration of therapy or expected duration of overall health and health care resource impacts. In this case, the clinical evaluation would need to be **extrapolated** to the intended duration of therapy or expected health and resource impacts. Examples of premodelling studies of extrapolation include extrapolating integrals of time-to-event analyses and a review of the literature for single-arm follow-up studies of the natural history of the condition to estimate rates of disease progression.

- The outcomes measured in the trial might not be the patient-relevant final outcomes of treatment. In this case, the clinical evaluation would need to be **transformed** to take account of the patient-relevant final outcomes (in terms of quality-adjusted life-years gained). Examples of premodelling studies of transformation include transforming comparative treatment effects measured on surrogate outcomes to final outcomes and scenario-based studies to value health outcomes using utilities.
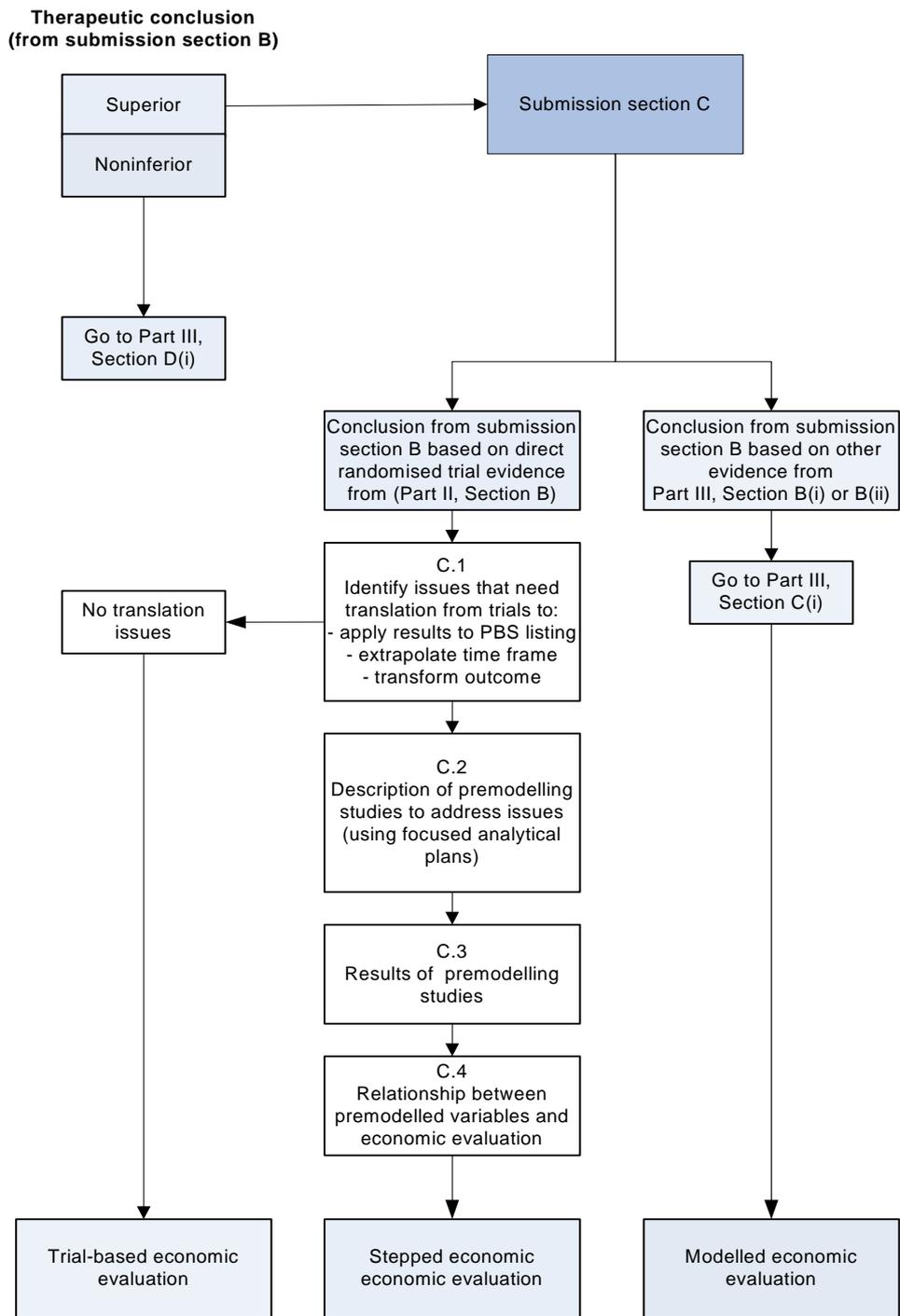
Figure C.1   Key information requests for submission section C of a major submission to PBAC

Thus, the results of the trials might need to be applied, extrapolated and transformed (collectively referred to in these guidelines as '*translated*') into a decision analysis appropriate for the intended clinical use of the proposed drug on the PBS in Australia, taking into account the above issues. These premodelling studies provide a clearer and more systematic basis to support the necessary variables for inclusion in the economic evaluation (see Section D). As indicated by the examples above, the types of premodelling studies relevant to this process of translation can vary widely.

These methods are described in Subsection C.2. The methods also help examine any impact of reintroducing sources of random error (the play of chance) and systematic error (bias), which were minimised in the systematic overview of the direct randomised trials presented in submission section B. Given that these sources of error cannot be minimised to the same extent for indirect comparisons of randomised trials and nonrandomised studies (see Part III, Sections B(i) and B(ii)), there is less basis to guide corresponding analyses in these circumstances. For submissions based on these types of studies, the information requests for submission section C are shown in Part III, Section C(i).

The results of premodelling studies are intended to inform:

- the underlying structure of the model and the selection of options for examination in an analysis of the structure of the model and the scenarios it is examining

- the selection of values for variables in the economic evaluation and ranges of plausible extremes to include in the associated sensitivity analyses.

Importantly, Section C requests a consistent format for the presentation of all premodelling studies. Each has the following components:

- a succinct question to address a particular issue (Subsection C.1)

- a focused analytical plan that is presented and justified (Subsection C.2)

- a set of results (Subsection C.3)

- an explanation of how these results contribute to the economic evaluation presented in submission section D (Subsection C.4).

C.1 Identification of issues to be addressed

Information requests

- **Define application issues**: Describe any ways in which the participants and circumstances of use in the trial differ from the proposed population for treatment (including the baseline risk of participants and circumstances of use).

- **Define extrapolation issues**: State whether there is a need to extrapolate the outcomes reported in the clinical evaluation beyond the trial or study horizon.

- **Define transformation issues**: State whether there is a need to transform the nature of the outcome measured in the clinical evaluation.

- **Define any other translation issues**: State whether there is any other need to translate from the clinical evaluation.

- Convert each defined translation issue into a succinct question that can be addressed in a premodelling study.

In many circumstances, the direct randomised trial evidence identified in submission section B can be used to directly support the listing requested; for example, in the context of a therapeutic conclusion that the proposed drug is no worse than the main comparator. However, in other circumstances, additional argument and associated analyses are needed to translate the evidence more rigorously to the listing requested.

The following guidance is intended to help a sponsor decide whether additional analyses are needed and to identify methodological options that might be considered. It is recognised that not all the necessary information will be available to inform every aspect of each circumstance and the resulting analyses. Methodological experts might also disagree over the most appropriate methodological option to pursue in particular circumstances. However, this detailed guidance is warranted because many submissions have had difficulties in this area.

Applicability issues

Define any issues that indicate a need to apply the trial data to the intended population and circumstances of use. Applicability issues might arise due to differences between participants enrolled in the trials and patients who would be likely to obtain the drug on the PBS, and between the circumstances of use in the trials and those that would occur on the PBS in Australia.

Some important patient factors that might affect outcomes are identified in Table B.4.2. There might also be important differences in the mix of patients who would receive the drug on the PBS. For example, it is a concern of PBAC that there might be patients in the community who have a disease that is less severe than that of participants in the randomised trials. There might also be patients in the community for whom the main comparator can be expected to perform better than in the trials. Both could diminish the difference in effectiveness between the proposed drug and the main comparator and, therefore, make the incremental cost-effectiveness ratio less favourable for the proposed drug.

Some factors relating to the circumstances of use are identified in Table B.4.3. These factors might also include extrapolating results of trials conducted in hospitals to use outside the hospital and the effect of more rigorous follow-up, which might swamp important differences in the convenience and acceptability of the drug compared with alternative treatments, with resulting effects on patient compliance and subsequent response to treatment.

The fact that one or more differences might be demonstrated does not necessarily raise an applicability issue, because the differences may not help to predict any variation in treatment response. However, the demonstration of such differences does identify areas that could be examined, such as in the following examples.

Population characteristics
- There might be evidence within the trials and/or other sources to indicate that patients vary in their expected risk of adverse major clinical outcomes. In such cases, which are common for many medical conditions, additional analysis of the comparative treatment effect detected in the trials, presented as a premodelling study, may indicate that this effect is best summarised as a constant relative reduction in the risk of these outcomes across the trial population of varying baseline (expected) risks.

If this is the case, such an analysis forms an acceptable basis to apply the trial data to specific subgroups. For example, this evidence would be sufficient to justify targeting a requested restriction to those patients with a greater expected absolute risk of future events at the point of deciding whether to start therapy with the proposed drug (ie a poorer prognosis) as being the patients likely to benefit most from the proposed drug. Any thresholds of greater expected absolute risk to identify the population that would be eligible to start the proposed drug according to the requested restriction (see Subsection A.2) would need to be justified and supplemented by sensitivity analyses on different thresholds. The absolute or incremental treatment effect would then be calculated by multiplying the expected absolute risks across the eligible population by the estimated overall relative treatment effect. As a check, present the results of the targeted subgroup that may be recruited in the randomised trials as the absolute risk difference, or explain why this is not possible.

- The comparative treatment effect detected in the trials might indicate that this effect is best summarised as a varying relative reduction in the risk of these outcomes across the trial population of varying baseline risks.

   In this case, which is less common than the previous example, the premodelling analysis would need to identify treatment effect variation when measured in relative terms (eg relative risk, hazard ratio, odds ratio). This analysis of the relative treatment effect would need to show sufficient heterogeneity within the set of direct randomised trials available to support statistically a claim regarding the nature (qualitative or quantitative) and extent of each treatment effect variation and thus any resulting subgroup analysis.

   Variations in the relative treatment effect might arise with varying characteristics of the patient, the intervention(s) or the medical condition. Together with a justification of any thresholds as necessary (supplemented by sensitivity analysis on different thresholds), this evidence contributes to an argument to target a requested restriction to these patients (see Subsection A.2) and to calculate the absolute treatment effect by applying the estimated relative treatment effect for the subgroup to the expected risk for the subgroup.

Circumstances of use

- One or more of the direct randomised trials might include dose regimens (dose and/or duration) and/or co-administered drugs that are not recommended by the TGA or that might otherwise have an impact on the direction and/or magnitude of the treatment effect.

- One or more of the direct randomised trials might have been conducted in settings that are not applicable to the requested listing on the PBS or with some trial participants who would not be eligible for the proposed drug according to the requested restriction.

There is no limit to the types of difference in populations and circumstances of use, but only a small number of these might modify the extent of treatment effect detected by the overall results of the trial or meta-analysis. Thus, the general rule is to apply the overall treatment effect from the intention-to-treat population, rather than to explore for possible variations in treatment effects in subgroups.

As discussed in Subsection C.2, an analysis to support a claim of treatment effect variation according to a particular patient characteristic or circumstance of use is more

convincing if it was prespecified with a biologically plausible rationale before the collection of any data in the trial(s) providing the source data for the analytical plan. Thus, for each analytical plan relying on direct randomised trial(s) and examining an applicability issue, state whether the data was collected before or after finalisation of the analytical plan (see below).

If an applicability issue involves introducing one or more diagnostic criteria or tests specifically to identify patients who are eligible according to the requested restriction that was not relied on in the trials, then separately present additional information on the validity (specificity, sensitivity, positive predictive value and negative predictive value), reliability and comparability of these criteria and tests, both across all trials presented and in regular Australian practice. This is necessary to examine the impact of false positive and false negative identification of eligible patients, as well as the impact of false positive and false negative identification of treatment response, on the application of the trial results. This is particularly the case if the latter are used in any proposed continuation criteria in the requested restriction. Subsections A.2 and D.5 provide further advice on specifying and costing these diagnostic criteria and tests in the diagnostic and treatment algorithm, and on the implications of misclassification for estimating incremental effectiveness and incremental cost-effectiveness.

If there is no applicability issue, state this.

Extrapolation issues

Define any issues that indicate a need to extrapolate the within-trial patterns of resource provision (cost) and within-trial health outcome results, including time-to-event data, beyond the time horizon of the direct randomised trials. Such extrapolation might be considered necessary in the context of a modelled economic evaluation, to determine comparative effectiveness and cost-effectiveness beyond the median duration of therapy and/or follow-up in the presented direct randomised trials.

If there is no need to extrapolate the evidence from the clinical evaluation, state this.

Transformation issues

Define any issues with outcomes that indicate a need to transform the nature of the outcome(s) measured in the direct randomised trials to those relied on in the economic evaluation. For example, the direct randomised trials might only report outcomes that are of less patient relevance than intended final outcomes of treatment. These less relevant outcomes are known as surrogate outcomes. Arguably, the closer a surrogate outcome is to the final outcome, the more useful it is, but generally the more difficult it is to measure accurately.

To transform the surrogate outcomes measured in the trials to final outcomes and to extend the range of outcomes (for instance, the number of patients with unhealed peptic ulcers who eventually need surgery), the trial results might need to be supplemented by estimates obtained from other sources (see Subsection C.2).

For most drugs the ultimate outcome of therapy is to improve quality of life and/or survival, and in theory all outcomes could be expressed as quality-adjusted life-years (QALYs) gained (see Appendix 6). In practice, few randomised trials have measured the

impact of drug therapy on QALYs, because few are large enough or long enough to measure changes in final outcomes directly. For instance, the ultimate aim of lowering moderately elevated blood pressure with a new antihypertensive medication is to reduce the risk of death and impaired quality of life from a stroke or possibly a myocardial infarction. The ultimate aim of treating a patient with severe asthma is to prevent death, to prevent hospitalisation and to return the patient to a normal level of functioning. The response measures used in many trials will usually be readily measured physiological variables (surrogate outcomes). For the two examples given above, this would be blood pressure and spirometry.

Another common need is to transform the outcome(s) measured in the clinical evaluation to value them in utility terms (see Appendix 6) for the economic evaluation. If this transformation supplements any other transformation (eg from surrogate outcomes measured in the direct randomised trials to patient-relevant outcomes), present the links between these two transformations and any assumptions involved in combining them.

Other transformations that have been considered include:

- converting outcomes reported as continuous data to dichotomous data
- converting outcomes reported as dichotomous data to time-to-event data to estimate periods of time in one or more health states, or periods of time free from being in one or more health states.

Although these transformations increase uncertainty, they can allow for a more readily interpretable health outcome (see Subsection C.2).

If there is no need to transform the outcomes measured in the direct randomised trials, state this.

Other translation issues

Define any other issues that required premodelling studies in order to justify an aspect of the economic evaluation (see Section D). Examples of other issues that may be included here are as follows.

- One or more of the direct randomised trials was less successful in minimising bias (eg inadequate concealment of randomisation, inadequate blinding of subjective outcomes, unable to reconstruct full ITT analysis).

- One or more of the direct randomised trials reported less patient-relevant outcomes or no patient-relevant outcomes.

- One or more of the direct randomised trials was of insufficient duration to detect the most patient-relevant outcomes.

- The patterns of resource provision measured in the direct randomised trials did not closely reflect those in Australia (and/or the likely changes in patterns of resource provision were not measured in the trials).

  Randomised trials performed overseas are an acceptable basis for an economic evaluation relevant to Australian practice. However, although the overall estimate of the change in a final or surrogate outcome might be transferable to Australia, estimates of the costs of resources provided (drugs or other interventions, such as investigations, procedures or operations) are often not readily transferable.

– It is usually apparent that the unit costs are quite different.

– Less apparent, but also important, is the fact that the frequency or patterns of resource provision might not be relevant to Australia because of major differences in medical practice or different incentives in different economies and health care systems.

Sometimes assumptions need to be made during the translation of overseas randomised trials to create a modelled economic evaluation that is relevant to the Australian context. This is particularly important when the main comparator is a nonpharmacological therapy.

- The trials did not measure provision of all types of health care relevant resources (which might change and therefore would need to be added in a model).

- The protocols of the trials required more resources to be provided than would be typical in normal management of the medical condition (such as extra blood tests to demonstrate safety or effectiveness). In this case, only resources provided or avoided in regular clinical practice need to be included in a model.

If there are no other issues that require premodelling, state this.

C.2   Focused analytical plan

Information request
- Present and justify a focused analytical plan (which specifies details of data, sources, methods and analyses) to address each translation issue identified.

For each translation issue identified in Subsection C.1, provide a focused analytical plan that clearly describes:

- the issue
- the specific question to be addressed by a premodelling study
- the data to be used and their sources
- the methods of the premodelling study (with sufficient details to enable independent verification of the analysis).

A range of methods that may inform the development of an analytical plan are shown below. Justify the choice of method where more than one option exists. Comment on any implications of this choice for the results of the premodelling study, including how the choice of the method will be assessed, for example in the sensitivity analyses of the economic evaluation.

Methods to address applicability issues

Addressing applicability issues might involve investigations of heterogeneity, treatment effect variation, subgroup analysis and/or meta-regression.

Heterogeneity analysis

Assess the statistical analyses of heterogeneity in the meta-analyses presented in Subsection B.6. For dichotomous outcomes, separately assess these analyses for the relative risk and the risk difference. The results of a Mantel–Haenszel fixed effect model could be presented in addition to the DerSimonian–Laird random effects model, to help examine the assessment of heterogeneity.

Discuss and explain any suggested heterogeneity of trial results. Reasons for heterogeneity might include differences in trial population or design. If there are strong biological or methodological grounds for heterogeneity, consider presenting a premodelling study to examine the impact of these grounds for heterogeneity by comparing relevant pooled analyses with the overall estimate. Unexplained heterogeneity, depending on its direction and magnitude, generally makes the summary estimator less meaningful.

Assessment of heterogeneity is an important aspect of interpreting meta-analyses where there are a large number of trials. Refer to biological, pharmacological and/or clinical reasoning as appropriate when justifying the inclusion of further analyses in premodelling studies to take into account heterogeneity when considering the application of the results of the trials.

Explain and justify the presentation of any additional meta-analyses in which trials listed in response to Subsection B.2 are excluded (eg on the grounds of inadequately minimising bias or of reporting less patient-relevant outcomes) and examine the impact each exclusion has on the overall meta-analysis. Similarly, explain and justify the presentation of any additional meta-analysis in which trial groups are excluded (eg on the grounds of additional arms in a dose-finding trial using a dose outside the TGA-recommended dose) and examine the impact each exclusion has on the overall meta-analysis.

Support any claimed treatment effect variation on the basis of observed heterogeneity with reference to the excluded trials and/or trial groups and the covariate that predicts the treatment effect variation, such as:

- dose-response considerations
- varying duration of use
- drug interactions
- settings of use
- patient baseline characteristics, including risk factors and disease severity.

If any heterogeneity is thought to be due to the trials having different periods of follow-up, presenting the pooled incidence rate differences might be useful.

Assessment of possible publication bias, where there are sufficient trials, might be assisted by presentation of a funnel plot.

Presenting and justifying a subgroup analysis or a meta-regression

In general, an estimate of treatment effect is interpretable with respect only to the **whole** population of a randomised trial (or whole population of randomised trials within a meta-analysis) rather than by testing within each individual subgroup. Subgroup analysis, to

determine whether a treatment effect varies across patient groups, should be interpreted with caution if it is not adequately prespecified. This would occur if, before any data was collected, the subgroups were not defined, treatment allocation was not stratified or an alpha-spending plan was not formally included in the trial design. Justify any decision to identify the treatment effect obtained from a patient subgroup as the basis for the estimate of treatment effect for a requested listing.

Information presented in support of any presentation of a subgroup analysis or meta-regression in Section C should include each of four elements:

- a discussion of the plausibility of a variation in treatment effect

- an indication of whether the hypothesis underpinning the analysis was developed before or after the trial data were collected

- a statistical analysis of the variation in treatment effect

- an account of the number of prespecified subgroup analyses conducted.

In isolation, no single element is convincing either in support of or against a subgroup analysis or meta-regression based on a claim of substituting the comparative treatment effect from this analysis for the estimate from the whole population in the trial or meta-analysis. Congruence of support across these elements (which are outlined in more detail below) strengthens the claim; conflicting conclusions across the elements weaken the claim. Each claim and its supporting information need to be judged on a case-by-case basis. A degree of judgment is often required, and this judgment can be influenced by other relevant factors.

These elements apply when subgroups consist of participants within randomised trials, a single randomised trial, or groups of randomised trials within a meta-analysis. Some of the underlying principles **cannot**, however, be used to translate a treatment effect from a first- to a second-line setting, although subgroup analyses might be constructed if separate subgroups of trial participants in both treatment arms are treated in either the first- or second-line setting. Similarly, as discussed in Subsection A.2 under continuation criteria in restrictions, the underlying principles might not readily apply to groups of patients who become identifiable after therapy has commenced (such as patients who achieve an early marker of response to therapy or who withdraw early from therapy). Such patients might appear to generate comparatively important impacts on an economic evaluation. However, these early effects also introduce a range of confounders (such as regression to the mean), which means that it is difficult to attribute the impacts to the substitution of the proposed drug for the main comparator.

Plausibility of treatment effect variation
- Discuss the pharmacological, biological and clinical plausibility of the claim for sufficient variation of comparative treatment effect to justify the use of results other than for the whole population. An unexplained variation is difficult to accept, but in many instances reliance on plausible explanations has subsequently proven to be misplaced.

Prespecification of treatment effect variation
- A conclusion of sufficient variation of treatment effect to justify the use of results other than for the whole population is strengthened if the subgroup analysis arises from an explicit hypothesis relating to the given subgroup included in the prespecified analytical plan of the trial protocol. This is related to the previous element, because it

is difficult to specify implausible subgroups before collecting and analysing randomised trial data, whereas it is relatively easy to develop a plausible explanation for an unpredicted variation observed in the relative treatment effect data. A subsequent trial can be conducted to test a subgroup hypothesis generated from an earlier trial. If this is relevant to the submission, respond with reference to the most recent trial. The first statistical finding of treatment effect variation is usually sufficient to generate a hypothesis; its confirmation in a prespecified analysis in a subsequent trial is more persuasive.

Statistical analysis of variation of the comparative treatment effect

An important distinction exists between absolute treatment effect variation (eg of the absolute risk difference or weighted mean difference) and relative treatment effect variation (eg of the relative risk, relative risk reduction, odds ratio or hazard ratio).[17] Absolute treatment effect variation is common and has been observed more frequently than relative treatment effect variation. In several disease states, treatment effect variation has been observed across varying expected risks at baseline (ie the predicted risks of events before treatment) for the absolute effects, but not for the relative effects. This supports a conclusion of constant relative risk and has formed an accepted basis for targeting therapy to patients likely to benefit most (ie those with the greatest absolute risk difference) on the grounds that they have the greatest predicted risks of events at the point of deciding whether to start therapy with the proposed drug. This is calculated by multiplying the predicted risks of events in the intended subgroup(s) of the population at this decision point by the relative risk estimated from the whole population of the randomised trial(s) to calculate the absolute risk difference in the subgroup(s) for whom therapy with the proposed drug might be targeted.

In any presentation of a subgroup analysis or meta-regression, present tests for variation of the absolute and relative treatment effects, where possible, using appropriate tests for interaction between the treatment effect and the subgroup populations. The test should support and quantify the association between the treatment effect and the covariate defining the subgroup. This covariate provides a threshold that defines the restricted population; if a continuous variable is used, perform a sensitivity analysis on the threshold value chosen to define the subgroup.

For a subgroup analysis using dichotomous data from a single randomised trial, the test for interaction should compare across the nominated subgroup and its complement of all other participants in each arm of the trial. Present the treatment effects (measured on the prespecified primary outcomes and any relevant secondary outcomes) as the relative risk and the risk difference, each with the chi-square test (presented as the *P*-value), using the *Q* statistic. Present the I^2 statistic with its 95% uncertainty interval. As discussed above, statistically significant variation of relative treatment effects is a more unusual finding; statistically significant variation of absolute treatment effects is more common and might simply reflect constant relative treatment effect with varying baseline (expected) risks across the trial population. Table C.2.1 shows a suggested format to present tests for interaction across subgroups on treatment effects from a single randomised trial.

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[17] Absolute treatment effect variation is also known as 'treatment effect variation on the additive scale', and relative treatment effect variation is also known as 'treatment effect variation on the multiplicative scale'.

Table C.2.1 Assessment of treatment effect variation across subgroups

Primary outcome	Proposed drug n with event/N, (%)	Main comparator n with event/N, (%)	Relative risk (95% CI)	Risk difference (95% CI)
Identified subgroup				
Complement of subgroup				
Meta-analysis of subgroups using random effects model	–	–		
Test for treatment effect variation	–	–	$P =$	$P =$
I^2 statistic with its 95% uncertainty interval	–	–		
Overall trial results as reported				
Each other outcome	Proposed drug n with event/N, (%)	Main comparator n with event/N, (%)	Relative risk (95% CI)	Risk difference (95% CI)
Identified subgroup				
Complement of subgroup				
Meta-analysis of subgroups using random effects model	–	–		
Test for treatment effect variation	–	–	$P =$	$P =$
I^2 statistic with its 95% uncertainty interval	–	–		
Overall trial results as reported				

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

To extend this to more than one randomised trial in a meta-analysis, adopt a similar approach. Pool the subgroups and then their complements across trials, each using a random effects model, and analyse the chi-square test (presented as the *P*-value), using the Cochran Q statistic across the pooled results. Present the I^2 statistic with its 95% uncertainty interval. Tables C.2.2 and C.2.3 show a suggested format to present tests for interaction across subgroups on a treatment effect from a pooled analysis of randomised trials. The presentation includes a forest plot showing the individual trials, followed by a pooled analysis for each of the two subgroups. In this case, the vertical line for the forest plot should run through the point estimate of the overall treatment effect (rather than the null), and some indication of the 95% confidence interval around this estimate of treatment effect should be highlighted (eg by shading). Finally, present a pooled analysis across the subgroups and compare this with the results for the overall population.

Where there are many analyses of outcomes for a subgroup, present a summary table as shown in Table C.2.4.

Table C.2.2 Assessment of relative treatment effect variation across subgroups

Primary outcome	Proposed drug n with event/N, (%)	Main comparator n with event/N, (%)	Forest plot here	Relative risk (95% CI)
Identified subgroup				
Trial 1				
etc				
Meta-analysis of subgroup using random effects model	–	–		
Complement of subgroup				
Trial 1				
etc				
Meta-analysis of subgroup using random effects model	–	–		
Meta-analysis of subgroups using random effects model	–	–		
Test for treatment effect variation	–	–	–	$P =$
I^2 statistic with its 95% uncertainty interval	–	–	–	
Meta-analysis of whole population using random effects model as reported	–	–		

Each other outcome	Proposed drug n with event/N, (%)	Main comparator n with event/N, (%)	Forest plot here	Relative risk (95% CI)
Identified subgroup				
Trial 1				
etc				
Meta-analysis of subgroup using random effects model	–	–		
Complement of subgroup				
Trial 1				
etc				
Meta-analysis of subgroup using random effects model	–	–		
Meta-analysis of subgroups using random effects model	–	–		
Test for treatment effect variation	–	–	–	$P =$
I^2 statistic with its 95% uncertainty interval	–	–	–	
Meta-analysis of whole population using random effects model as reported	–	–		

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

Table C.2.3 Assessment of absolute treatment effect variation across subgroups

Primary outcome	Proposed drug n with event/N, (%)	Main comparator n with event/N, (%)	Forest plot here	Risk difference (95% CI)
Identified subgroup				
Trial 1				
etc				
Meta-analysis of subgroup using random effects model	–	–		
Complement of subgroup				
Trial 1				
etc				
Meta-analysis of subgroup using random effects model	–	–		
Meta-analysis of subgroups using random effects model	–	–		
Test for treatment effect variation	–	–	–	$P =$
I^2 statistic with its 95% uncertainty interval	–	–	–	
Meta-analysis of whole population using random effects model as reported	–	–		
Each other outcome	**Proposed drug** n with event/N, (%)	**Main comparator** n with event/N, (%)	**Forest plot here**	**Risk difference (95% CI)**
Identified subgroup				
Trial 1				
etc				
Meta-analysis of subgroup using random effects model	–	–		
Complement of subgroup				
Trial 1				
etc				
Meta-analysis of subgroup using random effects model	–	–		
Meta-analysis of subgroups using random effects model	–	–		
Test for treatment effect variation	–	–	–	$P =$
I^2 statistic with its 95% uncertainty interval	–	–	–	
Meta-analysis of whole population using random effects model as reported	–	–		

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

Table C.2.4 Summary of assessment of treatment effect variation across subgroups

Primary outcome	Relative risk (95% CI)	Risk difference (95% CI)
Pooled results for identified subgroup using the random effects model		
Pooled results for complement of subgroup using the random effects model		
Meta-analysis of subgroups using random effects model		
Test for treatment effect variation	$P =$	$P =$
I^2 statistic with its 95% uncertainty interval		
Other outcomes	Relative risk (95% CI)	Risk difference (95% CI)
Pooled results for identified subgroup using the random effects model		
Pooled results for complement of subgroup using the random effects model		
Meta-analysis of subgroups using random effects model		
Test for treatment effect variation	$P =$	$P =$
I^2 statistic with its 95% uncertainty interval		

CI = confidence interval

As discussed above, a test for interaction is more likely to suggest a possible signal for variation across the absolute risk difference (ie on the additive scale). However, given that this is more likely to be explained by varying baseline (expected) risk across the subgroups, the results for the subgroup should generally not be used where the test for interaction for the relative risk (ie on the multiplicative scale) does not suggest treatment effect variation. In this circumstance, it is usually more reasonable to conclude an overall constant relative risk and therefore to apply the results of the trial(s) from the full (intention-to-treat) trial population to any subgroup identified by a greater expected risk. It is less common for the test for interaction to suggest a possible signal for variation across the relative risk (ie on the multiplicative scale). In this circumstance, it might be appropriate to apply the results from the subgroup analysis rather than the full (intention-to-treat) trial population. A strong basis is needed to justify substituting the results of a subgroup analysis for the full population because of the greater risk of random error (play of chance) due to smaller sample sizes in the subgroups and the impact of multiple analyses.

Indicate whether the results of the identified subgroup and its complement are qualitatively different from the primary analysis of the trial(s) and/or the corresponding secondary analysis for the full trial population (ie a different conclusion on treatment effect might be drawn), or whether they are quantitatively different (ie a similar conclusion on treatment effect might be drawn, but the magnitude of effect might be different).

Meta-regression refers to analyses in which the characteristics of the randomised trials or of participants in the randomised trials are used as explanatory variables (covariates) in a multivariate regression analysis with the relative effect size (or some measure of deviation from the summary measure of effect) as the dependent variable. Meta-regression has a potential advantage over the stratified analyses based on subgroups described above, in that it examines more than one covariate simultaneously to determine whether there is more than one potential explanation of treatment effect variation. The data can be analysed at the trial level (more commonly done, but potentially confounded),

or at the individual patient level (with the trial as a covariate). In meta-regression, the unit of observation is the trial or the subgroup. Where meta-regression is used, clearly describe the method.

If a regression-based approach is adopted, then to minimise over-fitting, enough data points are required to detect any underlying relationships between the covariate defining the subgroup and the treatment effect measured as the absolute risk difference and the relative risk. At the trial level, this approach is only useful where the number of trials is large. It cannot be sensibly attempted when small numbers of trials are being combined (eg at least five to ten trials are needed for each covariate examined).

Multiplicity of treatment effect variation analyses

Report the number of prespecified subgroup analyses conducted. If a subgroup analysis or a meta-regression is presented that was not prespecified, report the number of such subgroup analyses or meta-regressions conducted of the data in total. Report any adjustment for multiple comparisons.

Methods to address extrapolation issues

Extrapolating time-to-event data

There are several different methods that may be used and a range of assumptions that need to be tested in an extrapolation of survival or time-to-event data beyond the horizon of the trial. Justify the assumption (whether made directly or indirectly) in relation to the hazard ratio reflecting the comparative treatment effect beyond the time horizon of the trial(s). This should be consistent with the duration of therapy and should be biologically plausible with its expected impact on the medical condition being managed. Provide particularly strong justification to maintain a hazard ratio more favourable than one beyond the trial follow-up and duration of therapy.

Examine several alternative methods of extrapolation. Present the results of each method of extrapolation superimposed on the corresponding Kaplan–Meier curves from the randomised direct trials (see Subsection B.6). Present tests of goodness-of-fit as part of the justification of the choice of the preferred method of extrapolation of these curves and examine the sensitivity of any extrapolation that relies on observed data beyond the median duration of follow-up. Also apply these extrapolations to 95% confidence limits of each of these curves in order to appropriately reflect the uncertainty of the unextrapolated curves.

If the economic evaluation is based on an extrapolation of time-to-event data, also present the within-trial case (ie within the time horizon of the trial evidence) alongside the extrapolation, because this allows an at-a-glance assessment of the extent to which the incremental gains arise within the time horizon of the trial compared with the extrapolated time horizon. Similarly, if the proposed approach to extrapolating the time-to-event results does not result in a convergence of the two extrapolated curves, present an analysis that incorporates a linear triangulation from each of the observed curves at the point of median duration of follow-up to a single common maximum end point justified as being clinically plausible. Another method to converge these curves would be to project the curve representing the outcome with the main comparator beyond the median duration of follow-up of the trial, and apply a hazard ratio of one to estimate the projection of the curve representing the outcome with the proposed drug from this time

point. Particular justification would be needed to apply a hazard ratio representing a continued differential treatment effect beyond the median duration of the trial.

Use of data from nonrandomised studies to extrapolate beyond the evidence from randomised trials

Data from nonrandomised studies are sometimes useful in order to extrapolate beyond the results of direct randomised trials. This is because the trials might have been of insufficient size or duration to capture the full impact of therapy on the outcomes of the disease, or the typical resource provision measured in an overseas trial might need adjustment to reflect patterns of resource provision observed in Australia (this is particularly important for resource estimates where the main comparator is a nonpharmacological therapy). In contrast, the nonrandomised studies might involve longer follow-up for an active main comparator, or the natural history of the medical condition if the main comparator is no active intervention. Given that the data from nonrandomised studies are subject to bias, assumptions based on those data made during a modelling exercise should be cautious.

When presenting data from nonrandomised studies for extrapolation purposes in a modelled economic evaluation, demonstrate that a systematic approach has been taken to search for, locate and select the nonrandomised studies for presentation. The selection process should be presented and justified. Provide a report of each study in a technical document or attachment. The results of the nonrandomised study might contribute to finding and justifying a variable in the economic evaluation. This variable may vary from a single point estimate to a regression formula. The results of the nonrandomised study might also help identify risk factors that contribute to the expected risks of the comparator arm in a model.

When indicating which results are being extrapolated, explain how the extrapolations are achieved by the model for the streams of costs and outcomes for the proposed drug and the main comparator. In particular, if noncomparative data are used (eg from single-arm studies), it is necessary to make an assumption about how the other arm in the model would change. The usual practice, in the absence of empirical evidence to the contrary, is to assume that the comparator arm would change so that the relative risk between the two arms measured in the randomised trial(s) remains constant across the duration of therapy. Justify the use of this (or any other) assumption in the model presented in the submission.

Methods to address transformation issues

Use of surrogate outcomes to estimate final outcomes

The claim that an incremental treatment effect on a surrogate outcome measured with the proposed drug quantitatively predicts a subsequent incremental treatment effect on a final outcome is more persuasively shown if attention is given to the following issues.

- **Step 1** — Present a systematic review of the literature to examine whether epidemiological evidence and biological reasoning has established that there is a relationship between the surrogate outcome and the final outcome independent of any intervention. In a few instances, relationships have been established, or have been proposed, between surrogate outcomes and final outcomes. Examples include blood left ventricular ejection fraction and survival after myocardial infarction, or viral load and cure of viral hepatitis.

- **Step 2** — Present a systematic review of the literature to examine whether randomised trial evidence using other drugs has shown that there is a basis to conclude that a treatment effect on the surrogate outcome has satisfactorily predicted a treatment effect on the final outcome. (If there is evidence of this type for the proposed drug, this might help support a biological argument for the treatment.) Based on this evidence, quantify the relationship between these treatment effects with an assessment of the uncertainty of the relationship. Discuss the reproducibility of these findings (eg whether they have been consistently shown across more than one trial and for more than one alternative drug and mechanism of action).

- **Step 3** — Explain why this relationship between the treatment effects on these outcomes with these other drugs is likely to apply to the proposed drug. Refer in this explanation to the mechanism of action of the proposed drug compared with the mechanism(s) of action of the drugs contributing evidence to Step 2 (a so-called 'class effects' argument). At present, it is difficult to give categorical advice. Consider which outcomes are most appropriate and most feasible, given the data available. The clinical importance and patient relevance of the outcomes should be established and, where possible, supported with data.

Having addressed the three steps above in transforming a treatment effect on a surrogate outcome to a treatment effect on a final outcome, explain in response to Subsection D.4 how this is included in the economic evaluation, including by specifying and referencing the sources of the longer term natural history (eg longitudinal population studies) as well as the transformed treatment effects.

Valuing health outcomes

Where the final outcome of the proposed drug is a change in quality of life (with or without a change in the number of projected life-years gained), a separate utility analysis is appropriate to transform this change into a preference-based measure. Appendix 6 provides further guidance on the presentation of a premodelling study to elicit the utility valuations.

Other useful transformations of outcomes measured in direct randomised trials

Outcomes that are expressed as dichotomous outcomes measured on a per patient basis (eg proportion of participants in response to treatment or for whom blood pressure was 'controlled' following the stated period of time after randomisation at which these data were collected in the trial) are easier to interpret and to incorporate into an economic evaluation than a difference in means for a quality-of-life scale or a physiological variable. Further, converting these proportions, as appropriate, to estimate periods of time free of an event, time with an event or time in a health state allows for a more interpretable incremental cost-effectiveness ratio if there is no limit to the duration of drug therapy. Consider providing a technical document or an attachment to the submission to give the details of the methods of these transformations.

Methods to address other translation issues

Examination of exclusion of trials from the meta-analyses presented in Subsection B.6

Examination of the impact of removing trials from a meta-analysis can sometimes suggest explanations for translating the clinical evaluation. If one or more trials are to be excluded from a meta-analysis, identify the aspect(s) of each trial that justify the exclusion (see

Table C.2.5). Indicate whether each reason relates to an applicability, extrapolation or transformation issue (see above), or whether a translation issue arises because one or more of the direct randomised trials was less successful in minimising bias, or reported fewer or no patient-relevant outcomes. Present greater detail of each aspect (as a minimum, to the extent requested in the relevant text in Subsection B) or refer to the information provided in Table B.2.4.

If there is more than one type of reason for exclusion, arrange the trials for exclusion in Table C.2.5 by reason for exclusion. Present each relevant meta-analysis both with and without the trial(s) excluded. Discuss any implications of the exclusions for the interpretation of the results of the meta-analysis.

Table C.2.5 Reasons to exclude each direct randomised trial

Trial ID	Ground(s) for seeking exclusion	Details[a]
Trial 1		
Etc		

a Cross-reference each set of details to the source of information (specifying the trial report with page, table, figure number).

Adjustment of resource provision estimates

A survey of patterns of resource provision in Australia may be needed if resource provision in the direct randomised trials reflects patterns of resource use that are different from those used and likely to be replaced in Australia (eg if they reflect overseas health care systems or the requirements of the trial protocol) or were incompletely measured. This survey could be a cross-sectional study observing and recording patterns of resource provision in Australia. An alternative but less preferred option could be a survey of Australian expert opinion on the likely patterns of resource provision, either describing overall Australian practice or advising on modifying overseas patterns that are more relevant to Australia (see Appendix 4).

Justify the application of these cross-sectional data into a longitudinal model and consider any possible implicit assumptions. For example, if response to the proposed drug involves returning to a less severe health state, the associated patterns of resource provision might not necessarily reflect those of an earlier health state before the disease progression meant that the patient became eligible for the proposed drug. As an extreme example of this, applying patterns of resource provision for asymptomatic patients would obviously not be reasonable if those patterns ascertained for patients with watchful waiting at an early stage of an indolent disease were related to patients achieving full symptom control on analgesics at a terminal stage of the same disease.

If any patterns of resource provision from a trial are to be modified in a model (such as the exclusions of 'protocol-derived' resource provision), discuss the extent to which these resources might have affected the results of the trials in terms of health outcomes (eg high-intensity screening for deep vein thromboses in trials associated with lower rates of pulmonary embolism than in usual care). This might raise broader applicability issues in terms of changing the circumstances of use.

C.3   Results of premodelling studies

Results

Where possible and appropriate, present the results of each analysis for which a plan is presented in Subsection C.2 and estimate the comparative treatment effect as results separately for:

- the proposed drug

- its main comparator

- the increment with its 95% confidence interval.

Where a scenario-based valuation study has been used to transform the trial results or any other health state into utility valuations, present these as disaggregated results corresponding to each health state presented as a scenario (see Appendix 6). Also include an estimate of statistical uncertainty around each result.

Discuss the implications of each analysis on the conclusions from the results of the overall clinical evaluation in Subsections B.6 and B.8. Variations in the extent of comparative effectiveness are more likely than variations in the classification of the drug based on Table B.8.1.

Where a cross-sectional study or expert opinion survey has been used to estimate patterns of resource provision, report that provision where possible on a per patient basis and on a per period of time basis.

Clear presentation of premodelling studies is expected to increase PBAC's confidence in the economic evaluations that rely on those translations. At all times in premodelling studies, it is important to maximise the confidence of PBAC in the primary inference that substituting the proposed drug for the main comparator according to the PBS listing alone causes the differences in the subsequent streams of costs and outcomes. In practical terms, this means that if any stream of costs for a therapy is to be modified in a model, consideration should be given to any consequential impact on the corresponding stream of outcomes. Similarly, if any stream of outcomes for a therapy is to be modified in a model, consideration should be given to any impact on the corresponding stream of costs to ensure that the modification is plausible. Discuss these considerations whenever they are applicable to the results of a particular premodelling study.

Justify any results to be used in submission section D where more than one option exists. Comment on any uncertainties in this selection, including how they will be assessed in the sensitivity analyses of the economic evaluation. Also comment on any combinations

of the results of more than one analytical plan in constructing the economic evaluation and any uncertainties arising from those combinations, including how they will be assessed in the sensitivity analyses of the economic evaluation.

Original sources and electronic calculations

Separately provide copies of the original sources of all data (beyond those already presented with submission section B) and reports of studies commissioned for the submission in an attachment or technical document. Cross-reference the extraction of data from each source to the level of the page, table or figure number of the source document.

Also, to enable independent verification of each analysis, provide an electronic copy of any computer-based calculations of the analysis (see Part I, Subsection 6.2).

C.4 Relationship of each premodelling study to the economic evaluation

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Information requests

- Discuss the results of each premodelling study and explain how they will be used in the economic evaluation (submission section D).

- Provide a summary table of results from Subsection C.3 and their uses in responses to Section D.

Uses of premodelling study results

Each premodelling study has the objective of providing support for one or more inputs in the economic evaluation. There may be more than one premodelling study to support more than one translation step between the overall clinical evaluation and the economic evaluation. When this occurs, the combination of premodelling studies may compound the effect of uncertainty. This may need examination in the sensitivity analysis in Subsection D.6.

Section D provides more guidance on how to present the impacts on the economic evaluation of more than one translation step.

Summary table

Table C.4.1 provides a suggested format to summarise the main results of each premodelling study presented in submission section C and their use in the economic evaluation presented in submission section D, including in the sensitivity analyses presented in Subsection D.6. This will facilitate cross-referencing across the responses to information requests in the two sections and thus the transparency of the presentation of this information.

Table C.4.1 Summary of results of premodelling studies and their uses in the economic evaluation

Premodelling study	Results	Use in Section D	Cross-reference	Use in Subsection D.7	Cross-reference
Applicability premodelling studies					
Study 1					
Etc					
Extrapolation premodelling studies					
Study 2					
Etc					
Transformation premodelling studies					
Study 3					
Etc					
Other translation premodelling studies					
Study 4					
Etc					

Section D
Economic evaluation for the main indication

Introduction

The purpose of submission section D is to present an economic evaluation of substituting the proposed drug for the main comparator in the context of the listing requested. Requests are made for a full and transparent description of the economic evaluation, as well as the presentation of sensitivity analyses to demonstrate the robustness of the economic valuation.

As already described in Subsection B.8 and shown in Figure D.1, the economic evaluation of the proposed drug initially depends on whether the therapeutic conclusion shows:

- the proposed drug is therapeutically superior to the main comparator, or
- the proposed drug is noninferior (equivalent) to the main comparator.

This Section D provides information requests for submissions for which there is a therapeutic conclusion of superiority (see Subsection B.8). Information requests for economic evaluations based on a therapeutic conclusion of noninferiority are provided in Part III, Section D(i).

Furthermore, the approach described in this section mainly refers to submissions where the economic evaluation is based on results from direct randomised trial comparisons (see Section B), with premodelling if required (see Section C). Thus, it is intended to maximise PBAC's confidence in an economic evaluation based on this most preferred means of detecting and estimating incremental treatment effects on health outcomes, resource use and cost effects relevant to the requested listing.

For economic evaluations that rely on incremental treatment effects based on results from either indirect comparisons (see Part III, Section B(i)) or comparisons based on nonrandomised studies (see Part III, Section B(ii)), consider adapting the stepped approach described here to enhance the transparency of the economic evaluation (see also Part III, Section C(i)).
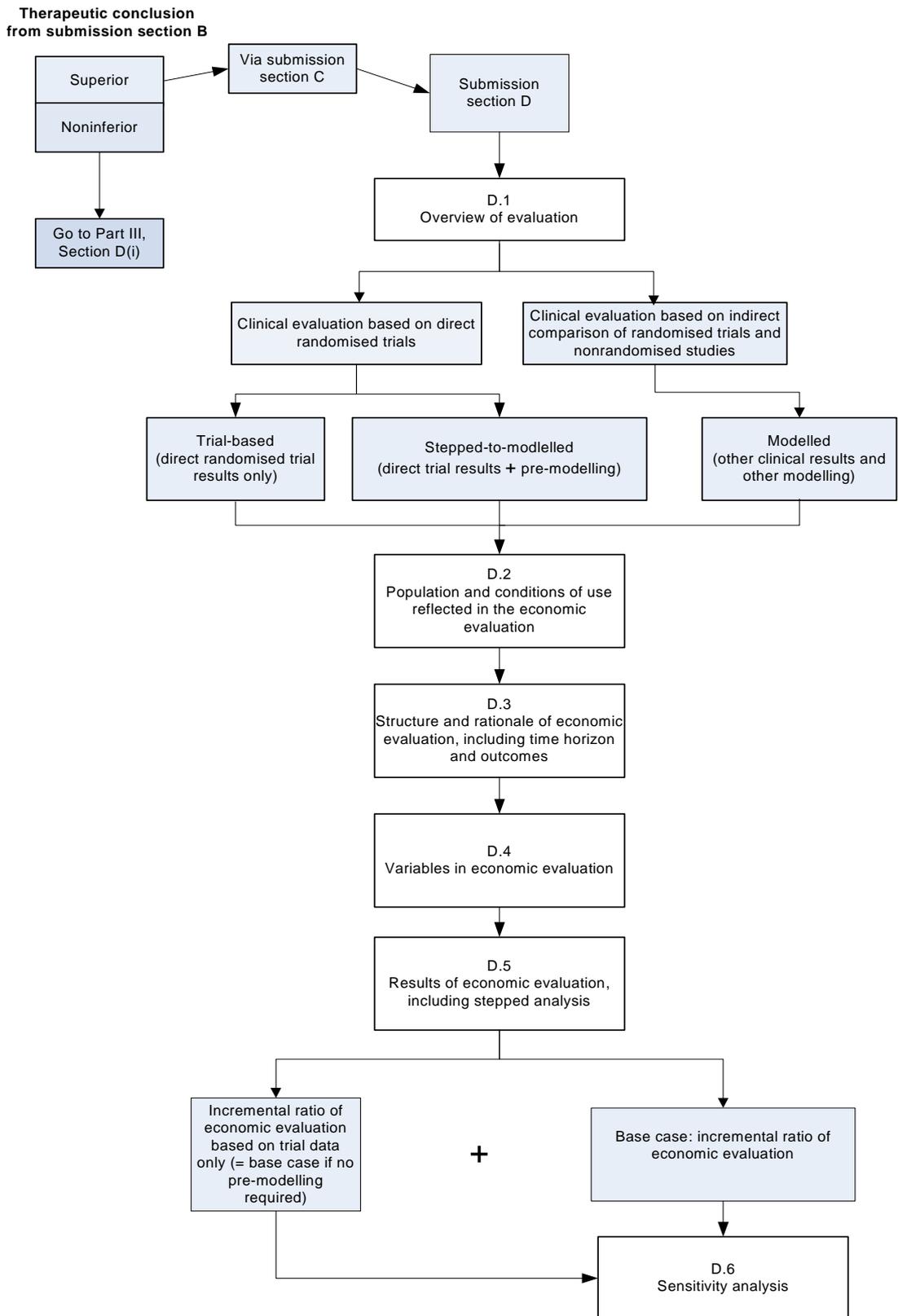
Figure D.1   Key information requests for submission section D of a major submission to PBAC

D.1   Overview of the economic evaluation

Information requests

- State whether the base case of the economic evaluation is generated by:
    - a trial-based economic evaluation (ie based on direct randomised trials)
    - a stepped economic evaluation (ie derived from direct randomised trials using variables reported in submission section C)
    - a modelled economic evaluation based on an indirect comparison of randomised trials or nonrandomised studies.
- State which type or types of economic evaluation are presented.
- Provide copies of all the original sources of all data or opinion used, and cross-reference the extracted data to the source documents.

Generation of the base case economic evaluation

The three steps described below show the preferred approach to an economic evaluation based on a therapeutic conclusion of superiority derived from direct randomised trials.

In keeping with the primary intent of submission section C to translate transparently the results of the direct randomised trials as presented in submission section B, additional steps to enhance transparency are requested for economic evaluations using evidence from such trials. The additional steps involve demonstrating the impact on the economic evaluation of the stepwise adoption of the approaches presented in submission section C and translating them into incremental resource use, costs and outcomes for the population for which listing is sought, and the circumstances of use reflecting likely subsidised usage on the PBS. The identification of issues in submission section C will identify whether any step is not necessary for a particular submission.

Step 1: Trial-based economic evaluation

The first step involves an economic evaluation based on the unmodified trial-based estimate of treatment effect on incremental provision of health care resources and incremental health outcomes (ie using the most internally valid evidence from the direct randomised trials presented in submission section B). If the direct randomised trial(s) recruited patients directly representative of those for whom listing is sought, trialled the proposed drug in the circumstances of use expected to apply to the requested PBS listing, and directly measured and reported patient-relevant end points over an appropriate time horizon (ie if no premodelling studies are reported in submission section C), the trial-based evaluation is sufficient to provide the base case of the economic evaluation and steps 2 and 3 are not required.

Step 2: Applying treatment effects on health care resource use to proposed PBS use

Frequently, the results of the direct randomised trials provide insufficient information on which to base a judgment about the full clinical and economic performance of the proposed drug compared with its main comparator. In these instances, use a modelled economic evaluation to inform PBAC using the results of premodelling studies presented in submission section C.

The first stage of the economic modelling is to examine the impact of applying the treatment effects on health care resources and health outcomes to the intended PBS population and the circumstances of use identified by the requested restriction (as presented in submission section C).

Step 3: Extrapolating and transforming health care resource use and health outcomes to proposed PBS use

The final stage is to examine the additional impact on the modified economic evaluation from step 2 of extrapolating the health care resource use and health outcomes to the time horizon of the economic evaluation and/or any transformation to final outcomes (also presented in submission section C). This generates the stepped base case of the economic evaluation for submissions that present premodelling studies in submission section C.

Justify any proposal to reverse the order of steps 2 and 3 (ie to extrapolate and/or transform the treatment effect before applying it). In this case, the final step would still generate the base case of the economic evaluation.

Wherever relevant to information presented in response to requests in this Section D, cross-reference to analyses summarised in Subsection C.4 to address the above issues.

Type of economic evaluation

Table B.8.1 in Section B is a guide to determining the appropriate type of economic evaluation to match the therapeutic conclusion for the proposed drug over its main comparator and hence the category assigned to the proposed drug in response to Subsection B.8.

If the proposed drug has been shown to be noninferior (equivalent) to the main comparator, cost-minimisation analysis is appropriate (or cost analysis under limited circumstances where the proposed drug is noninferior to the main comparator, but has a superior safety profile that generates cost offsets from reduced use of health care resources to manage adverse reactions). Part III, Section D(i) provides the information requests associated with these evaluations.

If the proposed drug has been shown to be therapeutically superior to the main comparator, there are four types of economic evaluation that may apply, depending on the outcome of the clinical evidence (see Subsection B.8):

- *Cost-utility analysis (generally preferred)*
  A cost-utility analysis presents the health outcome in terms of the life-years gained from the start of the analysis, with each life-year adjusted by a utility weight that is society's preferences for the health outcome experiences in that life-year relative to full health. The ultimate benefit of restored health is the restoration of health-related quality of life, for example restoration of opportunities to undertake activities of daily living. Economists have attempted to identify the value placed by individuals on different health states. The basis for this valuation is that each increment in health-related quality of life gives satisfaction (measured as the strength of preference for the restored health over the pretreatment state of health and termed 'utility' by economists), which is the ultimate outcome of life. The denominator in a cost-utility analysis is most commonly the incremental QALY gained, which is the difference between the two profiles following the use of the proposed drug or its main

comparator, each calculated as the times spent in successive varying health states, with each period of time weighted by the strength of preference for, or the utility weight of, its respective health state (see Appendix 6 for further guidance on valuing health outcomes in utility terms).

- *Cost-effectiveness analysis*
  A cost-effectiveness analysis measures the incremental cost per extra unit of health outcome achieved. That is, it differs from a cost-utility analysis in that the health outcome is reported in its natural units. If the proposed drug is demonstrated to offer more of a given health outcome than its main comparator (eg it achieves the desired health outcome in a higher proportion of patients), this goes beyond cost-minimisation. The outcomes reported from the clinical evaluation might need to be transformed in a modelled cost-effectiveness analysis; where this is done, the choice of outcome should be justified.

- *Cost-benefit analysis (supplementary option)*
  A cost-benefit analysis expresses all outcomes (health and nonhealth) valued in monetary rather than natural or utility units. This is in contrast to other forms of economic evaluation and requires a monetary valuation of these outcomes (see Section A7.2 of Appendix 7). Cost-benefit analysis can also include both health and nonhealth outcomes.

- *Cost-consequences analysis (if disaggregation of outcomes would be helpful)*
  A cost-consequences analysis compares the incremental costs of the proposed drug over its main comparator with an array of outcomes measured in their natural units rather than a single representative outcome as presented in a cost-effectiveness analysis. It can be presented if the proposed drug is demonstrated to have a different profile of effects that are not adequately captured by a single outcome measure; there might be trade-offs between the two drugs in terms of the directions of the changes in effectiveness and safety (and within effectiveness and safety). As such, it is a form of disaggregated analysis of changes in patterns of health care resource provision and changes in health outcomes and can be presented before presenting other types of aggregated economic evaluation, such as a cost-utility analysis (see footnotes to Table B.8.1 and general guidance, below).

The common output of these evaluations is a comparison of changes in outcomes and changes in costs of achieving those outcomes across the proposed drug and the main comparator, with the objective usually being to justify a price advantage for the proposed drug over its main comparator. A statistically significant improvement in effectiveness alone is not necessarily sufficient to support a conclusion of acceptable cost-effectiveness. Consideration is also given to whether the detected differences are clinically important overall and whether the extent of improvement is sufficient to justify any requested price advantage (after accounting for any justified cost offsets).

General guidance on preferred and supplementary types of economic evaluation

As indicated in Table B.8.1, the various types of economic evaluation are not necessarily mutually exclusive and it might be appropriate to present more than one type (eg both cost-effectiveness and cost-utility analyses). Depending on the circumstances, there might be a trade-off between the most appealing approach from a theoretical point of view and the degree of uncertainty in the estimate of incremental cost-effectiveness. For example, estimating the incremental cost-effectiveness based directly on the outcome from a trial might be relatively robust. However, in moving to a cost-utility analysis (which is

theoretically easier to interpret and compare across submissions and medical conditions, but for which assumptions of utility weights for various health states might be required), additional sources of uncertainty might be introduced. The three steps described above to enhance transparency for economic evaluations are designed to help make these trade-offs and their implications explicit.

Given these considerations, a cost-utility analysis is the preferred form of economic evaluation for either or both of the following situations:

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

- where relevant direct randomised trials report results using a MAUI.

However, for the reasons given above, the preference for a full cost-utility analysis is less clear in other situations, even where there is a claim of quality-of-life or disability improvements, or where there are differential quality-of-life impacts arising from the therapies being compared in a submission in order to derive a common outcome across submissions. Therefore, in the situation of an improvement in quality of life but not in quantity of life, a submission should present a cost-utility analysis or justify the decision to not transform the quantified health outcomes via a utility valuation.

Cost-benefit analysis is not preferred because it is not likely to be helpful to most PBAC deliberations (further reasons are given in Appendix 7). Thus, although monetary valuation of health outcomes is allowed, it is considered to be supplementary to utility valuation presented in a cost-utility analysis. If a cost-benefit analysis is presented in the absence of a cost-utility analysis, PBAC might not consider it to have the same weight.

Similarly, the base case economic evaluation should be focused on material incremental changes in the provision of health care resources and on material incremental changes in health outcomes. Supplementary analyses can be used to present any material incremental changes in the provision of nonhealth care resources and/or in nonhealth outcomes (see Appendix 8 for rationale).

Sources of information

Separately provide copies of the original sources of all data (beyond those already presented in submission sections B and C) or expert opinion used in the model in an attachment or technical document. Cross-reference the extraction of data from each source to the level of the page, table or figure number of the source document.

D.2   Population and circumstances of use reflected in the economic evaluation

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Information requests

- Describe and justify the demographic and patient characteristics of the population included in the economic evaluation.

- Describe and justify the circumstances in which the proposed drug and main comparator are used in the economic evaluation.

- Assess the consistency of the demographic and patient characteristics and of the specified circumstances of use across the study populations, the population in the economic evaluation and the population for whom listing is sought.

Demographic and patient characteristics

Use summary statistics (where appropriate) to describe the demographic and clinical characteristics for the population entering the economic evaluation. Include information about the distribution around means where appropriate.

Examples of patient characteristics are provided in Subsection A.2.

When justifying the definition of each characteristic of the population in the economic evaluation in relation to the population for whom listing is sought, use cross-references, as appropriate, to Subsections A.2 and A.5. Also highlight any difference in relation to the study populations for whom evidence of effectiveness and safety are presented (using cross-references, as appropriate, to Subsection B.4, and to Subsection C.4 if premodelling studies are presented to apply these results).

Circumstances of use

When describing and justifying the definition of each circumstance of use assumed in the economic evaluation in relation to the medical condition under which listing is sought, use cross-references, as appropriate, to Subsections A.2 and A.5. Also highlight any difference in relation to each circumstance for which evidence of effectiveness and safety is presented from the studies (using cross-references, as appropriate, to Subsection B.4, and to Subsection C.4 if premodelling studies are presented to apply these results).

Examples of types of circumstance are provided in Subsection A.2.

Consistency across characteristics

Assess the degree of consistency of the demographic and patient characteristics and of the specified circumstances of use across:

- the *study populations and circumstances of use* described in Subsection B.4 (and in Subsection C.4 if premodelling studies are presented to apply the results of these trials)

- the population included in the economic evaluation (ie the *target population and circumstances of use*), which should reflect the clinical management algorithms presented in Subsection A.5)

- the population for whom government subsidy of the drug is being examined (ie the *wider population and circumstances*).

The population for whom subsidy is being examined might be less well defined than the other two groups, but its inclusion captures the potential for use of the drug in a broader population and/or broader circumstances than the target population and circumstances, should PBS subsidy of the drug be implemented. It might also be used to capture any limitations of the economic evaluation in truly replicating the target population and circumstances. The importance of examining the incremental cost-effectiveness of the proposed drug in this population increases with increasing risk of substantial use of the proposed drug beyond the intention of the requested restriction (see also Subsection D.6).

The suggested format of Table D.2.1 helps summarise those characteristics and circumstances for which sensitivity analysis shows that the variable is important.

Table D.2.1 Comparison of characteristics of trial and requested populations and circumstances of use

Population and circumstance[a]	As defined in trial(s) using ITT population	As defined by the requested restriction	If use beyond the requested restriction might arise
Medical condition of the population			
Age of the population			
Restriction criteria (including any severity or preconditions or prior therapies, or continuation rules)			
Limitations on dose, frequency or duration of use of proposed drug			
Repeat for each other variable that varies across these populations and circumstances and for which sensitivity analysis shows the variable is important			

ITT = intention to treat
a For each identified population characteristic and circumstance of use, provide a footnote explaining any differences between these populations and relating this to any premodelling study presented in Subsection C.2 to apply the evidence from the overview of the trial(s) to the requested restriction.

D.3   Structure and rationale of the economic evaluation

Information requests

- Conduct a review of relevant economic literature and present the results.

- Specify any software used to conduct the economic evaluation.

- Ensure that all variables in the electronic copy of the economic evaluation can be changed independently during the evaluation, including allowing the base case of the economic evaluation to be completely respecified and allowing a new set of sensitivity analyses to be conducted with each respecified base case.

- Describe the structure of the economic evaluation.

- Justify the appropriateness of the structure in reflecting the context of use of the compared alternatives and the outcomes of their use.

- Define and justify the time horizon and nature of the outcomes used in the economic evaluation.

- Describe the methods used to calculate the results of the economic evaluation (eg cohort expected value analysis, Monte Carlo simulation).

- Provide copies of identified papers in an appropriately labelled attachment separate from the main body of the submission.

By definition, the economic evaluation is intended to inform a decision. Therefore, the structure of the evaluation allows the comparison of the streams of outcomes and resources following the use of either the proposed drug or its main comparator in order to calculate incremental outcomes and costs of these streams. PBAC has a preference for a decision-analytical framework that clarifies the comparison of these streams of outcomes and resources.

Literature review

Present the results of a search of the literature for reports of economic evaluations of similar decision analyses (in terms of similarity to the treatment algorithm and/or the proposed and similar drugs). Where the submission's model is different from the literature-sourced models, explain the basis for the selection of the submission's approach.

Software package

Specify the name and version of any software package used to conduct the economic evaluation. Software packages that support decision analyses and can be readily evaluated by the Pharmaceutical Evaluation Section currently consist of:

- TreeAge Pro Suite®

- Excel 2003®, including @RISK®, but not necessarily including all advanced features and plug-ins (eg Crystal Ball® and customised macros developed using Visual Basic).

Economic evaluations constructed using any of these may be submitted without earlier arrangement with the Pharmaceutical Evaluation Section (see page iv and Part I, Subsection 6.2).

Fully accessible electronic copy of the economic evaluation

Ensure that all variables in the electronic copy of the economic evaluation can be changed independently, including allowing the base case of the economic evaluation to be completely respecified and allowing a new set of sensitivity analyses to be conducted with each respecified base case.

Structure of the economic evaluation

The description of the economic evaluation should include:

- a statement defining in detail the therapy options for which costs and outcomes are estimated in the economic evaluation

- a description of each of the types of event and health states possible in the economic evaluation, together with a justification of the selection of each health state for inclusion in the evaluation and a justification for those that were considered potentially suitable but that were excluded to avoid excessive complexity

- a description of the relationships and interactions between the various events and health states possible in the economic evaluation (including, where relevant for a state transition model, a detailed description of all possible transitions between the health states; see below)

- a description of all assumptions made in the construction of the economic evaluation

- a decision tree diagram summarising the structure of the economic evaluation.

Justification of the structure

Justify the overall structure of the economic evaluation in relation to the pre- and postlisting clinical management algorithms (and the requested restriction, as appropriate) presented in submission section A and the treatment algorithms represented in the studies presented (using cross-references, as appropriate, to submission sections B and C). When justifying the overall structure of the economic evaluation in relation to the pre- and postlisting clinical management algorithms, discuss the consistency across:

- the alternative therapy options examined in the economic evaluation and those considered appropriate in response to Subsection A.5

- the clinical management algorithms assumed in the structure of the economic evaluation before and after the implementation of the requested listing and the algorithms presented in response to Subsection A.5

- the clinical management algorithms assumed in the structure of the economic evaluation and the clinical management algorithms for which clinical evidence is presented in submission sections B and C.

Identify and consider implicit assumptions built into the structure of the economic evaluation and comment as appropriate.

Time horizon and outcomes used in the evaluation

Time horizon

Define and justify the time horizon over which the costs and outcomes of the proposed drug and its main comparator are estimated in the economic evaluation. The appropriate time horizon for follow-up relates to the natural history of the medical condition, the treatment patterns, and an estimation of the time period(s) over which outcomes from the two therapies would be expected to occur. For example, a relatively short time horizon could apply when treating an acute event (eg 15–20 days for an antibiotic to treat a urinary tract infection), whereas a longer time horizon would be required for a chronic illness (eg several years for peptic ulcer disease or full life expectancy for the management of cancer or of risk factors of adverse major health outcomes).

Outcomes

Indicate whether the outcomes generated by the economic evaluation represent the final outcomes of treatment. Where the economic modelling structure is used (rather than a separate premodelling study; see Section C) to transform a quantified treatment effect measured on a surrogate outcome in the trials to predict a subsequent quantified treatment effect on the intended final outcome, explain and justify the method of this transformation, including a justification for how the relationship might vary over time. Use a premodelling study to show that a systematic approach has been taken to select and justify the modelling approach taken to estimate the final outcome(s).

Methods used to generate the results

Describe the methods used to calculate the results of the economic evaluation (eg directly trial-based, cohort expected value analysis, Monte Carlo simulation).

If the economic evaluation is directly based on individual patient data on costs and outcomes from a relevant, direct randomised trial, indicate whether a probabilistic sensitivity analysis has also been conducted. If so, indicate whether it has been calculated parametrically (eg Fiellers method) or nonparametrically (eg bootstrapping) and justify the choice of method.

Where quantified estimates of outcomes are generated over time, explain the underlying assumptions and rationale. For instance, the number of relapses of peptic ulcer is unlikely to remain constant over successive time periods. In other medical conditions, assuming a linear relationship between outcomes and time might be clinically plausible. Identify and consider inferential assumptions built into the structure of the economic evaluation and comment as appropriate. Show that a systematic approach has been taken to select and justify the assumptions made to quantify the outcomes over time, for example, by reference to the literature search for similar economic evaluations and/or using a premodelling study to present the search for studies of the natural history of the condition.

State transition models

For models involving more than one time period (eg state transition models), present the transition diagram (or matrix). This complements the decision tree diagram by identifying the health states possible in the economic evaluation, indicating the presence and direction of transitional paths between health states, and defining the type of each health state as appropriate (eg temporary, absorbing).

Describe the model mechanics: define and justify the cycle length and the follow-up time and comment as necessary. Define and justify the time points at which events are assumed to occur and the duration of time spent in health states. For a Markov model, specify whether a half-cycle correction has been included or justify its exclusion.

Clearly link each patient-relevant outcome and resource item in the model to its relevant health state(s).

Comment as appropriate on the impact of implicit assumptions inherent in the method chosen. For example, for an economic evaluation that includes Markov components, it is relevant to check the following assumptions:

- Is the 'memorylessness' assumption of the model valid in this case (ie is it correct to assume no memory for previous states, such that transition probabilities are independent of previous states)?

- Are there (non) constant transition probabilities? If the transition probabilities are constant or homogenous across cycles in the model, they are assumed to be independent of time and thus independent of time-related probabilities, such as ageing of the population and variation in competing risks of the population over time. Allowing for ageing and variation in competing risks of the population over time requires transition probabilities that can vary (are nonhomogenous) across time (number of cycles) in the model.

Describe how the model is calculated (eg hypothetical cohort or Monte Carlo simulation). If a Monte Carlo simulation is used, then also:

- specify the number of iterations used per simulation and justify this selection in terms of whether it samples the distribution(s) adequately

- specify the number of simulations per analysis and justify this selection

- indicate whether second-order (or parameter) uncertainty has been simulated and hence whether probabilistic sensitivity analysis is enabled.

Sources of information

Copies of papers identified from the literature review are a useful resource for assumptions relating to the structure and variables in the economic evaluation. Provide copies of all identified papers used in the evaluation in an appropriately labelled attachment separate from the main body of the submission.

D.4   Variables in the economic evaluation

Information requests

- Present, as a minimum, the following information for each variable used in the economic evaluation:
  - name (and definition, as necessary)
  - quantity in natural units (as appropriate; for example, this is not applicable for unit costs)
  - source.
- Identify and list the direct health care resource items for which there would be a change in use associated with substituting the proposed drug for the main comparator and define each in terms of natural units.
- Estimate the present value of direct health care resource costs and health outcomes.
- Discuss the implications for the economic evaluation of any important deficiencies in the available evidence base.
- Summarise this information in a table for each type of variable and provide further details of calculations, as necessary.

Variables used in the evaluation

Variables used in the economic evaluation may include:

- health care resource items provided (unit costs should be presented and sourced, quantities should be provided as appropriate)
- outcomes (presented in such a way as to allow the three steps to enhance transparency to be distinguished)
- probabilities within each branch of a decision analysis (including transition probabilities or rates in a state transition decision analysis)
- the discount rate applied to costs and outcomes (discount costs and outcomes incurred beyond the first year at a rate of 5% per year).

The names and definitions of variables should be sufficiently precise to permit verification and replication of the economic evaluation. For example, an Australian Redefined Diagnosis Related Group (AR-DRG) item number is more precise than an episode of hospitalisation. For each source, provide full citation details, including item number or page number as appropriate. It might be necessary to cite more than one source for some variables (eg the quantity and unit cost of a resource item).

Each economic evaluation should consider explicitly all material differential effects between the proposed drug and its main comparator (ie all advantages and disadvantages are to be included in the analysis). To help demonstrate this, Subsection D.5 requests the presentation of the results of the economic evaluation first in disaggregated form (ie as an array of all material costs and consequences; see the definition of a cost-consequences analysis in Subsection D.1).

For the results of trials and premodelling studies conducted to provide variables for the economic evaluation, cross-refer to the responses to Subsections B.6 and C.4 as appropriate.

Justify and assess the impact of any change in the source of information for a variable used in the evaluation from that given or recommended elsewhere (eg if using data or opinion that differs from the evidence on incremental treatment effects provided in response to Subsections B.6 or C.4, or if the proposed unit cost of a resource item is different from that recommended by the *Manual of Resource Items and their Associated Costs* (see Part I, Section 2.1.3). For some variables where there is no recommended source and there are several different options available (eg rates of progression of a chronic medical condition), it might be important to show that a systematic approach has been taken to select and justify the option used in the economic evaluation, for example using a premodelling study. The judgment of this importance should be influenced by the sensitivity of the results of the economic evaluation to substituting the different options for the selected option.

Discuss the implications for the economic evaluation of any important deficiencies in the available evidence base. For example, some variables might be estimated imprecisely, or evidence might have been gathered in different populations and circumstances of use or in other health care systems (which is arguably more important for costs). In such cases, explain the limitations of the data and provide details of any attempts to overcome those limitations. Assess the implications using sensitivity analyses (see also Subsection D.6).

Adverse reactions

Including information on adverse reactions in an economic evaluation can be difficult. Adverse reactions have two main impacts on an economic evaluation — they affect the health outcomes of drug treatment and they contribute to the total cost of therapy. Avoidance of an adverse reaction typically associated with the use of the main comparator may be an important and intended outcome of therapy with the proposed drug. Adverse reactions may affect quality of life, particularly if they have to be tolerated over long periods. Adverse reactions may also lead to discontinuation of the drug and subsequent substitution of another drug or other medical intervention. A comparative analysis of time to treatment cessation of the proposed drug and the main comparator on the basis of 'intention-to-treat' is useful in this situation. Adverse reactions can contribute to costs through unintended hospitalisations, additional procedures and investigations. Deal appropriately with these impacts to avoid double-counting in the economic evaluation. The generally preferred approach is to include them in a full economic evaluation. However, in some circumstances, presenting a cost analysis may suffice (see Part III, Section D(i)).

Direct health care resources

The health care resource items for which there would be a change in use associated with substituting the proposed drug for the main comparator need to be identified (see also the *Manual of Resource Items and their Associated Costs*).

The following should be considered where appropriate:

- drugs (direct costs of treatment and drugs used to treat adverse reactions)
- medical services, including procedures

- hospital services
- diagnostic and investigational services
- community-based services
- any other direct medical costs.

Define the natural units, such as number of general practitioner consultations or admissions per diagnosis-related group, used to measure the change in the amount of each resource item (see also the *Manual of Resource Items and their Associated Costs*).

Present value of direct health care resource costs

For each type of health care resource, quantify the number of natural units provided for each alternative (eg number of packs of drug dispensed, number of general practitioner consultations, number of episodes of hospital admission). The amount of resource provided (eg the amount of drug dispensed) is the relevant economic measure, rather than the amount of resource consumed.

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

For each type of health care resource provided, multiply the number of natural units by the price per unit (in Australian dollars) recommended in the current *Manual of Resource Items and their Associated Costs*. This document seeks to take the perspective of society in estimating, with some pragmatism for consistency across submissions, each resource's opportunity cost (ie the value of the forgone benefits because the resource is not available for its best alternative use). This means that Section D adopts a broad perspective for the valuation of health care resources, so all contributions to the costs of health care resources, including those paid for by patients, governments, health insurance agencies and any other part of society, should be considered for inclusion in the economic evaluation. In contrast, Section E primarily considers contributions to resources paid for by the PBS/RPBS only (Subsections E.2, E.3 and E.4) and by government health budgets only (Subsection E.5).

It might be reasonable to exclude types of resources that have such a small impact on incremental costs that they would not have a material influence on the conclusion of the economic evaluation.

The unit prices should be as current as possible at the date of the submission. If there are particularly pressing reasons to use different unit prices, justify each and supply its source or describe its generation. Ensure that any different unit price is consistent with the broad perspective of including all contributions to the costs of health care resources, in keeping with the rest of this document and the *Manual of Resource Items and their Associated Costs*. To permit PBAC to gauge the effect of using the alternative unit costs, present the

results of the economic evaluation using first the unit costs recommended by the manual and then the alternative unit costs.

A format for summarising the minimum dataset of resource items and their associated unit costs relevant to the economic evaluation is suggested in Table D.4.1. It is helpful to group items into categories in the order of the *Manual of Resource Items and their Associated Costs* as laid out in the suggested format. Some rows have been completed to clarify the suggested format. These are samples for each identified category, which are consistent with the manual, but are not comprehensive of all types of health care resource items, natural units of measurement, or sources of unit costs.

Table D.4.1 List of health care resource items and unit costs included in the economic evaluation

Type of resource item	Natural unit of measurement	Unit cost	Source of unit cost
Pharmaceutical products			
PBS drug, form and strength	Dispensed maximum quantity for item	A$x	PBS item code according to current PBS as dispensed price for maximum quantity
Non-PBS drug, form and strength	Pack	A$x	Details from Arrow Private Prescription Program
Medical services			
Type of medical practitioner attendance	Consultation	A$x	MBS item code according to current MBS as schedule fee
Hospital services			
Hospitalisation admission	Episode for identified AR-DRG	A$x	DRG Item code according to current AR-DRG Public Sector Estimated Cost Weights as average cost
Outpatient clinic	Nonadmitted clinic occasion of service of identified type	A$x	Service type according to current National Hospital Cost Data Collection Round as average cost per occasion of service
Emergency department	Nonadmitted emergency triage category of identified type	A$x	Triage category according to current National Hospital Cost Data Collection Round as average cost per presentation
Diagnostic and investigational services			
Type of service	Visit	A$x	MBS item code according to current MBS as schedule fee
Allied health care services			
Type of allied health consultation	Consultation	A$x	Table 1, Section 8.2, *Manual of Resource Items*[a]

AR-DRG = Australian Refined Diagnosis Related Group; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme
a See Part I, Section 2.1.3

All steps taken to calculate costs in the economic evaluation should be presented in a way that allows independent verification of the calculations. If a complete presentation is likely to make the main body of the submission too bulky, the calculations should be presented in a technical document. Provide clear cross-references between the

calculations and the main body of the submission. Include an electronic version of the detailed calculations.

Value future costs at current prices. This is consistent with using constant prices in the economic evaluation. Accordingly, no allowance for future inflation should be included in the calculations.

The present value of future costs should also be estimated. This means that where costs extend over a number of time periods (beyond one year), they should be discounted. Discounting of future costs and benefits is a standard feature of economic evaluation. Costs or benefits are discounted at an annual rate of 5%. If discounting is important in an economic evaluation, this can be examined in sensitivity analyses using different discount rates (see Subsection D.6).

Present value of health outcomes

Nominate and justify the outcome that is considered to reflect best the comparative clinical performance of the interventions being compared. This should generally be based on the outcome measure that most closely and validly estimates the final health outcome from a patient perspective. The outcome on which the economic evaluation is based might need to reflect more than one type of intermediate outcome (eg where desired and adverse outcomes need to be considered). Justify the choice of any other outcome measure included in the economic evaluation.

For each relevant outcome, quantify the effect of the proposed drug on the course of the medical condition being managed (either in terms of direct increments, or as streams of effects for the proposed drug and main comparator in separate arms of the decision analysis with the increments determined across the arms). Where possible and appropriate, quantify this effect in terms of the patient's health-related quality of life, distributed across different health states over time. Where utility weights were not elicited via a multi-attribute utility instrument (MAUI) in the direct randomised trials, this might form a basis for valuing these effects in a manner that reflects the preferences of the general population (see Section C and Appendix 6). Describe and justify the basis for these estimates, specifying the source of the information, including by reference to the data presented in submission sections B or C. Distinguish between data on outcomes that are directly derived from the primary evidence and extrapolations or modelling of outcomes beyond that available from the primary evidence. For example, refer to any analysis presented in submission section C to transform an outcome as measured in the direct randomised trials into an outcome presented in the economic evaluation. This includes transforming a modelled final outcome from a measured extent of treatment effect in the trials (see Subsection C.2).

List and document all variables influencing the estimate of outcomes in a table. In the table, highlight the variables that generate the incremental treatment effect on the final outcome estimated in the economic evaluation. These variables include the health states representing the patient-relevant outcomes and the probabilities in each branch of the decision analysis that together simulate a treatment effect by differing between the two arms (each representing the proposed drug and its main comparator) of the economic evaluation. Explain the mechanics of this simulation, because it is usually an important driver of an economic evaluation, and assess the resulting estimate of incremental treatment effect in the context of the analyses presented in submission sections B or C.

The present value of future health outcomes measured from the trials or estimated from the model should also be calculated using the approach described above for costs.

If health-related quality of life is not measured directly in the randomised trials through a MAUI, which allows direct translation to utility weights via the associated preference-based scoring algorithm, the economic evaluation may include scenario-based utility weights to transform the outcomes measured in those trials into a cost-utility analysis (see Subsection C.4 and Appendix 6).

Transition variables can affect both the streams of costs and outcomes. It is usually easier to discuss them alongside the outcome variables.

State transition models

Present the transition probabilities of the model, preferably in a matrix. Provide the source of each transition probability and justify the estimate used. Pay particular attention to the transition probabilities that simulate a treatment effect by differing between the proposed drug and its main comparator. For each transition probability and for any other time- or age-dependent variable, indicate whether it is assumed to be constant or to vary over time and justify the assumption. If a transition probability is modelled as varying according to time or age, describe how this is achieved in the model.

Where probabilistic cost-effectiveness modelling is presented, list the probability distribution around each variable and justify the selection of each type. For example, gamma or lognormal distributions (ie non-negative) could be used for cost parameters, beta distributions for transition probabilities in a control arm, and lognormal distributions for relative risks. For a modelled estimate of incremental effectiveness derived from direct randomised trial evidence, explain how the assumed distribution of the variable reflects the 95% confidence interval around the estimate reported in the trial(s). For each other variable, explain and justify how the selected distribution reflects the extent of statistical imprecision associated with the variable. Also explain and justify each assumed correlation (or lack of correlation) of distributions across the variables.

Time-to-event data (extrapolated)

Present the calculations of the integrals between the two Kaplan–Meier curves from within the horizon of the median duration of follow-up in the trial(s), with appropriate discounting of any patient-relevant events occurring beyond 12 months of commencement of therapy. Similarly, but separately, present the corresponding calculations based on the methods justified in response to Subsection C.2 to extrapolate beyond the horizon of the median duration of follow-up in the direct randomised trial(s).

Where patients transit unidirectionally in a modelled economic evaluation from one mutually exclusive health state to the next, more than one time-to-event analysis can be applied in the same economic evaluation ('partitioned survival'). A particular application of this in economic evaluations of late-stage cancer treatment has involved the quality-adjusted time without symptoms of the disease or toxicity (Q-TWiST) health state. Time with toxicity is measured using mean time-to-treatment cessation for each arm of the trial; time in the Q-TWiST health state is measured as the difference between mean time-to-disease progression and mean time-to-treatment cessation for each arm of the trial; and time with symptoms of the disease is measured as the difference between mean time-to-death and mean time-to-disease progression. These health states are assigned utilities to then calculate quality-adjusted life-years gained.

Additional considerations relating to necessary diagnostic criteria

A number of issues arise when an economic evaluation needs to reflect the impact of requesting that diagnostic tests and/or criteria be specifically used to determine eligibility to commence or continue PBS-subsidised therapy (see Subsection A.2 for advice on identifying and specifying tests and criteria).

Ensure that the costs of conducting tests and/or implementing criteria are included in the economic evaluation and are generated for the population tested, not just the population with positive results. The costs should include assessments that show the individual does not meet the eligibility criteria and for repeat assessments of such individuals.

Also examine the overall impact of false positive and false negative results on the identification of eligible patients and/or treatment response on the application of the trial results for the economic evaluation, particularly if the latter are used in any proposed continuation criteria in the requested restriction. This examination of predictive value typically requires a separate presentation of additional information on the reliability, sensitivity and specificity of the relevant tests and/or criteria, both across all trials presented and in regular Australian practice. As predictive value also varies by varying prevalence, evidence of varying prevalence should also be provided. False positives and false negatives both tend to diminish the ability of the tests and/or criteria to make the incremental cost-effectiveness ratio more favourable than an analysis that does not include the tests and/or criteria (noting that the costs of the diagnostic work-up alone make the ratio less favourable).

When considering the impacts of diagnostic tests, distinguish between health outcomes and nonhealth outcomes. Affected health outcomes include a risk of harm to individuals examined for the diagnostic test, or a risk of harm that arises from changes in treatment that result from the diagnostic test. Include health outcomes only in the base case analysis. Consider including any nonhealth related impacts in a supplementary analysis.

D.5   Results of the economic evaluation

Information requests

- Present the cost per patient per course if the proposed drug is for acute or self-limited therapy, or the cost per patient per year if the proposed drug is for chronic or continuing therapy.

- Present the remaining results of the economic evaluation first in a disaggregated form, then in increasingly aggregated forms. Use discounting as appropriate.

- Present the appropriately aggregated and discounted results separately for outcomes and costs, and separately for the proposed drug and its main comparator.

- Present separate estimates of the incremental cost and the incremental effectiveness of substituting the proposed drug for the main comparator.

- For cost-effectiveness and cost-utility analyses, present the incremental cost-effectiveness ratio as the incremental cost of achieving each extra unit of outcome with the proposed drug substituted for the main comparator (the base case of the economic evaluation).

- Draw a conclusion from the base case economic evaluation that reflects the degree of uncertainty around the presented incremental cost-effectiveness ratios.

> **Additional information requests if the evaluation includes variables reported in Section C**
>
> - Present the results of the three steps described in Subsection D.1 to derive a stepped base case economic evaluation.
>
> - Identify components of the evaluation that have more important impacts on the incremental cost-effectiveness ratio.
>
> - Assess the strength of the evidence that supports the components with the more important impacts and as the basis for identifying matters for the sensitivity analyses.

Cost per patient

Present an estimate of the affordability of the proposed drug as the cost per patient per course for an acute or self-limited therapy, or the cost per patient per year for a chronic or continuing therapy. Justify the calculation of the cost per patient per year for a therapy used episodically, because this is more difficult.

Other results

The presentation of disaggregated results depends on the methods used to generate the results of the economic evaluation. For example, where possible, present the quantity of each type of resource provided in its natural units as well as its cost valued in dollar terms, and/or present the costs and outcomes associated with each branch in the tree of the decision analysis, and/or each health state where the economic evaluation involves a state transition model.

Health care costs

Present the estimated health care costs in disaggregated form (ie separately for each type of resource provided). The nature of this disaggregation is likely to vary across types of economic evaluations.

For a decision analysis that does not calculate costs and outcomes over multiple intermediary time periods (eg a decision analysis that is not a state transition model), estimate and present the number of each type of resource item provided in its natural units at each stage in each branch of each arm of the economic evaluation. Then sum the numbers of each type of resource item in each arm before multiplying by the appropriate unit cost for the resource item. In this circumstance, it is helpful to present a table similar to Table D.5.1.

For a comparison across state transition models that calculate costs and outcomes over multiple intermediary time periods (eg Markov models), present in a table the number of each type of resource item provided in their natural units in each cycle of each health state of the models. Then multiply by the appropriate unit cost for the resource item before summing to estimate the costs for each cycle of the health state (see Table D.5.2).

Present a table that partitions the costs according to their health states across all cycles of the models (see Table D.5.3).

Table D.5.1 List of health care resource items and summary of cost impacts in the economic evaluation

Type of resource item	Cost for proposed drug	Cost for main comparator	Incremental cost	% of total incremental cost
Pharmaceutical products				
PBS drug form and strength	A$x	A$y	$x – $y	z%
Non-PBS drug form and strength	A$x	A$y	$x – $y	z%
Medical services				
Type of medical practitioner attendance	A$x	A$y	$x – $y	z%
Hospital services				
Hospitalisation admission	A$x	A$y	$x – $y	z%
Outpatient clinic	A$x	A$y	$x – $y	z%
Emergency department	A$x	A$y	$x – $y	z%
Diagnostic and investigational services				
Type of service	A$x	A$y	$x – $y	z%
Allied health care services				
Type of allied health consultation	A$x	A$y	$x – $y	z%
Total	**A$x**	**A$y**	**$x – $y**	100%

Note: For a decision analysis that does not calculate costs and outcomes over multiple intermediary time periods

Table D.5.2 Cost per cycle of each health state in a state transition model

Type of resource item	Number of items in natural unit of measurement	Unit cost	Total cost
Health state 1			
Resource type 1		A$x	A$x
Resource type 2		A$x	A$x
Etc		A$x	A$x
Total for health state 1			A$x
Health state 2			
Etc		A$x	A$x

Table D.5.3 List of health states and summary of cost impacts included in the economic evaluation

Health state in model	Cost for proposed drug	Cost for main comparator	Incremental cost	% of total incremental cost
Health state 1	x_1	y_1	$x_1 - y_1$	$z_1\%$
Health state 2	x_2	y_2	$x_2 - y_2$	$z_2\%$
Etc	x_{etc}	y_{etc}	$x_{etc} - y_{etc}$	$z_{etc}\%$
Total	**$x**	**$y**	**$x - $y**	100%

Calculate and present the present value of the direct health care costs for each therapy (ie separately for the proposed drug and its main comparator).

Calculate and present the incremental direct health care costs by subtracting the present value of direct health care costs of the main comparator from those of the proposed drug.

The incremental costs are therefore the costs of any increase in resource use minus offsets resulting from any improvement in outcome. For example, an expensive drug might result in fewer hospitalisations and the net direct costs might be less than those of a cheaper competitor.

Health outcomes

Present the estimated present value of the health outcomes in disaggregated form (ie separately for the proposed drug and its main comparator).

Calculate and present the incremental health outcomes by subtracting the present value of the health outcomes of the main comparator from those of the proposed drug.

For a comparison across state transition models that calculate costs and outcomes over multiple intermediary time periods (eg Markov models), also present a table that partitions the outcomes in the models according to their health states (see Table D.5.4).

Table D.5.4 List of health states and summary of health outcomes included in the economic evaluation

Health state in model	Outcome for proposed drug	Outcome for main comparator	Incremental outcome	% of total incremental outcome
Health state 1	x_1	y_1	$x_1 - y_1$	$z_1\%$
Health state 2	x_2	y_2	$x_2 - y_2$	$z_2\%$
Etc	x_{etc}	y_{etc}	$x_{etc} - y_{etc}$	$z_{etc}\%$
Total	**x**	**y**	**x - y**	100%

Additional disaggregations of state transition models

Where the economic evaluation involves a state transition model, present model traces (eg Markov traces) that plot key outputs on a graph with time on the x-axis against the changing outputs on the y-axis in tabulated or graphical form or, preferably, both forms. For some state transition models, such as those calculated by Monte Carlo simulations, tracker variables could be used to record the information necessary to construct the model traces. Comment on whether each of the model traces makes sense.

For each arm (ie for the proposed drug and its main comparator) and after each cycle, present model traces that:

- identify the proportions of the cohorts in each health state (both for the increment of each cycle over the previous cycle and as cumulative results)

- correspond to observed data (eg a model of a drug used in oncology that generates life-years gained from disease-free survival can be compared with a Kaplan–Meier curve of overall survival, or a model of a medical condition that generates clinical events can be compared with observed data on the natural history of the medical condition)

- sum the outcomes (eg QALYs) and the costs (both for the increment of each cycle over the previous cycle and as cumulative results), discounted as appropriate.

For the increment of the proposed drug over its main comparator after each cycle, present model traces that calculate the incremental costs, incremental outcomes and incremental

cost-effectiveness, each discounted as appropriate. For each of these, present model traces both for the increment of each cycle over the previous cycle and as cumulative results.

Where possible, compare those model traces that correspond with observed or empirical data (eg overall survival or partitioned survival) as a means of validating the model. Comment on and explain any differences indicated by this comparison in order to help validate the model (see below).

Incremental costs and effectiveness

Present the base case incremental cost-effectiveness ratio calculated as the incremental costs divided by the incremental health outcomes.

If the outcome in the denominator of the incremental cost-effectiveness ratio does not include time as part of the units of measurement (eg the outcome is expressed on a per-patient or on a per-event basis rather than a per life-year gained basis or a per QALY gained basis), then also specify the duration of the economic evaluation when presenting these results (for example 'per extra responder at six months'). This helps in the interpretation of the ratio because, except when limited to a defined course of therapy, the cost of drug therapy per patient usually increases over time.

Reflect the degree of uncertainty (see Subsection D.6) around the incremental cost-effectiveness ratios from the presented results when drawing conclusions from the economic evaluation. Avoid terms such as 'dominant' and 'dominated' except in situations where one alternative both costs less and is more effective than the other under a wide range of plausible assumptions.

Where probabilistic cost-effectiveness modelling is undertaken or a probabilistic cost-effectiveness analysis is based directly on a direct randomised trial, present the distribution of overall results both in a scatter-plot on the cost-effectiveness plane and in a tabulated format, including the percentages of the distribution of the results in each quadrant of the cost-effectiveness plane. Also present cost-effectiveness acceptability curves. Avoid overinterpreting these results. For example, unless the data contributing to this analysis are derived directly from individual patient data collected in the context of a direct randomised trial, important sources of nonstatistical uncertainty also need to be examined separately from this analysis.

If the incremental cost-effectiveness ratio is based on a disease-specific outcome (ie other than extra life-years gained or extra QALYs gained), consider whether this ratio can be compared to a similar ratio known to the sponsor that might be related to one or more previous PBAC decisions. Such previous decisions might provide a narrower benchmark or frame of reference than the more widely conceptualised 'league table' based on the two more widely comparable outcomes above. The precedence value is not necessarily determinative because it is indirect at best and might not capture all elements of an overall comparative cost-effectiveness assessment, let alone the influence of other relevant factors (such as disease severity; see Subsection F.3 for an opportunity to identify and comment on these). However, a proposed drug with a less favourable incremental cost-effectiveness ratio in a particular restriction than another comparable drug and restriction previously rejected is unlikely to be recommended.

On the other hand, a proposed drug with a more favourable incremental cost-effectiveness ratio in a particular restriction than another comparable drug and restriction previously

recommended is likely to be recommended. Examples of listed drugs that might provide possible benchmarks include:

- a listed drug that is not widely used due to its perceived disadvantages compared to the proposed drug (and so the appropriate main comparator for the proposed drug is no active intervention, see Subsection A.4)

- a listed drug that has a restriction that is similar to the requested restriction for the proposed drug (eg there might be different thresholds determining eligibility according to risk factors that are specified in both restrictions; see also Subsections A.2 and A.5).

If a claim is made for a change in nonhealth care resource costs or a change in nonhealth outcomes such as production changes, present a supplementary analysis with these included (see Appendix 8 for rationale).

Validating the incremental cost-effectiveness ratio

Consider developing and presenting any approaches to validate the results of a modelled economic evaluation. The comparison of model traces with observed or empirical data (see above) is one such approach where the economic evaluation involves a state transition model. Comment on and explain any differences indicated by this comparison in order to help validate the model.

Related approaches might compare the output of the model assuming no intervention with any epidemiological data on the natural history of the medical condition being modelled, or might compare the output of the model assuming a particular intervention with any available long-term longitudinal observational data on that intervention.

Where a model relies on one estimate of treatment effect (eg a treatment effect used to transform a surrogate outcome to a final outcome or a treatment effect on one component of a composite outcome) and there is a comparable estimate of treatment effect on another outcome generated by the model (eg the final outcome or another component in the composite outcome), consider using this as a basis to validate the results of the model.

Stepped economic evaluation (requested if the evaluation includes variables derived from Section C)

As explained in Subsection D.1, if premodelling studies are presented in Section C, a stepped approach is requested to help PBAC gauge the impact of making these modifications on an unmodified trial-based economic evaluation. See Tables D.5.5 and D.5.6 for further advice on presenting this analysis.

The preferred order of considering the translation of the trial-based economic evaluation (Step 1) is to consider next the impact of applying the treatment effect (Step 2) where applicable. To facilitate this consideration, the structure of Table D.5.5 is aligned to the structure of Table D.2.1. More flexibility is warranted in considering the impact of extrapolating and transforming the treatment effect (Step 3). Table D.5.6 therefore suggests three alternative next steps to combine the results of Step 2 with either an extrapolation step or a transformation step (Step 3a). Each of these represents the incorporation of a possible premodelling study; a submission need only report the option for Step 3a that is relevant to its economic evaluation. The final row of Table D.5.6 incorporates all premodelling studies to complete the impacts of translation (application,

extrapolation and transformation) of the trial-based economic evaluation into a modelled economic evaluation. The incremental cost-effectiveness ratio should therefore correspond to the base case of a stepped economic evaluation presented in a submission.

If it would further clarify the impacts of translation of the clinical evaluation to the economic evaluation, present more steps and/or more detail of each step (eg costs for the proposed drug and the main comparator as well as the incremental costs).

The three steps also help identify assumptions and approaches to be examined in more detail in the sensitivity analyses. For example, if the main impact is achieved by extrapolating the final outcome over time, discuss the rationale for the important underlying assumptions for the extrapolation, such as an assumption about the duration of treatment effect (continued divergence of survival curves) or an assumption that a difference generated by one point in time is maintained (at which point the survival curves remain parallel), rather than the more biologically plausible assumption of eventual convergence of survival curves. In this example, it is therefore important that the biological plausibility and validity of the extrapolations are considered (eg an assumption of a linear relationship between outcomes and time might not be clinically plausible for many medical conditions).

Consider also the compounding impact on uncertainty of combining these steps to estimate the overall treatment effect on the final outcome in the economic evaluation.

Table D.5.5   Assessment of the implications for the economic evaluation of applying the clinical evaluation (Step 1 then Step 2)

Population and circumstances of use	As defined in trial(s) using ITT population	As defined by the requested restriction[a]
Costs		
Costs of therapy involving the proposed drug	(Trial-based)	(Trial-based)[b]
Costs of therapy involving the main comparator	(Trial-based)	(Trial-based)[b]
Incremental costs	(Trial-based)	(Trial-based)[b]
For each trial-based outcome relied on in the economic evaluation before any extrapolation and/or transformation		
Extent of outcomes with the proposed drug		
Extent of outcomes with the main comparator		
Incremental effectiveness (with 95% CI)	(From Subsection B.6)	(From Subsection C.4)
Incremental cost-effectiveness ratio (ICER)	(Step 1)	(Step 2)
Sensitivity analysis of ICER substituting the upper 95% confidence limit of the difference in outcomes achieved		
Sensitivity analysis of ICER substituting the lower 95% confidence limit of the difference in outcomes achieved		

CI = confidence interval; ICER = incremental cost-effectiveness ratio; ITT = intention to treat
a If there is no need to apply the results of the clinical evaluation, the data in this column should be identical to the data in the adjacent column reporting the incremental impacts using the results for the ITT population.
b Justify any variation in estimate of incremental costs from the trial-based costing.

Table D.5.6 Assessment of the implications for the economic evaluation of extrapolating and transforming the clinical evaluation (Step 3)

	Incremental costs	Incremental effectiveness	Incremental cost-effectiveness[a]
For each trial-based outcome relied on in the economic evaluation without further modification	(From corresponding row of Step 2 in Table D.5.5)	(From corresponding row of Step 2 in Table D.5.5)	(From corresponding row of Step 2 in Table D.5.5)
For any trial-based outcome relied on in the economic evaluation *with any extrapolation from the time horizon of the trial(s) only*[b]	(Based on corresponding extrapolation of duration of treatment, if any)	(From Subsection C.4 if extrapolation is required)	**(Alternative Step 3a)**
For any important outcome *generated for or by the economic evaluation* from the trial-based outcome(s) ('*transformation of nature of outcome' only*)[c]	(Include here any modelled increases in the provision of some resources and any modelled offsetting decreases of others)	(From Subsection C.4 if possible, or if this approach is used, explain why a presentation here is not possible)	**(Alternative Step 3a)**
For the final outcome relied on in the economic evaluation *generated as a valuation of the trial-based outcome(s) ('value transformation' only)*	(Should not change from Step 2 because nature of outcome does not change)	(From Subsection C.4 if possible, or if this approach is used, explain why a presentation here is not possible)	**(Alternative Step 3a)**
For the final outcome relied on in the economic evaluation **combining** any extrapolation from the time horizon of the trial(s) **with** any transformation of the trial-based outcome(s)			(Completed Step 3 and expected base case)[d]

a With sensitivity analyses substituting the upper and lower 95% confidence limits of the difference in outcomes achieved
b Justify and explain the methods of the approach taken to align the changes in the incremental costs (or incremental effectiveness) to correspond to the changes in incremental effectiveness (or incremental costs) reported by any premodelling study summarised in Subsection C.4 to extrapolate the evidence from the trial(s) to the time horizon of the economic evaluation.
c Where the approach to transforming the nature of the outcome also involves extending the time horizon of the analysis, justify and explain the methods of the approach taken to align the changes in the incremental costs to correspond to the changes in incremental effectiveness reported by any premodelling study summarised in Subsection C.4.
d Justify if claiming a different base case analysis from that defined above.

D.6   Sensitivity analyses

Information requests

- Present univariate (one-way) sensitivity analyses on all variables using plausible extremes of values, and justify the selection of those extreme values.

- Tabulate all univariate sensitivity analyses alongside the base case.

- Present multivariate sensitivity analyses combining variables shown to be sensitive in the univariate analyses.

- Examine and present the sensitivity of the results of the economic analysis to any changes in assumptions concerning the structure of the modelled economic evaluation that are important but uncertain.

The purpose of a sensitivity analysis is to examine the effect of uncertainty around estimates and assumptions included in the economic evaluation on the results of the base case economic evaluation. Statistical (probabilistic) uncertainty involves random error and can be reduced by increasing sample size. The many other sources of uncertainty involve systematic error, are harder to identify and cannot be reduced by increasing sample size. For example, they arise in the selection and measurement of information, the specification of the structure of a model and the plausibility of the implicit and explicit assumptions relied on for the model, particularly in aggregating across the various sources of information.

Univariate sensitivity analyses

The univariate (one-way) sensitivity analyses on all variables should use plausible extremes of values. Justify the selection of the plausible extreme values of each variable, for example the upper and lower 95% confidence limits of the relevant incremental treatment effect variables reported in direct randomised trials, the considerations summarised in Table C.4.1, or the range of estimates from the available studies of the natural history of a medical condition.

Tabulate all univariate sensitivity analyses alongside the base case. A tornado diagram with incremental cost-effectiveness on the x-axis can be used, where possible, as an efficient and informative way of summarising the results of the univariate sensitivity analyses.

Use the univariate sensitivity analyses to highlight the variables that are important drivers of the economic evaluation. Consider providing a matrix with the effects of variables on various outcomes that differ across the two arms (eg in terms of health outcomes, mortality and utility).

The three steps to enhance the transparency of the economic evaluation are intended to help identify the basis of plausible extreme values of variables for further examination. For example, when curves have been fitted to time-to-event data to extrapolate the results beyond the duration of observed follow-up, the sensitivity analysis should examine both the uncertainty in fitting the curves for the extrapolation and the upper and lower 95% confidence limits of the time-to-event results measured within the direct randomised trials.

Multivariate sensitivity analyses

The multivariate sensitivity analyses should combine variables shown to be sensitive in the univariate analyses. Explain the selection of these variables and their combination, for example, varying more than one of the steps to enhance transparency at the same time. Present the analyses in tabular and graphical format.

Where a probabilistic sensitivity analysis is provided, also examine the sensitivity of base case estimates of incremental cost, incremental effect and incremental cost-effectiveness to changes in one variable at a time as univariate sensitivity analyses conducted on each variable using plausible distributions.

Sensitivity of the results to changes in the modelled economic evaluation

Examine assumptions concerning the structure of the modelled economic evaluation that are uncertain to assess their importance by the extent to which they affect the results of the evaluation. The three steps to enhance the transparency of the economic evaluation may help identify structural issues for further examination.

Similarly, if there is a risk of substantial usage beyond the intended population and circumstances of use defined in the requested restriction, examine the sensitivity of the results to the assumption of usage within these intentions. As discussed in Subsection D.2, this wider population and circumstances would be expected to have demographic and patient characteristics and circumstances that differ from the target population and circumstances. If the intention of the restriction is to limit usage to the population for which the proposed drug is most cost-effective, these sensitivity analyses should examine the extent to which the incremental cost-effectiveness ratio would become less favourable with increasing usage beyond the restriction. Table D.6.1 gives advice on presenting this analysis in a format that is comparable to Tables D.2.1 and D.5.5.

Table D.6.1 Analyses of the implications for the economic evaluation of usage beyond the requested populations and circumstances of use

Population and circumstances of use	As defined by the requested restriction	If use beyond the requested restriction might arise
Incremental costs		
Incremental effectiveness		
Incremental cost-effectiveness ratio		

If a cost-utility analysis is presented, also present the results of the economic evaluation with the utility in all health states set to one to generate the incremental cost per extra life-year gained. This helps identify the contribution of any life extension component to the incremental effectiveness claim.

If discounting has been necessary, the robustness of the results to different discount rates (including a zero discount rate on non-monetary outcomes alone and on both costs and outcomes) should be tested.

Section E
Estimated extent of use and financial implications

Introduction

The purpose of this section is to generate the most likely utilisation and financial estimates by requesting a set of budget impact analyses. These analyses are relevant to both PBAC and the Australian Government. In the event of a positive recommendation by PBAC, the Australian Government needs utilisation and financial estimates to help provide the necessary funds.

Figure E.1 shows the two broad bases for developing utilisation and financial estimates (epidemiological and market share). As the flowchart shows, these are not mutually exclusive. It also helps explain the logic behind the steps that build on the epidemiological basis and that support the preferred format of calculating and presenting these estimates using the utilisation and cost model spreadsheets supplied alongside these guidelines (see Subsection 2.1.3), based on a standardised Excel 2003 workbook. Together with this section, this preferred workbook format is primarily designed to present the necessary calculations using the epidemiological basis consistently across submissions. This workbook is *not* designed for presentation of utilisation and financial estimates for vaccines to be funded under the National Immunisation Program (NIP) or for the market-share approach (see Part III, Section E(i)) and may need adapting.

An epidemiological base is usually preferred for generating utilisation and financial estimates if (in response to Subsection B.8) the submission concludes that, overall, the proposed drug has a therapeutic advantage over its main comparator(s). This decision parallels the cost-effectiveness approach that would be taken in submission section D. The epidemiological approach first estimates the number of people with the medical condition and then uses several steps to estimate the use of the proposed drug (see Subsection E.2) and of other drugs in the context of the main indication (see Subsection E.3).

However, a market-share base might be preferred to generate the utilisation and financial estimates if (in response to Subsection B.8) the submission concludes that, overall, the proposed drug is no worse than (ie noninferior to) its main comparator(s). This decision parallels the cost-minimisation approach that would be taken in submission section D, in response to Part III, Section D(i). The market-share approach first estimates the extent of the current market represented by the main indication and consequently the share likely to be taken by the proposed drug.

Subsections E.1 to E.6 focus on the presentation of estimates adopting an epidemiological basis. Part III, Section E(i) presents the different requests that apply if adopting a market-share approach. Both approaches may be informative for some submissions — for example, where there is uncertainty in the therapeutic conclusion, or where there is large uncertainty in the expected utilisation (see Subsection E.6). Presenting both approaches and demonstrating a concordance of comparable results across the approaches might reduce uncertainty in the utilisation and financial estimates. Appendix 9 shows the steps in each process and the relationship between the two approaches.
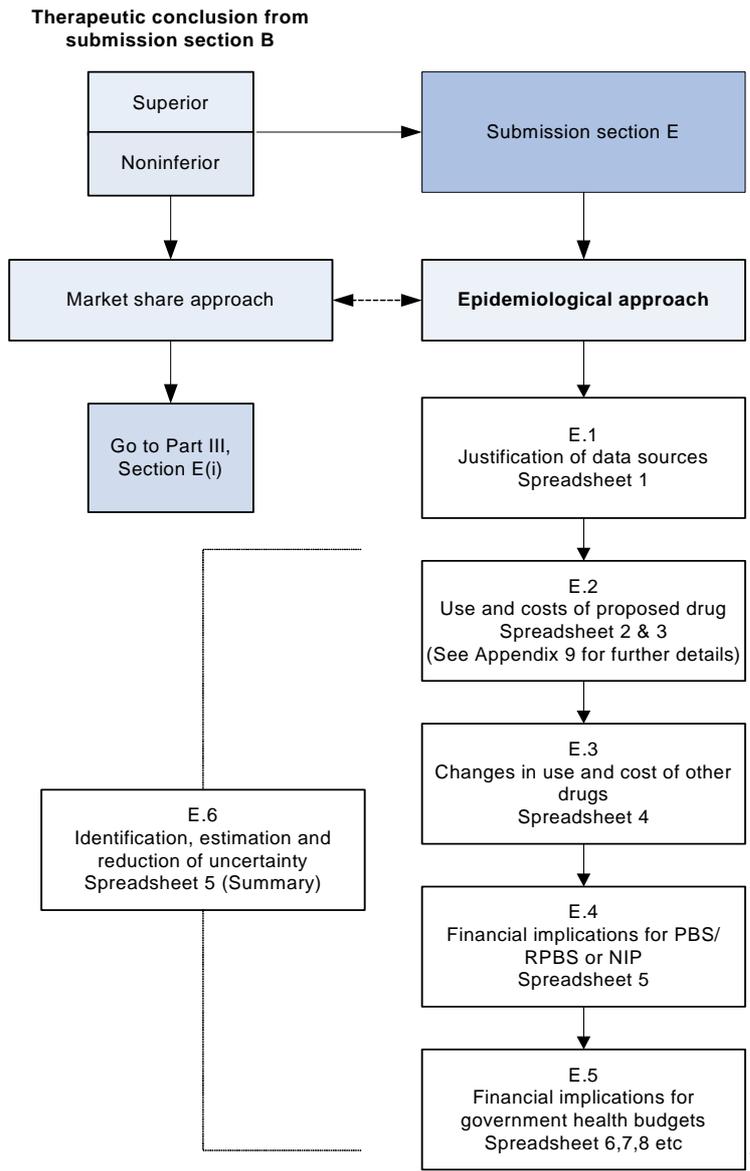
Figure E.1   Key information requests for submission section E of a major submission to PBAC

Subsections E.2 to E.4 request financial analyses relevant to the funding program (eg PBS or NIP budgets) by only considering health care resources subsidised through those programs. Subsection E.5 requests that these analyses be broadened to include health care resources funded through government health budgets in Australia. In contrast to the economic evaluation presented in submission section D, these financial analyses exclude health outcomes, scale up estimates to assess the impact for the program overall, do not use discounting, and exclude any resource item or co-payment from a source other than the identified budget (typically, this means that patient co-payments should be excluded; see Chapter 9 of the *Manual of Resource Items and their Associated Costs* for further details).

The following sections lay out a preferred stepwise process to generate utilisation and financial estimates. Whenever it is thought appropriate to include an approach that is not requested below, justify the approach in the main body of the submission. Whenever it is

thought appropriate not to take an approach that is requested below, a particularly strong justification should be provided and, where possible, the alternative approach should be presented separately and in addition to the requested approach.

Where a submission seeks listing for more than one indication (see Subsection A.2), present a separate standardised Excel 2003 workbook for each indication. As a final step in each of Subsections E.4 and E.5, these results can be aggregated across the indications.

E.1 Justification of the selection of sources of data

Information requests

- Where data are available (published or unpublished) from one or more types of data sources:
  - summarise the methods used to obtain the data
  - present the relevant main results
  - interpret the findings
  - discuss the limitations (including the representativeness of the results) and biases of the method adopted.
- Where data are obtained via one or more studies commissioned for the submission:
  - describe the gap in the information to be addressed by the commissioned analysis
  - summarise the methods used to obtain and analyse the data
  - present the relevant main results
  - interpret the findings
  - discuss the limitations (including the representativeness of the results) and biases of the method adopted.
- Use Spreadsheet 1 of the standardised Excel 2003 workbook to summarise all the background information, primary (noncalculated) variables and assumptions essential to the calculation of results presented in this section.
- Provide a copy of the data from each published and commissioned study with the attachments to the submission. Include the correspondence that requested the data for a commissioned study.

Published data sources

Data sources suitable to the approach taken should be stated and discussed in the submission. Data availability for prevalence and incidence is variable, but the best available data should be justified and used where possible. Data sources fall under the broad headings listed in Table E.1.1; however, there might be other suitable data sources.[18] In each case, the methods used should be summarised and the results presented and interpreted, including a discussion of the limitations and biases of the method used.

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[18] See Section 2.1.3 for citation details of *Sources of Epidemiological Data for Use in Generating Utilisation Estimates* for suggested sources of data that might be suitable for the medical condition relevant to the submission.

Sources include data from Australia or overseas, such as PBS/Repatriation Pharmaceutical Benefits Scheme (RPBS) data for therapeutically equivalent drugs that are already listed and overseas data on the use, in markets similar to Australia, of a proposed drug that has no PBS-listed comparator. Where there are multiple sources of data, assess the validity and applicability of both the source and the data in relation to their use in the submission's calculations. The demonstration of concordance across multiple data sources of similar validity and applicability is encouraged to reduce uncertainty. Present sensitivity analyses reflecting the variation in the estimates from the available data.

Table E.1.1   Categories of data sources

Disease epidemiological data (provide estimates of prevalence or incidence in the population)
• Australian case or mortality registers estimate the incidence or prevalence of a disease
• Large, well-designed Australian studies estimate the incidence or prevalence of a disease
• Australian national health surveys estimate the prevalence of a disease
Pharmacoepidemiological data (provide estimates of treated prevalence)
• Surveys of the treated prevalence of the disease in Australia
• Studies using utilisation databases, including PBS/RPBS data
Market data (see 'Introduction', above)
• Quantitatively describe the existing market
• Estimate relative market shares
• Estimate the impact of the requested PBS listing on current treatment paradigms based on similar previous listings.

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Commissioned data sources

Studies commissioned for the submission may include drug usage evaluations (DUEs), data requests to disease registries, established epidemiological studies or ongoing utilisation studies seeking specific analyses. In each case, the information gap to be filled should be clearly described, and the results presented and interpreted, including a discussion of the limitations and biases of the method used.

In the absence of Australian observed data, a range of observed data from overseas sources could be used. When presenting this data, also discuss the applicability of the estimates from an overseas source to the Australian population. In the case of pharmacoepidemiological data, this discussion should further assess the impact of any variations in the subsidy arrangements between overseas health care systems and those in Australia.

Where multiple sources of data are available to address a single assumption or estimate, compare the results, assess their concordance or lack of concordance, and justify the selection of the base case estimate and the estimates used in the sensitivity analyses. Present a summary table where multiple sources or multiple variables are being compared.

In the absence of observed data, expert opinion might be required (see Appendix 4). A commissioned DUE of recent practice has many similarities with a survey of expert

opinion; a distinguishing characteristic might be that a DUE measures what was done, whereas experts are asked to report what they would do now or in the future.

Each time an assumption is required in the absence of data, state the assumption concisely and explain its basis. Describe the nature and likely magnitude of uncertainty for each assumption (see Subsection E.6). Present an examination of the impact of each assumption by altering it in sensitivity analyses.

Spreadsheet 1 ('Background and assumptions')

When using Spreadsheet 1 of the standardised Excel workbook to summarise the data sources, background information, primary (noncalculated) variables and assumptions, it might be helpful — if the analyses are complex — to add one or more other supporting spreadsheets in the workbook to provide more detail, such as identifying the sources of variables relied on and supporting the assumptions made. The remaining spreadsheets, which calculate the estimates (see below), should be fully integrated so that changes to any variable for the purposes of sensitivity analyses flow on appropriately through succeeding calculations to all results.

Copies of data

To allow independent assessment of the data, include copies of the data used (published, unpublished and commissioned) in an attachment to the submission. Ensure that the responses to submission section E and Spreadsheet 1 provide adequate cross-references of the extraction of all data used to generate the estimates in these analyses from each attached data source (to the level of the page, table or figure number of each source document).

E.2 Estimation of use and costs of the proposed drug

> **Information requests**
> * Estimate the number of patients with the medical condition targeted by the proposed drug, the number who would be eligible for the requested restriction and the number of patients likely to take the proposed drug.
> * Use Spreadsheet 2 of the standardised Excel 2003 workbook to calculate the results presented in this part of the section.
> * Estimate the number of packs dispensed for each form and strength of the proposed drug in each year over five years (disaggregated into proportions for PBS and RPBS, and by beneficiary type).
> * Estimate the costs for each form and strength of the proposed drug in each year over five years, multiplying by the following unit costs:
>   – dispensed price for maximum quantity (DPMQ)
>   – DPMQ with each appropriate patient co-payment removed.
> * Aggregate both these cost calculations for the proposed drug overall in each year over five years.
> * Use Spreadsheet 3 of the standardised Excel 2003 workbook to calculate the results presented in this part of the section.

Numbers of patients

Use of incidence or prevalence data

The choice between using incidence and prevalence data is important in estimating the likely number of patients eligible for the drug in any one year. This choice depends on the nature of the medical condition and its treatment.

In general, an incidence-based approach is preferred for a therapy of short duration, with 12 months being a suggested upper limit, because estimates should be presented in periods of one year (see below). Examples include an acute self-limiting medical condition, each episode of which is treated with a single course of therapy, and a medical condition that is managed by a single course of therapy given once in a lifetime. Incidence should be estimated on a 12-month basis.

In general, a prevalence-based approach is preferred for a therapy that is to be used for long periods, with 12 months being a suggested lower limit; for example, chronic medical conditions for which medication (for either treatment or prevention) is taken regularly (ie without breaks in the standard dosage regimen).

For some therapies, a combination of incidence and prevalence bases might be informative. Examples include intermittent treatment of a series of acute episodes of a chronic medical condition, treatment for which is restricted to each episode and in which the proposed drug is expected to prolong the duration of disease, including by an extension of expected overall survival.

The first example (regular treatment for chronic medical conditions) is complex because, although the number of patients who have the condition might be determined using an epidemiological approach, the number of presentations for treatment can be more difficult

to determine. In the second example (intermittent treatment), allowance for an increase in prevalence might be necessary. If disease duration or life expectancy is expected to increase from fewer than five years in the current situation before the listing of the proposed drug, it would generally be appropriate to increase the initial prevalence pool estimate on an annual basis by the difference in the 12-month incidence of new patients and the 12-month incidence of cured patients or of deaths. This should be continued either until a new steady state is achieved, with constant rather than increasing prevalence, or until the five-year horizon of the analyses is reached.

Expert epidemiological advice should be sought when estimating prevalence from incidence data or estimating incidence from prevalence data, particularly where there is doubt that the duration of disease has not remained constant over time or where it is not expected to remain constant after the listing of the proposed drug.

Estimate the number of patients with the medical condition

Estimate the likely number of patients in the current year and in the first year of listing using one of the bases above (incidence or prevalence). These estimates should also incorporate the most probable estimates of patients who are misdiagnosed (ie where there might be pressure to diagnose the patient as having the medical condition in order to be eligible for the proposed drug and where the differential diagnosis is unclear). Then project the numbers of patients on an annual basis for a total of five years, accounting for population growth and expected changes in prevalence and/or incidence of the condition. If appropriate, more frequent periods (eg monthly or three-monthly) could be calculated in the supporting spreadsheets. If so, summarise the presentation of these aggregated data as annual aliquots for a total of five years from listing (Year 1, Year 2, Year 3, Year 4 and Year 5).

Estimate the number of patients eligible for the requested restriction

Using these annual numbers of patients with the medical condition for Years 1–5, estimate the proportions who would be expected to be eligible for therapy according to each of the requested restrictions for PBS listing. These estimates should also include the most probable estimate of patients who are misclassified — that is, in situations where there might be pressure to assess the patient as meeting a requested restriction in order to be eligible for the proposed drug, and where the requested restriction retains elements of subjectivity or is not reinforced, or where a diagnostic test specified in the requested restriction produces false positives or false negatives on one or more occasion.

Estimate the number of patients likely to take the proposed drug

Using these annual numbers of eligible patients, estimate the proportions likely to take the proposed drug in each of the five years. The resulting estimates should reflect the likely share of the proposed drug compared with the other treatment options currently used for eligible patients.

Spreadsheet 2

Calculate the above three sets of estimates of patient numbers in Spreadsheet 2 ('Epidemiology of the disease and patient numbers') of the standardised Excel 2003 workbook.

Number of packs dispensed

Three elements are involved in translating the numbers of patients likely to be treated to the numbers of packs dispensed. There is no basis to suggest a preferred order in which they should contribute to the calculations.

The first element is the rate of uptake of the proposed drug across the five years from listing. If appropriate, shorter periods (eg monthly or three-monthly) could be calculated in the supporting spreadsheets. If so, summarise the presentation of these aggregated data as annual aliquots for a total of five years from listing.

The second element is the dose, frequency and duration of therapy involving the proposed drug. Duration of therapy might be affected by adherence to therapy and rates of discontinuation (eg due to poor tolerance or disease progression). Consistent with the information requests in Section D, the estimates should be in terms of the quantities of drug provided rather than consumed (ie as the amounts likely to be dispensed, taking wastage into consideration). In determining the impact of this element, the variation in duration of therapy between the context of the available randomised trials and probable use of the drug once listed on the PBS should be considered. Aspects of this include patient preferences, physician's preferences, switching of drugs, comorbidity in the patients and co-administration of other drugs. Determining estimates of drug use for the PBS context is therefore based on a number of assumptions and uncertainties that are difficult to quantify and that therefore should be justified and subjected to sensitivity analyses.

The third element is the mix of forms and strengths of the proposed drug. Where more than one form or strength and, sometimes, more than maximum quantity or number of repeats is specified in response to Section A.1, there will be more than one product or item listed on the PBS to distinguish between these forms, strengths and quantities. The estimates should be disaggregated to the level of the proportions of use of each of these products of the proposed drug.

Estimate the number of packs dispensed for each form and strength of the proposed drug in each year over five years by applying these three elements to the patient number estimates from Spreadsheet 2. The definition of a 'pack' should be based on the usual prescribed maximum quantity for each form and strength as requested in response to Subsection A.1.

Disaggregation of estimates

Justify a basis to break down these estimates for the proposed drug into proportions for the PBS and the RPBS, each broken down further into proportions of beneficiary type as follows:

- PBS General
- PBS General Safety Net
- PBS Concessional
- PBS Concessional Safety Net
- RPBS
- RPBS Safety Net.

One option, which would need to be assessed for its suitability in each case, would be to apply the breakdown for the closest therapy that is currently listed (and specifically the main comparator if that is PBS-listed). These breakdowns are available from the Medicare Australia website. If different weights can be demonstrated as being likely to apply, those should be presented instead.

Costs over five years

Two sets of unit costs should usually be applied to the disaggregated estimates of numbers of dispensed packs of each of the forms and strengths of the proposed drug. The first is the dispensed price for maximum quantity (DPMQ). The second is the DPMQ with each appropriate patient co-payment removed. The amounts of the co-payments are stated in the Schedule of Pharmaceutical Benefits and are available on the PBS website.[19] Where these prices do not apply (for example, for products to be listed under section 100 arrangements or to be funded under the NIP), apply the following as unit costs:

- the Commonwealth price
- the Commonwealth price less any amount charged as a patient co-payment.

For these calculations, use constant prices, make no allowance for inflation and use a zero discount rate. Further guidance is provided in Chapters 4 and 9 of the *Manual of Resource Items and their Associated Costs*.

Aggregated cost calculations

Estimate the costs to the PBS/RPBS of the proposed drug in each year over five years by applying these breakdowns and unit costs and then aggregating each set of cost estimates (DPMQ and DPMQ less the appropriate patient co-payment).

Previous submissions have commonly calculated the weighted average patient co-payment and applied this to estimate the costs of the proposed drug. The alternative approach to disaggregating the estimates of the numbers of packs into proportions of beneficiary types is preferred because it facilitates ready access to useful information. This information should include the split between PBS and RPBS in utilisation and costs, and the submission should assess the implications of prices of the proposed drug and drugs considered in Subsection E.3, which may be larger or smaller than the general beneficiary co-payment.

Spreadsheet 3

Calculate the above sets of estimates of packs dispensed and costs in Spreadsheet 3 ('Cost of the drug to the PBS/RPBS') of the standardised Excel 2003 workbook.

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[19] http://www.pbs.gov.au/html/healthpro/browseby/explanatory-notes?ref=section1-patientcharges

E.3   Estimation of changes in use and cost of other drugs

> **Information requests**
> - Identify the other PBS-listed drugs that are likely to be affected by listing the proposed drug.
> - For each drug, estimate the extent of change in the number of packs (of each form and strength) in each year over five years (disaggregated into proportions for the PBS and the RPBS, and by beneficiary type).
> - Estimate the costs of each form and strength of each affected drug in each year over five years, multiplying by the following unit costs:
>   – DPMQ
>   – DPMQ with each appropriate patient co-payment removed.
> - Aggregate both these cost calculations for the other affected drugs in each year over five years.
> - Use Spreadsheet 4 of the standardised Excel 2003 workbook to calculate the results presented in this section.

Drugs likely to be affected by the listing of the proposed drug

PBS-listed drugs likely to be affected by the listing of the proposed drug include:

- PBS-listed drugs substituted by the proposed drug
- other PBS-listed drugs with decreased usage
- other PBS-listed drugs with increased usage.

As an initial step, identify and list all PBS-listed drugs that fall into each of these three categories. The list should include those PBS-listed drugs identified in Subsection A.3.

Of the three categories, substituted drugs usually have the largest impact on the financial implications of listing the proposed drug. There would be no substituted drugs if the proposed drug has no competitors or if it is designed to replace a medical procedure. Where all substituted PBS-listed drugs come from a single group of drugs listed on a cost-minimisation basis, the cost differential of each against the proposed drug should be similar. However, where the cost differential is expected to vary to an important extent across the substituted drugs, also estimate the breakdown of the proportions of the overall substitution in order to capture the cost implications of the variation.

PBS-listed drugs with expected decreased usage after the listing of the proposed drug include those that are co-administered with substituted drugs, those used to treat adverse reactions to substituted drugs, and those used to treat the clinical end points that might be reduced after therapy involving the proposed drug.

PBS-listed drugs with expected increased usage after the listing of the proposed drug include those that are co-administered with the proposed drug and those used to treat adverse reactions to the proposed drug.

The impact of adverse reactions might have less weight if the information provided in Subsection B.7 shows that they are of insufficient clinical importance to require

management with PBS-listed drugs or if they are similar for the proposed drug and its major competitors. If there is insufficient information available from Subsection B.7 to include the impact of adverse reactions on PBS expenditure, this should be noted.

Number of packs dispensed

Justify the approach adopted for estimating the extent of change for the forms and strengths of each affected drug, where the approach and calculations involve uncertainty. Use the information provided in Subsections A.3 and E.2. Identify and justify any inconsistency between submission sections D and E in the identification of PBS-listed drugs that would change as a result of listing the proposed drug, and the extent of change per patient in the first five years of listing.

Disaggregation of estimates

Disaggregation into proportions for the PBS and the RPBS and by beneficiary type should usually be based on the most recent 12 months of usage data from Medicare Australia. An exception could be where the expected substitution is for a distinctive subgroup of current use of the substituted drug(s), in which case the disaggregation should be based on the subgroup.

Costs over five years

Estimate the costs in each year over five years of each of the forms and strengths of each of these drugs substituted, decreased and increased on the basis of each of the estimated utilisation changes. For these calculations, use constant prices, make no allowance for inflation and use a zero discount rate. Where the standard PBS/RPBS prices do not apply (for example, for products listed under section 100 arrangements or vaccines funded under the NIP), apply the following as unit costs:

- the Commonwealth price
- the Commonwealth price less any amount charged as a patient co-payment.

Aggregated cost calculations

Estimate the cost offsets to the PBS/RPBS of the other affected drugs in each year over five years by applying these breakdowns and unit costs and then aggregating each set of estimates (DPMQ and DPMQ less the appropriate patient co-payment) by subtracting the costs of substituted drugs and the costs of drugs with decreased usage from the costs of drugs with increased usage.

Spreadsheet 4

Calculate the above sets of estimates of packs dispensed and costs in Spreadsheet 4 ('Cost implications to the PBS/RPBS from substitutions and other increases and decreases') of the standardised Excel 2003 workbook.

E.4 Estimated financial implications for the PBS/RPBS or the NIP

> **Information requests**
>
> - Estimate the net financial implications for the PBS and the RPBS (or the NIP) in each year over five years by subtracting the net cost offsets for both the aggregated estimates calculated in Subsection E.3 from the corresponding estimates calculated in Subsection E.2.
>
> - Use Spreadsheet 5 of the standardised Excel 2003 workbook to calculate the results presented in this section.

If a PBAC recommendation arising from a major submission is expected to increase the cost of either the NIP or the PBS (inclusive of the RPBS), by a net amount of $10 million or more in any 12-month period within the first four full years of listing, the presented utilisation and financial estimates will also be used as a basis for the subsequent submission to Cabinet. This financial estimate uses the DPMQ with appropriate patient co-payments removed, or the Commonwealth price as appropriate for drugs to be listed under section 100 arrangements or vaccines to be funded under the NIP.

Spreadsheet 5

Calculate the two sets of net financial implications in Spreadsheet 5 ('Net cost of drug to the PBS/RPBS') of the standardised Excel 2003 workbook.

E.5 Estimated financial implications for government health budgets

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Information requests

- Estimate the extent of net change in the number of prescriptions processed by Medicare Australia for payment (and, where appropriate, the net change in the number of authorisations by Medicare Australia) in each year over five years.

- Estimate the net financial implications for Medicare Australia in each year over five years of:

  – processing prescriptions for payment

  – authorising prescriptions based on a telephone application, where applicable

  – authorising prescriptions based on a written application, where applicable

  – all these costs aggregated together.

- Estimate the extent of net change in the number of each type of affected Medicare Benefits Scheme (MBS) item provided in each year over five years.

- Estimate the net financial implications for each affected MBS item in each year over five years, multiplying the extent of change of each MBS item by the following unit costs:

  – the schedule fee

  – the appropriate benefit (ie with the appropriate patient co-payment removed).

- Aggregate both these cost calculations across all affected MBS items to estimate the net financial implications for the MBS in each year over five years.

- Estimate the net financial implications for government health budgets in each year over five years.

- Use Spreadsheets 6, 7, 8 and other new spreadsheets, as required, to calculate the results presented in this section as indicated in the information on individual requests below.

Implementing a PBAC recommendation might have financial implications for other parts of the Australian Government's health budget, including Medicare Australia and the Medicare Benefits Scheme (MBS). It might also have implications for state and territory government health budgets, including public hospitals. This section extends the financial analyses presented in response to Subsection E.4 to estimate those implications. If implications for other components of government health budgets are identified, the general approach outlined here should be applied.

Net changes in the numbers of prescriptions and authorisations

To estimate the numbers of prescriptions processed by Medicare Australia, use the estimates of the numbers of dispensed packs of the proposed drug from Subsection E.2 and the net changes in the numbers of packs of other drugs dispensed from Subsection E.3.

Where the proposed drug or the drugs considered in Subsection E.3 include drugs with a relevant restriction requiring authorisation by Medicare Australia, estimate the extent of net change in the number of authorisations in each year over five years, taking into account the number of repeat packs authorised to be dispensed for each drug before a new

prescription needs to be authorised by Medicare Australia. Where applicable, distinguish authorisations requiring a written application from those requiring a telephone application and estimate each type separately.

Financial implications for Medicare Australia

Refer to Section 9 of the *Manual of Resource Items and their Associated Costs* for the appropriate unit costs to calculate the costs to Medicare Australia.

Use **Spreadsheet 6** ('Cost implications to government from Medicare Australia changes') of the standardised Excel 2003 workbook to calculate the sets of net financial implications (the extent of net changes in the cost to Medicare Australia for processing prescriptions for payment, for authorising prescriptions based on telephone and written applications, and all the costs aggregated together).

Net changes in the types of MBS items provided

MBS items for which an *increase* in use might be expected include:

- MBS-funded procedures required to administer the proposed drug (eg an implant or an infusion)
- MBS-funded consultations to manage adverse reactions to the proposed drug
- MBS-funded consultations and tests to:
    - confirm diagnosis of the medical condition
    - determine eligibility for the proposed drug according to the requested restriction (see Subsection A.2)
    - ascertain whether any continuation criteria in the requested restriction for the proposed drug have been met (see Subsection A.2).

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 drugs.

Generate the estimates of MBS usage by relating the number of patients estimated in response to Subsection E.2 to the per-patient usage estimates generated in submission section D. Identify and justify any inconsistency between submission sections D and E in the identification of types of MBS items that would change as a result of listing the proposed drug and the extent of change per patient in the first five years of listing.

Financial implications for the MBS

The appropriate benefit (ie the MBS unit cost that removes the appropriate patient co-payment) varies according to whether or not the particular MBS service is provided while a patient is admitted to a hospital or day hospital facility (see the Medical Benefits Schedule for more details).

Calculate the extent of net changes in the cost to the MBS for each item affected before aggregating to estimate the net financial implications for the MBS overall.

Use **Spreadsheet 7** ('Cost implications to government from MBS changes') of the standardised Excel 2003 workbook to calculate the two sets of financial implications (schedule fee and appropriate benefit with patient co-payment removed).

Net implications for government health budgets

Other financial implications for the Australian Government health budget

Identify and justify any other financial implications for the Australian Government health budget. In presenting the calculations, follow the stepwise approach taken above to:

- estimate the numbers, in their natural units, of the disaggregated resources provided or freed

- apply the appropriate unit cost(s) to each type of resource to estimate the net financial implications for each type

- aggregate the newly identified financial implications in each year over five years.

Create a **new spreadsheet** in the standardised Excel 2003 workbook to present details of the calculations.

Australian Government health budget

Combine PBS/RPBS estimates using the DPMQ with the MBS estimates using the schedule fee. Separately combine financial implications with appropriate co-payments removed (ie PBS/RPBS estimated using the DPMQ with each appropriate patient co-payment removed and the MBS estimated using the appropriate benefit). Then incorporate any other identified financial implications for the Australian Government health budget, including the Medicare Australia budget.

Calculate the aggregated sets of net financial implications in **Spreadsheet 8** ('Net cost of the drug to government') of the standardised Excel 2003 workbook.

State and territory government health budgets

Identify and justify any financial implications for state and territory government health budgets, such as for public hospitals (including inpatient admissions, emergency department visits and outpatient clinic visits). In presenting the calculations, follow the approach taken above to estimate first the numbers, in their natural units, of the disaggregated resources provided or freed. There is controversy about valuing freed hospital resources in government health budgets because, in the Australian public hospital system, the freed resources are typically redeployed to improve the health of the next available patient rather than being realised as financial cost reductions.

Provide further justification to support any claim for financial cost offsets from any reduction in the need to provide a public hospital resource. For example, provide a basis for concluding that the expected change is large enough that a resulting change in the provision of the resource would become a viable option for hospital management or other appropriate decision makers. Another option could be to exclude the fixed costs from the marginal costs of the identified hospital resource type (the opportunity cost value used in submission section D is the full average cost of each resource, which represents its

maximum value assuming an infinite time horizon to manage health care resources). Then apply this justified unit cost to each type of resource to estimate the net financial implications for each type, and aggregate the newly identified financial implications in each year over five years.

Create a **new spreadsheet** in the standardised Excel 2003 workbook to present details of these calculations.

Combined government health budgets

Combine the estimates of net financial implications for state and territory health budgets with those for the Australian Government health budget to estimate the net financial implications for government health budgets in each year over five years.

E.6   Identification, estimation and reduction of uncertainty

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Information requests

- In each step of the calculations, assess the sources of uncertainty and distinguish the type and degree of uncertainty in utilisation and financial estimates.

- Where possible, explain the nature of each uncertainty and its impact on the overall estimates.

- Estimate the level of the uncertainly and propose ways to reduce it.

- Provide a separate workbook to generate the results of any calculations (eg sensitivity analyses and scenario analyses) to examine the impact of uncertainty. Summarise these in Spreadsheet 5 of the standardised Excel 2003 workbook.

Nature of uncertainty

When presenting the most likely utilisation and financial estimates, consider the degree of uncertainty of those estimates. Two types of uncertainty should be distinguished.

The first type — *usage that differs from expectations* — generally arises from uncertainty within and across particular variables in the analysis. Sensitivity analyses should be presented to examine the impact of this source of uncertainty.

The second type — *usage that extends beyond the restriction* (sometimes called 'leakage') — generally arises from uncertainty as to whether the requested restriction would achieve its intended objective in limiting use. Usage beyond the requested restriction raises doubts about the overall cost-effectiveness of the proposed drug where the intention of the restriction is to exclude its subsidised use in patients for whom that use would not be acceptably cost-effective. Scenario analyses might be relevant to examine the impact of this uncertainty or to examine the application of a proposed risk-sharing arrangement, which might seek to minimise the impact of the uncertainty (see Subsection F.2). The objective of these analyses of uncertainty is to generate estimates of both the likelihoods and the magnitudes of the differences from the most likely (base case) estimates.

Sources of uncertainty

The following lists summarise the factors that could be considered when assessing uncertainties in predicted utilisation patterns and financial implications resulting from the listing of a proposed drug as requested. The lists are not intended to be prescriptive, but generally reflect factors that have been considered previously by the Drug Utilisation Sub-Committee (DUSC) and PBAC and may arise from epidemiological data, pharmacoepidemiological data, expert opinion and assumptions used in generating the quantified predictions. Any of these factors might provide information that will increase understanding of the uncertainties present in utilisation estimates. It might be useful to consider these factors explicitly, but not all the factors will apply to all submissions. Thus, it might not be necessary to address any or all of these questions for each submission, as the uncertainties outlined might be very small or of little importance to the overall cost to the PBS. Therefore, consideration should be given to how relevant each of the factors might be for a particular submission.

Factors that could affect the extent of usage within the requested restriction

Consideration of the following factors might provide relevant information on uncertainties about the extent of use of the proposed drug within the requested restriction. Some factors might not be relevant in all submissions or might have a negligible impact on the overall estimates.

- Promotion might result in greater identification of the proposed drug, resulting in more prescribers considering patients for treatment.

- Indirect media exposure to consumers might result in some consumers being more aware of the proposed drug and seeking treatment with it. These patients might not be identified if a treated prevalence approach has been used.

- Outcomes of related research might have an impact on uptake of the proposed drug. This could be positive or negative, and could emerge at the time the submission is lodged or be expected to occur within five years of listing.

- More prescribers and patients might seek treatment if the proposed drug treats a medical condition for which the alternatives are considered to be substantially inferior to the proposed drug (eg in terms of effectiveness, tolerability or patient acceptability and convenience).

- Limited access to designated types of PBS prescribers or to designated diagnostic procedures in a requested restriction might limit uptake and utilisation.

- The duration of therapy might be longer than expected from the randomised trials, particularly when trials are truncated.

- Patients might be treated more often than expected, particularly in the case of medical conditions with episodic manifestations.

- There might be a likelihood of doses increasing over time.

Factors that could affect the likelihood of usage beyond the requested restriction

Some of the factors listed above might also affect the likelihood of usage beyond the requested restriction. Many of these factors relating to the requested restriction could be considered to be more applicable to risk-sharing arrangements that might be discussed in Subsection F.2. More detailed guidance is given in Subsection A.2 about ways of

designing a restriction to minimise usage beyond its intention, but the following factors might be considered.

- The requested restriction is for a subset of the types of patients who are eligible according to the TGA-approved indication(s).

- The requested restriction is for a subset of the types of patients who were eligible for the randomised trial(s) published for the proposed drug, 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 drug before or after PBS listing is implemented.

- The requested restriction is for a subset of the types of patients who have the underlying medical condition.

  – Identify whether there are any likely difficulties for prescribers in determining eligibility for the proposed drug (eg a difficult differential diagnosis, ambiguity in the wording of the restriction, or poor precision or accuracy in a diagnostic test) that might result in misclassifications of eligible patients from the population with the underlying condition.

  – Identify whether patient advocacy groups are likely to have an influence on determination of eligibility by prescribers.

Estimating and reducing uncertainty

The following three aspects should be addressed in any consideration of uncertainty:

- the direction of impact on the estimate (underestimate or overestimate)

- the impact on the magnitude of the estimate (small or large)

- the likelihood that another estimate should replace the base case estimate (probable or improbable).

Although quantitative estimates of uncertainty are preferred, semiquantitative assessments may need to be given in many instances. Where the effects of some uncertainties are difficult to quantify, this should be noted. As a general principle, the more sensitive the overall financial implications are to a particular source of uncertainty, the more important it is to minimise that uncertainty.

One way to reduce uncertainty is to use data from multiple sources, where available. Where estimates derived from different sources are concordant, there might be more confidence and therefore less uncertainty in the resulting estimates. Where this is not the case, the disparity between the estimates might contribute to the estimate of uncertainty. Similarly, more than one methodological approach may be applied (eg estimates based on a market-share base as well as an epidemiological base, or treated prevalence, where the prevalence of patients treated for a disease, determined from a pharmacoepidemiological database, is used as a surrogate for the true prevalence). Again, where estimates derived from different sources are concordant, there might be more confidence and therefore less uncertainty in the resulting estimates. This can be referred to as 'triangulation' (the use of

multiple sources of data or multiple approaches to determine the consistency or otherwise of the conclusions from those sources or approaches).

Summary of calculations

Summarise the results of any calculations (eg sensitivity analyses and scenario analyses) to examine quantitatively the impact of uncertainty in Spreadsheet 5 ('Net cost of drug to the PBS/RPBS') of the standardised Excel 2003 workbook. Do not include the supporting calculations in that workbook. If additional calculations need to be explained, a separate workbook should be provided for any analysis other than the base case (most likely) analysis. Spreadsheet 1 ('Background and assumptions') of the separate workbook should highlight the differences from the base case workbook.

Section F
Options to present additional relevant information

Introduction

Over time, a number of issues have arisen that are important for some submissions but are not necessary for all submissions. These have included include quality use of medicines (QUM), risk-sharing arrangements (RSAs), equity principles, 'rule of rescue' and other relevant factors that can affect PBAC's assessment of proposed drugs.

This section is intended to assist the consideration of such issues in relation to a submission. It does not cover all possible issues. Ultimately, a sponsor may include in a submission any information that is relevant to PBAC's decision.

F.1 Quality use of medicines

> **Information requests**
>
> - Identify any activities (planned or under way) of the sponsor that are intended to support QUM and to achieve the desired health outcomes for the population identified by the requested restriction (including activities integrated with other QUM service providers).
>
> - Where a postmarketing surveillance study is proposed, identify the rationale for the study and indicate how its methods would achieve its aims.

Relevance and definition of QUM

The cost-effectiveness of a medicine in regular clinical practice can be influenced by many factors that affect the achievement of the desired health outcome. Therefore, there is an extensive overlap between the concepts of QUM and of cost-effective subsidy arrangements for drugs delivered through the PBS. Many of the principles of QUM are embedded as design principles in earlier sections of these guidelines. These overlapping issues, such as a consideration of correct dose regimens (Subsection A.3), comparative benefits (Subsection B.6) and comparative harms (Subsection B.7), should therefore be addressed in the relevant context earlier in the submission and need not be repeated in response to this section.

The National Strategy for Quality Use of Medicines has been developed to guide QUM in Australia. This strategy is not isolated, but recognises the interdependence of its aims and those of the PBS. Because of this interdependence, the integration of activities both within and across these aims is critical.

QUM involves the following three elements:

- *Judicious selection of management options* — This means consideration of the place of medicines in treating illness and maintaining health, recognising that nondrug therapies may be the best option for the management of many disorders.

- *Appropriate choice of medicines, where a medicine is considered necessary* — This means selecting (when medicines are required) the best option from the range available, taking into account the individual, the clinical condition, risks, benefits, dosage, length of treatment, co-morbidities, other therapies and monitoring considerations. Appropriate selection also requires a consideration of costs, both human and economic. These costs should be considered for the individual, the community and for the health system as a whole.

- *Safe and effective use* — This means ensuring the best possible outcomes of therapy by monitoring outcomes and minimising misuse, overuse and underuse. It also means improving the ability of all individuals to take appropriate actions to solve medication-related problems (eg managing adverse effects or multiple medications).

This definition of QUM applies equally to decisions about medication use for individual patients (in primary and secondary care) and to decisions at the public health level (which affect the health of the population).

Activities to support QUM

Matters that uniquely apply to QUM but that could usefully be addressed in a submission for PBS subsidy should be provided in response to this section. Current or future sponsor activities to support QUM and thus to achieve the desired population health outcomes may include activities integrated with other QUM service providers, because this can help build partnerships that promote QUM. The range of activities may include:

- assisting in judicious management and appropriate selection of the proposed drug within the requested restriction (for example, if the restriction is narrower than the TGA-approved indication and/or if the therapeutic conclusion in the submission is of noninferiority rather than superiority, and it is planned that the promotional activities for the proposed drug will be aligned with these aspects of the submission, describe how this will be achieved)

- promoting the applicability of trial results to the population and circumstances of use identified for the requested listing

- minimising sources of uncertainty identified in estimating uptake and overall utilisation patterns of the proposed drug

- maximising safe and effective use once therapy has begun, such as development and distribution of consumer medicine information, appropriate packaging (eg vial strengths and blister pack quantities) and appropriate labelling, including by reducing unintentional adverse events.

These activities could reassure both PBAC and government that uncertainty about cost-effectiveness and usage within the requested restriction will be minimised.

Postmarketing surveillance

Where a postmarketing surveillance study is proposed, discuss the rationale for the study and indicate how its methods will achieve its aims. This might involve monitoring for the maintenance of a response to the proposed drug for longer than the follow-up of the submitted randomised trials, a pharmacovigilance study to detect serious but rare adverse reactions, or monitoring the achievement of the clinical event rates predicted in the

economic evaluation. Assess whether the interpretation of the results would be affected by the subsequent listing of another drug in a similar population.

F.2   Risk-sharing arrangements

Information request

- Where a risk-sharing arrangement (RSA) is proposed in a submission to PBAC:
    - identify the risk(s) that require management
    - propose the details of an arrangement that adequately monitors and manages each risk by an appropriate mechanism for sharing it between the sponsor and the Australian Government
    - indicate any elements that are requested to be kept confidential
    - anticipate and address the possibility that RSAs could be expanded to ensure fairness for competing drugs in the future
    - quantify the impacts of the RSA.

Relevance and definition of RSAs

RSAs may be proposed by the sponsor to PBAC, the Pharmaceutical Benefits Pricing Authority (PBPA) or DoHA. They may be recommended by PBAC (usually in relation to cost-effectiveness and/or health outcomes) or by PBPA or the department (usually in relation to overall costs). Given that RSAs typically rely on utilisation data, there are advantages to all parties if a sponsor puts any proposal for such an arrangement early in the process of application for a drug listing (eg in its submission to PBAC), rather than introducing the proposal later.

RSAs are negotiated with the sponsor by officers of DoHA on behalf of the Australian Government. They are finalised between the PBAC recommendation and PBS listing alongside the process of finalising prices. Finalisation is influenced by whether the PBAC recommendation to list modifies the request in the submission (for example, if PBAC recommends a restriction that is substantially different from that requested).

Identification of risks

RSAs (also previously called 'price–volume agreements') have been developed to address at least three types of risk:

- *the overall cost to the PBS/RPBS* — this is affected by uncertainties in the number of patients, daily dose and duration of therapy of the proposed drug

- *cost-effectiveness* — this is affected by the volume of use beyond the restriction(s) and by the volumes of use of categories within the restriction(s) where cost-effectiveness is known to vary across categories

- *the extent of overall gain in health outcomes* — this is a risk that has been less commonly addressed in RSAs.

These risks are not necessarily mutually exclusive. For example, usage beyond the restriction is also likely to affect the overall cost to the PBS/RPBS. However, usage

beyond expectations might affect the overall cost to the PBS/RPBS without affecting cost-effectiveness (for example, a greater than expected use of an unrestricted drug cannot, by definition, represent usage beyond the restriction). Less commonly, usage might be within expectations of overall cost to the PBS/RPBS, but beyond the restriction. This can arise because, despite the best efforts in the construction of the restriction, the restriction may be impossible to reinforce sufficiently; for example, the number of patients expected to receive the therapy might be so large that an authority required listing to reinforce adherence to the restriction would be impractical.

RSA proposal

Where an RSA is proposed in a submission to PBAC, indicate how the proposal manages each risk identified. Identify and define each and all relevant variables in the proposed RSA, such as volume thresholds, dates of commencement, time horizons, price reductions and rebate arrangements.

Subsection E.6 discusses the various sources of uncertainty in usage estimates that constitute many of the risks. Where applicable, options to monitor such risk should be feasible, practical and built on usage data that is accessible to government and/or is regularly supplied by the sponsor as part of the RSA. The advice of the DUSC Secretariat (see page iv) or Medicare Australia may be useful to explore some of these options.

Any suggested thresholds of risk at which price reductions or rebates might be offered in an RSA should be unambiguously identifiable from the data sources used to monitor this risk. The thresholds should also correspond with the most likely usage estimates for the PBS/RPBS reported in submission section E and thus would generally be assessed no less frequently than once a year.

Where a submission requests a change to the current listing of a drug that is already the subject of an RSA, a proposal should be included in the submission addressing whether and, if so, how the arrangement should be modified following a PBAC recommendation to change the listing.

Where an RSA is proposed, it might be particularly relevant to reassure PBAC that planned promotional activities (see Section F.1) are consistent with the risk-sharing proposa. Similarly, various bodies within and beyond the PBS seek to minimise the risk of usage beyond restrictions through the clarity of restrictions (the Restrictions Working Group provides advice on this aspect), reinforcement of restrictions (Medicare Australia implements this aspect) and education on reasons for particular restrictions (the National Prescribing Service provides this aspect through the RADAR program).

Confidentiality

Indicate any elements that are requested to be kept confidential. There is a general government preference for transparency in these arrangements, and a minimum requirement would seem to be to make public the fact that such an arrangement exists so that an earlier arrangement does not hinder the listing of a new PBAC-recommended alternative drug.

Possible future competitors

Anticipate how the proposed RSA could be expanded, if other drugs are subsequently listed for use in a similar population, to ensure fairness between the competing drugs. An RSA should not constitute a barrier to the listing of a subsequent drug.

Quantify impacts

If the risk relates to the overall cost to the PBS/RPBS, the application of the proposed RSA should be quantified in an Excel workbook aligned with that presented in submission section E to show the impact on usage and costs estimates, both with and without the implementation of the proposed RSA. Similarly, if the risk relates to cost-effectiveness, quantify the impact of the proposed RSA on the economic evaluation. If the risk relates to the extent of the overall gain in health outcomes, quantify how price and/or rebate, cost-effectiveness and total cost to the PBS/RPBS would change in response to smaller than expected gains in observed health outcomes.

F.3   Other relevant factors

Information requests

- If the submission raises any issue relating to equity principles, discuss it in descriptive terms.

- If the submission raises any equity assumption that particularly affects consideration of the cost-effectiveness of the proposed drug, describe the implications where appropriate with reference to a sensitivity analysis.

- If the submission is for a new antimicrobial agent, take account of relevant prudent use principles for such agents.

- If the submission makes any claim that the 'rule of rescue' is applicable, set out the basis for that claim.

- If the submission identifies any other relevant factor not requested elsewhere, discuss it in response to this section.

Equity principles

From a general policy viewpoint, the PBS promotes fairness in its subsidy arrangements by promoting affordable access to cost-effective drugs. Thus, any listing that is likely to particularly promote or hinder these or any other general equity principles should be discussed. For example, if the requested listing of the proposed drug would raise particular patient affordability considerations, their implications should be discussed.

Equity assumptions

From a technical viewpoint, many elements of an economic evaluation contain embedded equity assumptions (for example, see utility valuation in Appendix 6). In the rare cases in which such underlying assumptions might be important enough to influence a particular PBAC decision, a description of how the issue affects consideration of the cost-

effectiveness of the drug — and preferably an examination of its impact in a sensitivity analysis — should be sufficient.

Prudent use principles in relation to antimicrobial agents

The submission for a new antimicrobial agent should be aware of the government-endorsed prudent use principles proposed by the JETACAR 1999 report[20] when considering target populations, and should provide relevant data on the development of resistance as appropriate (with cross-referencing to the responses to Subsection B.6 or B.7 if the development of resistance has been demonstrated to affect health outcomes). Any issues arising should be addressed, and submissions should indicate whether any aspect of any restriction requested in response to Subsection A.2 is designed to minimise the development of resistance.

Guidance on the 'rule of rescue'

Three factors, which apply in exceptional circumstances, are particularly influential in favour of listing. When all three factors apply concurrently, this is called the 'rule of rescue'. The three factors are as follows.

- No alternative exists in Australia to treat patients with the medical condition meeting the criteria of the requested restriction. This is an absolute requirement. It 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 consideration by PBAC.

- 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 consideration by PBAC. However, PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.

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 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 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 PBAC would reverse a decision not to recommend listing if the rule of rescue is not relevant.

This guidance on the rule of rescue is kept deliberately narrow. Although there are relevant arguments for broadening the guidance, PBAC is concerned that doing this would reduce the relative influence of the rule of rescue when it is applied to a broader set of eligible submissions. In other words, the greater the proportion of submissions that the

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[20] http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pubs-jetacar-cnt.htm/$FILE/jetacar.pdf

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 drug to treat the medical condition considered to meet the requirements of the rule is not suitable for this consideration. This is because, by definition, the second drug does not meet the essential first factor of the three factors (ie that there is no currently alternative intervention). This causes a difficulty if listing of the second drug is sought on a cost-minimisation basis.

Another difficulty is that indiscriminate application of arguments such as the rule of rescue can lead to overall inefficiencies, unless PBAC compensates when considering drugs that clearly fall outside the rules.

Discuss any other relevant factor

If any other relevant factor is thought to be worth emphasising and is not already requested elsewhere for inclusion in the submission, discuss it in the response to this section.

PART III

FURTHER INFORMATION FOR PREPARING THE MAIN BODY OF A MAJOR SUBMISSION

Section B(i)
Clinical evaluation for the main indication: Presenting an indirect comparison of randomised trials

Introduction

Where relevant direct randomised trials (as defined in Part II, Subsection B.2) comparing the proposed drug directly with the main comparator are available, their analysis and presentation are preferred as the basis of the clinical evaluation (see Part II, Section B). However, in the absence of any such direct randomised trials, the second step in the hierarchy is to determine whether it is possible to present an indirect comparison based on two or more sets of randomised trials involving one or more common reference. Such an analysis indirectly compares the proposed drug with its main comparator by comparing one set of trials, in which participants were randomised to the proposed drug or to a common reference, with another set of trials, in which participants were randomised to the main comparator or to the common reference.

If an indirect comparison (as defined above) is also not possible, the third step in the hierarchy is to present a comparison across nonrandomised studies, including comparisons across single arms extracted from randomised trials that do not involve a common reference arm (see Section B(ii)).

The common reference is often placebo, but may be an active intervention, such as a drug from another therapeutic class. There may be more than one common reference (eg the proposed drug can be compared with the main comparator via common reference A and via common reference B). In these circumstances, all possible indirect comparisons should be presented and the conclusions compared. The indirect comparison may also involve more than one step (eg the proposed drug can be compared with common reference A in one set of randomised trials, common reference A can be separately compared with common reference B in another set of randomised trials, and common reference B can be compared with the main comparator in a third set of randomised trials). In this circumstance of a multi-step indirect comparison, there is limited basis for giving guidance on presenting the analysis. The greater the number of steps, the greater the uncertainty associated with the comparison.

This Section B(i) gives guidance on presenting a clinical evaluation based on an indirect comparison. The information requests are arranged in the same order, with the same issues for assessment of the evidence, as those for the presentation of direct randomised trials. For clarity, submissions should adopt the suggested section headings in the order presented here.
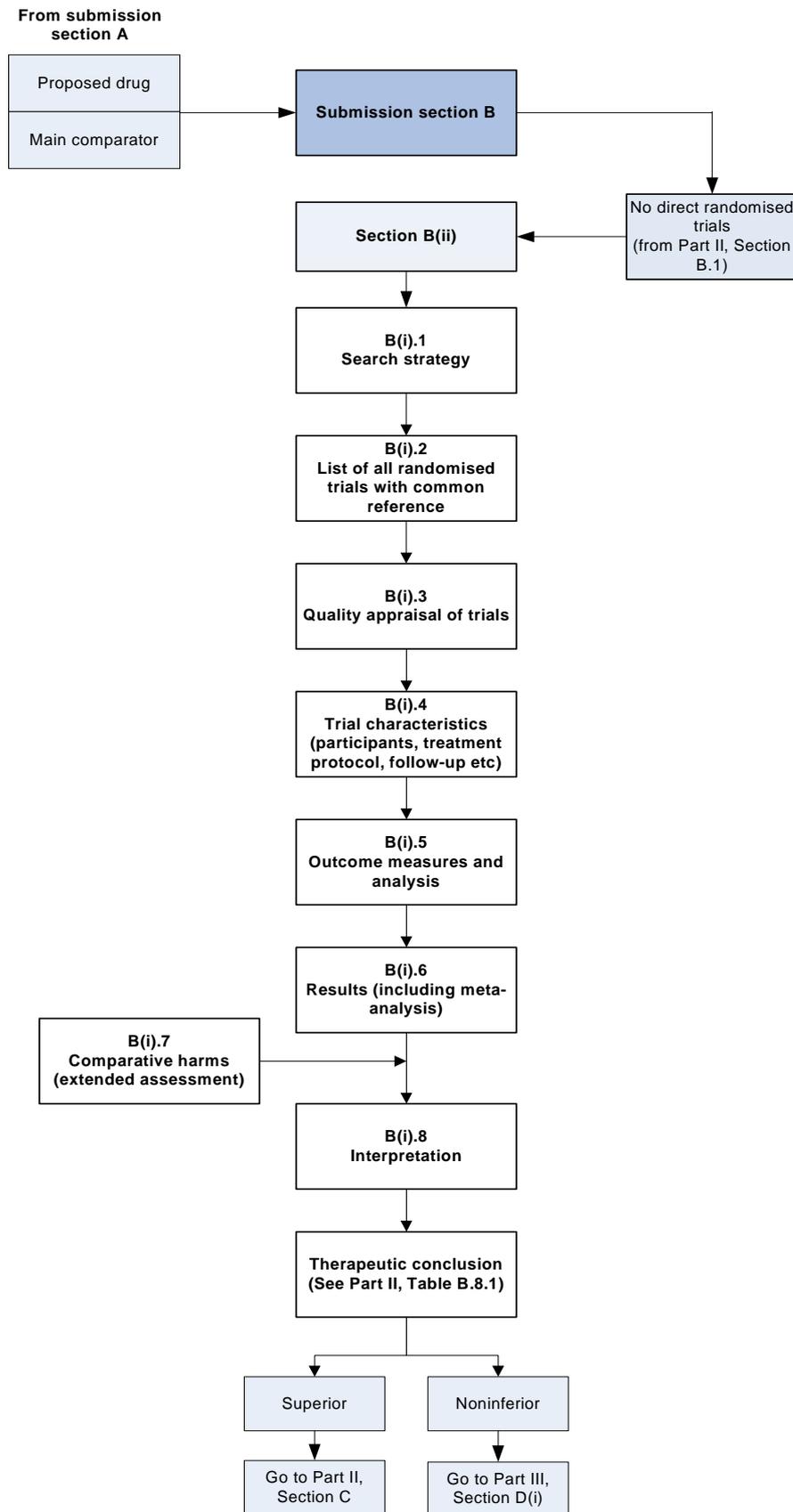
Figure B(i).1   Key information requests for submission section B of a major submission to PBAC with clinical data from an indirect comparison of randomised trials

B(i).1 Description of search strategies

Information requests

- After demonstrating that no relevant direct randomised trials exist, broaden the literature search criteria to identify all randomised trials relevant for an indirect comparison of the proposed drug and the main comparator.

- Describe the search strategies and characteristics used to locate reports of potentially relevant trials from the published literature, registers of randomised trials and unpublished sources held by the sponsor, as described in Part II, Subsection B.1.

If no relevant direct randomised trials have been retrieved in response to the systematic searches requested in Part II, Subsection B.1, the search criteria should be broadened to identify all randomised trials of the proposed drug and of the main comparator.

This involves relaxing the inclusion criteria to identify all randomised trials involving possible common references (ie therapies that are compared with the proposed drug or with the main comparator in separate trials). For the proposed drug, this includes a search internal to the sponsor of all trials conducted by, or on behalf of, the sponsor, its head office, its subsidiaries elsewhere and any co-licensing sponsor.

The search should follow the same methods as described in Part II, Subsection B.1, including provision of a detailed description of the search and printouts of the searches. As it is not possible to prespecify the common reference(s), these searches should identify, for the proposed drug and for the main comparator, all randomised trials that recruited participants with characteristics that overlap those of patients who would be eligible for the main indication.

B(i).2 Listing of all randomised trials considered for inclusion in an indirect comparison

> **Information requests**
>
> - Present tables listing all citations of randomised trials for the proposed drug and the main comparator that included a common reference and that recruited participants with characteristics that overlap those of patients who would be eligible for the main indication as identified from the expanded searches of the published literature, marketing dossier and other sources. Show the inclusion and exclusion criteria and state which trials have been published.
>
> - On the hard copy of each of the search printouts supplied as technical documents with the submission, annotate each citation to indicate excluded citations with the reason for the exclusion.
>
> - Collocate all reports of each randomised trial included in the indirect comparison to create a master list, arranging the randomised trials into sets for the proposed drug and the main comparator according to each identified common reference. Indicate the preferred identification (ID) for each trial to be used throughout the submission for consistency.
>
> - Before comparing the proposed drug with the main comparator, establish the comparability of the randomised trials, both within each set and across the two or more compared sets. Justify the exclusion of each randomised trial deemed noncomparable within each set.
>
> - Include copies (or sufficient details) of the included comparable trials as attachments in the main body of the submission. Include copies (or sufficient details) of the included, but noncomparable, trials in a separate volume of the submission.
>
> - In the absence of any relevant randomised trials to form an indirect comparison, include a 'nil return' in the submission.

Search results

Assess all citations retrieved by the expanded searches to extract all trials that meet the following inclusion criteria for randomised trials to support one or more indirect comparisons involving the identified common reference(s):

- the trial included a randomisation procedure in its design
- the trial compared the proposed drug or the main comparator against an identified common reference in separate arms
- the trial recruited participants with characteristics that overlap those of patients who would be eligible for the main indication.

Adapt the guidance given in Part II, Subsection B.2 to present the results of the searches and to list and provide details of all the randomised trials that meet the inclusion criteria separately for the proposed drug and the main comparator. In addition to the two tables presented to establish that there are no direct randomised trials, replicate the format of those tables to present the expanded searches for all randomised trials of the proposed drug. A fifth table is needed to present the literature searches for all randomised trials of the main comparator (the sixth table may not be needed, as it is unlikely that the sponsor would have access to any unpublished randomised trials of the main comparator).

Search printouts

Present annotated search printouts as described in Part II, Subsection B.2.

Master list of trials

From the two tables reporting the results of the expanded searches for the proposed drug, list all identified relevant citations of randomised trials for the proposed drug. Similarly, list all identified relevant citations of randomised trials for the main comparator. Table B(i).2.1 provides a suggested format for presentation of a master list of all the relevant randomised trials identified in the search for the indirect comparison.

Table B(i).2.1   Trials (and associated reports) presented in the submission

Trial	Description	Reports	Comparable?
Common reference A			
Proposed drug			
Unique identifier (ID) of trial used in remainder of submission	Brief description of trial	Internal study report title. Date. Author(s). Title. Journal Year; Vol(No):pages Author(s). Title. Journal Year; Vol(No):pages	Y/N
ID of trial used in remainder of submission	Brief description of trial	Internal study report title. Date. Author(s). Title. Journal Year; Vol(No):pages Author(s). Title. Journal Year; Vol(No):pages	Y/N
Main comparator			
ID of trial used in remainder of submission	Brief description of trial	Internal study report title. Date. Author(s). Title. Journal Year; Vol(No):pages Author(s). Title. Journal Year; Vol(No):pages	Y/N
Common reference B			
Etc			

If there is no basis for an indirect comparison as defined above, see Figure B.1 for the next step in the clinical evaluation. The third step in the hierarchy is to present a comparison across nonrandomised studies, including comparisons across single arms extracted from randomised trials that do not involve a common reference arm. To do so, follow Section B(ii) in place of the remainder of this Section B(i).

Presentation of noninferiority (equivalence) trials

If an indirect comparison is provided to support a therapeutic conclusion of noninferiority or equivalence in Section B(i).8, see Appendix 5 for additional guidance on the presentation of the information.

Assess comparability of identified randomised trials to justify any exclusions

Given that there is no randomisation step in the comparison of the proposed drug and the main comparator, it is appropriate, when establishing the comparability of the compared sets of randomised trials, to consider justifying the exclusion of randomised trials from those included in the list above in order to select similar trials for inclusion in the indirect comparison. The grounds for exclusion might include any aspect reported in

Subsections B(i).3 to B(i).5 (ie the quality of the trials, the patient characteristics and circumstances of use, and the outcomes reported in the trials; see examples below). Observable differences across the randomised trials should be minimised, or their contribution to heterogeneity across the trials examined and adjusted where possible. By definition, nonobservable differences cannot be minimised or adjusted, and this contributes to the residual uncertainty inevitably associated with indirect comparisons.

Aspects that may justify the exclusion of trials from an indirect comparison include:

- important differences in the quality of the trials (eg inadequate follow-up in one of the trials)

- important differences in baseline patient characteristics (eg the treatment effects detected in a trial of patients with severe disease might not be comparable with those detected in a trial of patients with mild disease)

- differences in outcomes reported (eg a trial might report outcomes that are not assessed in any other trial)

- differences in the 'common' reference — this might not be identical across the trials; for example, an active common reference might have a different dose regimen across the trials (an important aspect because the indirect comparison relies to a large extent on the consistency of the common reference).

In addition, it may be reasonable to exclude a trial because changes in medical practice and patient characteristics might also mean that nominally similar therapies might not be comparable when the randomised trials have been conducted at different times or in different geographical regions.

It is not possible to give unequivocal guidance on the exclusion of randomised trials from an indirect comparison at this stage. The justification to exclude a randomised trial should anticipate whether this would raise issues of selection bias, while the justification to include a randomised trial should anticipate whether this would raise issues of comparability. If a decision to exclude or include one or more randomised trials is likely to be controversial, it is usually wiser to also present a sensitivity analysis examining whether the decision makes a difference to the conclusions from the overall clinical evaluation.

If one or more trials are to be excluded from an indirect comparison, identify the aspect(s) of each trial that form the reasons for the proposed exclusion (see Table B(i).2.2). Indicate whether each reason relates to the quality of the trials, the patient characteristics and circumstances of use, and/or the outcomes reported in the trials. Present greater detail of each aspect (as a minimum, to the extent requested in the relevant text adapted from Part II, Section B). If there is more than one type of reason for exclusion, arrange the trials for exclusion in Table B(i).2.2 by the reason for exclusion.

Table B(i).2.2   Reasons to exclude each trial from the indirect comparison

Trial ID	Ground(s) for seeking exclusion	Details[a]
Quality of the trial		
Trial 1		
Patient characteristics and circumstances of use in the trial		
Trial 2		
Outcomes reported in the trial		
Etc		

a Cross-reference each set of details to the source of information (specifying the trial report with page, table, figure number).

Table B(i).2.3 shows a suggested format for presenting included trials that are used to indirectly compare the proposed drug and its main comparator. This presentation is useful because it also provides details of the common reference(s) and summarises the comparative strategy adopted for the submission.

Table B(i).2.3   Summary of randomised trials used to conduct the indirect comparison

Trial ID	Proposed drug	Common references				Main comparator
		Placebo	Drug A	Drug B	Drug C	
Trial 1	Dosage regimen	Dosage regimen	–	–	–	–
Trial 2	Dosage regimen	Dosage regimen	–	–	–	–
Etc	–	Dosage regimen	–	–	–	Dosage regimen
	–	Dosage regimen	Dosage regimen	–	–	–
	–	–	Dosage regimen	Dosage regimen	–	–
	–	–	–	Dosage regimen	Dosage regimen	–
	–	–	–	–	Dosage regimen	Dosage regimen

Trial details

Present the included comparable trials in the main body of the submission and attach a report of each to the main body of the submission. Provide a report of each included but noncomparable trial in a separate volume of the submission. Provide clear cross-references between the presentation of the trials and the reports.

B(i).3 Assessment of the measures taken by investigators to minimise bias in the randomised trials included in the indirect comparison

> **Information requests**
> - Adapt the guidance given in Part II, Subsection B.3, including the suggested tables, to describe the minimisation of bias within each included comparable randomised trial.
> - Compare and assess the minimisation of bias in the trials across each set of trials forming the indirect comparison.

It is not possible to minimise bias across the indirect comparison beyond the assessment of comparability and selection bias discussed in the section above. For trials deemed comparable for the submission, identify any differences that may exist in the quality of the trials across the indirect comparison.

B(i).4 Characteristics of the randomised trials included in the indirect comparison

> **Information requests**
> - Adapt the guidance given in Part II, Subsection B.4, including the suggested tables, to describe the characteristics of each included comparable randomised trial.
> - Indicate when and where each included comparable randomised trial was conducted.
> - Compare these aspects of the trials across each set of randomised trials forming the indirect comparison and assess any important differences.

The indirect comparison across trials does not have a randomisation step to allow the characteristics of the patients to differ only due to the play of chance. The description of the characteristics of each randomised trial should facilitate their comparison across the compared sets of trials. For trials deemed comparable for the submission, it is particularly important to assess the baseline risk of the patients recruited into the randomised trials and the dose regimens used for the common reference.

Similarly, assess how far apart in time and place the trials were conducted. This is necessary because changes in medical practice and patient characteristics might mean that nominally similar therapies may not be comparable when the randomised trials have been conducted at different times or in different geographical regions. Such changes may confound the indirect comparison.

B(i).5 Outcome measures of the randomised trials included in the indirect comparison

> **Information requests**
> - Adapt the guidance given in Part II, Subsection B.5, including the suggested tables, to present definitions of the patient-relevant outcomes measured, their natural units of measurement and the duration of follow-up when the outcomes were assessed in each included comparable randomised trial.
> - Compare and assess any important differences in the outcomes measured across each set of randomised trials forming the indirect comparison.

The methods of measurement of the same outcome may differ across the trials. The description of the patient-relevant outcomes should facilitate a comparison both within each set of trials and across the compared sets of trials. The distinctions between primary and secondary outcomes and between primary and secondary analyses are less important in an indirect comparison.

B(i).6 Results of the indirect comparison

> **Information requests**
> - Assess the results for each common reference for any important differences across the sets of randomised trials.
> - Present the results as follows:
>   - for dichotomous outcomes, present the results of each individual randomised trial as the relative risk with its 95% confidence interval between the common reference and the proposed drug and the main comparator
>   - for time-to-event outcomes, present the results of each individual randomised trial as the hazard ratio with its 95% confidence interval between the common reference and the proposed drug and the main comparator
>   - where there is more than one randomised trial in a set, separately pool the treatment effect between the common reference and the proposed drug, and between the common reference and the main comparator results as the relative risk (or hazard ratio) with its 95% confidence interval, using the random effects model
>   - calculate the indirect estimate of effect as the ratio of relative risks (or the ratio of hazard ratios) with its 95% confidence interval.
> - Clearly document and reference any additional or other methods used to quantify the results of the indirect comparison in terms of magnitude of effect and its 95% confidence interval.

First assess the results for each common reference across the sets of randomised trials for any important differences. This serves as a check of the comparability of the trials — ideally, the results should be similar for similar outcomes measured in similar patients given the same common reference.

When presenting the results for each randomised trial and for the pooled analysis for each set of trials, calculate relative treatment effects. For the indirect treatment effect across the sets of trials, calculate the ratio of relative treatment effects (with its 95% confidence interval). Using relative treatment effects might help to adjust for any differences in the results of the common reference and relies on a usual finding that the relative treatment effect varies to a lesser extent across populations than the absolute treatment effect (including different durations of follow-up; see Part II, Subsection C.1 for further explanation of this finding). A suggested manner of presentation is illustrated in Table B(i).6.1.

Table B(i).6.1   Summary of results of the indirect comparison

Trial ID	Trial(s) of proposed drug			Trial(s) of main comparator			Indirect estimate of effect[c] Indirect RR (95% CI)
	Treatment effect[a] RR (95% CI)	Proposed drug n with event/N (%)	Common reference n with event/N (%)	Common reference n with event/N (%)	Comparator n with event/N (%)	Treatment effect[b] RR (95% CI)	
Trial 1							–
Trial 2							–
Etc							–
Pooled[d]		–	–	–	–		

CI = confidence interval; n = number with event; N = number in group; RR = relative risk
a proposed drug over common reference
b main comparator over common reference
c inferred as proposed drug over main comparator
d pooled using the random effects model

When documenting and referencing any additional or other methods used to quantify the results of the indirect comparison, ensure that the methods are reproducible and able to be independently verified (see Part I, Subsection 6.2). For example, if there are enough randomised trials, meta-regression might also be used to analyse and present indirect treatment comparisons.

Where appropriate, assess the implications for the conclusions of the indirect comparison of excluding trials considered to be less comparable (eg in terms of trial populations or doses). Alternatively, justify, describe and present any other adjustment of the indirect comparison.

Where possible, assess whether there is statistical support for the underlying assumption that there is little variation in the relative treatment effect (see Subsection C.2 for guidance on assessing heterogeneity).

B(i).7 Extended assessment of comparative harms

The presentation of a wider basis of comparative harms is relevant beyond the context of indirect comparisons as well as beyond that of direct randomised trials (see Part II, Subsection B.7).

B(i).8 Interpretation of the clinical evidence

<div style="border: 1px solid black;">

Information requests

- Discuss the results and the interpretation of the indirect comparison cautiously.

- Based on the results of the clinical evaluation, state the category from Part II, Subsection B.8 that best describes the proposed drug.

</div>

Discuss the results and the interpretation of the indirect comparison cautiously, due to the inability to minimise important biases, such as selection bias across the indirect comparison.

Section B(ii)
Clinical evaluation for the main indication: Presenting nonrandomised studies

Introduction

Where relevant, direct randomised trials (as defined in Part II, Subsection B.2) comparing the proposed drug directly with the main comparator are available, their analysis and presentation are preferred as the basis of the clinical evaluation (see Part II, Subsection B). However, in the absence of any such direct randomised trials, the second step in the hierarchy is to determine whether it is possible to present an indirect comparison as defined in Subsection B(i). If this is also not possible, the third step in the hierarchy is to present a comparison across nonrandomised studies, including comparisons across single arms extracted from randomised trials that do not involve a common reference arm.

This Section B(ii) provides guidance on presenting a clinical evaluation based on nonrandomised studies. The information requests are arranged in the same order, with the same issues for assessment of the evidence, as those for the presentation of direct randomised trials. For clarity, submissions should adopt the suggested section headings in the order presented here.

B(ii).1 Description of the search strategies

Information requests

- Broaden the search criteria to identify all other randomised trials and all nonrandomised studies of the proposed drug that recruited participants whose characteristics overlap with those of patients who would be eligible for the main indication.

- Identify all other randomised trials and all nonrandomised studies of the main comparator that recruited participants whose characteristics overlap with those of patients who would be eligible for the main indication.

If neither direct randomised trials nor relevant randomised trials to construct an indirect comparison have been retrieved in response to the systematic searches requested in Part II, Subsection B.1 and Part III, Section B(i).1, the search criteria should be further broadened to identify:

- all nonrandomised studies of the proposed drug that recruited participants whose characteristics overlap with those of patients who would be eligible for the main indication (conducted by, or on behalf of, the sponsor, its head office, its subsidiaries elsewhere and any co-licensing sponsor).

- all nonrandomised studies of the main comparator that recruited participants whose characteristics overlaped with those of patients who would be eligible for the main indication.

Adapt the guidance provided in Part II, Subsection B.1 to describe the search.
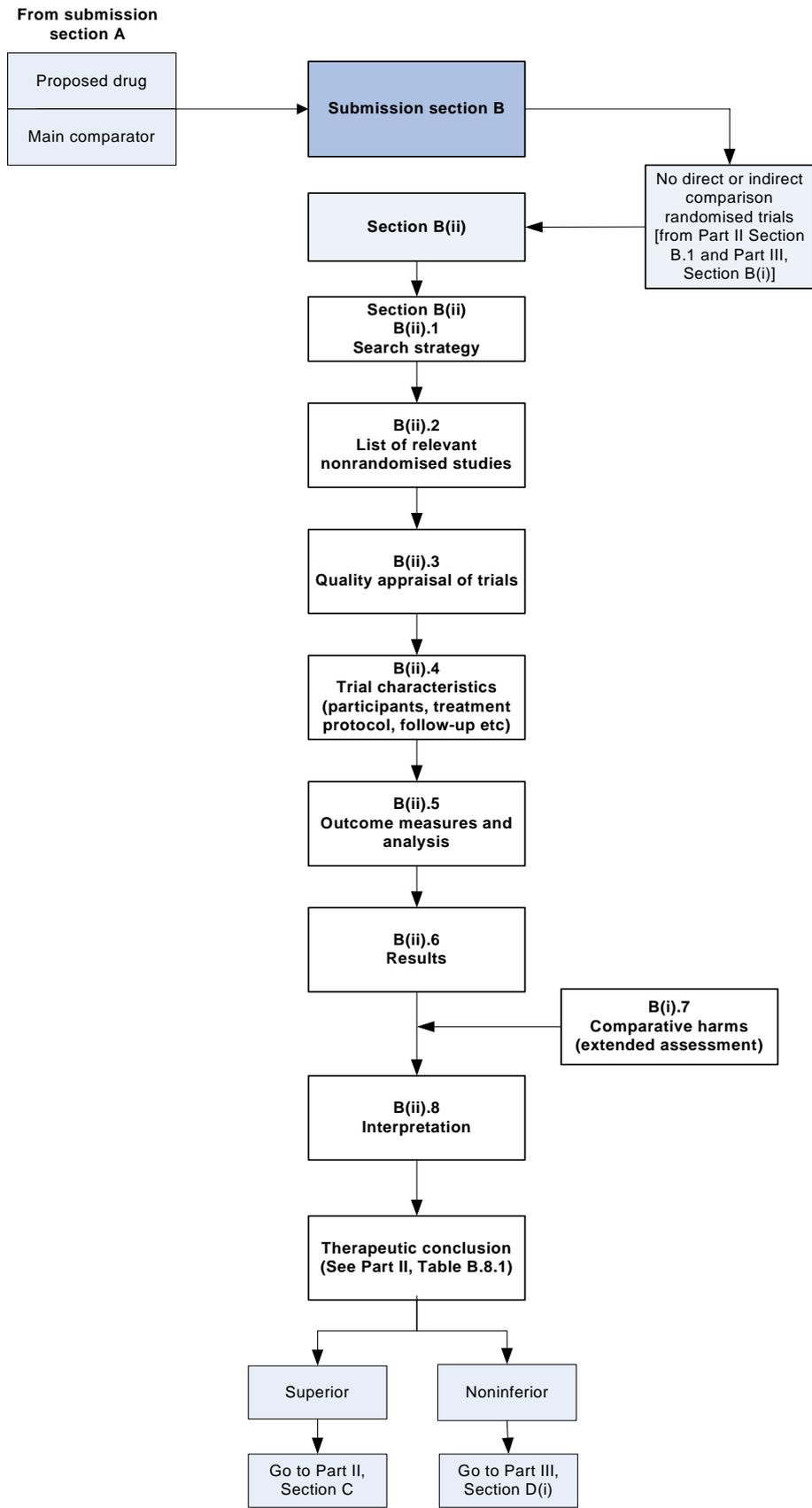
Figure B(ii).1   Key information requests for submission section B of a major submission to PBAC with clinical data from nonrandomised studies

B(ii).2 Listing of all nonrandomised studies

> **Information requests**
>
> - Present tables listing all citations of randomised trials and nonrandomised studies that recruited participants with characteristics that overlap those of patients who would be eligible for the main indication as identified from the expanded searches of the published literature, marketing dossier and other sources. Show the inclusion and exclusion criteria and state which trials have been published.
>
> - Collocate all reports of each randomised trial and nonrandomised study included to create a master list, arranging the studies for the proposed drug and the main comparator. Indicate the preferred identification (ID) for each trial to be used throughout the submission for consistency.
>
> - Before comparing the proposed drug with the main comparator, establish the comparability of the studies, especially for the comparison across studies for the proposed drug and studies for the main comparator. Justify the exclusion of each study deemed noncomparable within each set.
>
> - Include copies (or sufficient details) of the included comparable studies as attachments in the main body of the submission. Include copies (or sufficient details) of the included, but noncomparable, studies in a separate volume of the submission.

Search results

Assess all citations retrieved by the expanded searches to extract all randomised trials and nonrandomised studies that recruited participants with characteristics that overlap those of patients who would be eligible for the main indication. Adapt the guidance given in Part II, Subsection B.2 to present the results of the searches and to list and provide details of all randomised and nonrandomised trials. In addition to the tables presented to establish that there are no direct randomised trials and no basis to construct an indirect comparison, replicate the format of those tables to present the expanded searches for all nonrandomised studies of the proposed drug. A separate table is needed to present the literature searches for all nonrandomised studies of the main comparator (only a single table may be needed, because it is unlikely that the sponsor would have access to any unpublished nonrandomised studies of the main comparator).

Master list of studies

From the tables reporting the results of the expanded searches for the proposed drug, list all identified relevant citations of randomised trials and nonrandomised studies for the proposed drug. Similarly, list all identified relevant citations of randomised trials and nonrandomised studies for the main comparator. Table B(ii).2.1 provides a suggested format for presentation of a master list of all the relevant studies identified in the search.

Presentation of noninferiority (equivalence) studies

If nonrandomised studies are provided to support a therapeutic conclusion of noninferiority or equivalence in Section B(ii).8, adapt the additional guidance in Appendix 5 to identify the preferred approach for the presentation of the studies.

Table B(ii).2.1   Studies (and associated reports) presented in the submission

Study	Description	Reports	Comparable?
Proposed drug			
Single arms of randomised trials			
Unique identifier (ID) of study used in remainder of submission	Brief description of study	Internal study report title. Date. Author(s). Title. Journal Year; Vol(No):pages Author(s). Title. Journal Year; Vol(No):pages	Y/N
ID of study used in remainder of submission	Brief description of study	Internal study report title. Date. Author(s). Title. Journal Year; Vol(No):pages Author(s). Title. Journal Year; Vol(No):pages	Y/N
Nonrandomised studies			
ID of study used in remainder of submission	Brief description of study	Internal study report title. Date. Author(s). Title. Journal Year; Vol(No):pages Author(s). Title. Journal Year; Vol(No):pages	Y/N
Main comparator			
Etc			

Assess comparability of identified studies to justify any exclusions

Before comparing the proposed drug with the main comparator, establish the comparability of the compared sets of nonrandomised studies, including single arms extracted from randomised trials. Given that there is no randomisation step across the comparison of the proposed drug and the main comparator, it is appropriate to consider justifying the exclusion of studies from those included in the list above in order to select similar studies for inclusion in the nonrandomised comparison. Possible grounds for exclusion are provided in Subsection B(i).2.

It is not possible to give unequivocal guidance on the exclusion of studies at this stage. The justification to exclude a study should anticipate whether this would raise issues of selection bias; the justification to include a study should anticipate whether this would raise issues of comparability. If a decision to exclude or include one or more studies is likely to be controversial, it is usually wiser to also present a sensitivity analysis examining whether the decision makes a difference to the conclusions from the overall clinical evaluation.

If one or more studies are to be excluded, identify the aspect(s) of each study that form the reasons for the proposed exclusion (see Table B(ii).2.2). Indicate whether each reason relates to the quality of the studies, the patient characteristics and circumstances of use, the outcomes reported in the trials and/or any other reason. Present greater detail of each aspect (as a minimum, to the extent requested in the relevant text adapted from Section B or Appendix 9). If there is more than one type of reason for exclusion, arrange the studies for exclusion in Table B(ii).2.2 by reason for exclusion.

Table B(ii).2.2   Reasons to exclude each study

Study ID	Ground(s) for seeking exclusion	Details[a]
Quality of the study (see Appendix 10)		
Study 1		
Patient characteristics and circumstances of use in the study		
Study 2		
Outcomes reported in the study		
Study 3		
Other reasons		
Etc		

a Cross-reference each set of details to the source of information (specifying the trial report with page, table, figure number).

Study details

Present the included comparable studies in the main body of the submission and attach a report of each to the main body of the submission. Provide a report of each included but noncomparable study in a separate volume of the submission. Provide clear cross-references between the presentation of the studies and the reports.

B(ii).3 Assessment of the measures taken by investigators to minimise bias in the nonrandomised studies

> **Information requests**
> - For each included comparable nonrandomised study:
>   – categorise into the study type(s) defined below
>   – assess the quality of the study.
> - If the submission includes a number of studies of the same type, tabulate the responses.

As for the assessment of randomised trials, the purpose of the assessments in this section is to provide the sponsor and PBAC with a clear idea of which studies are of greater scientific rigour by assessing the measures taken by the investigators to minimise bias. There is no minimum standard, but PBAC is most likely to be persuaded by the data of the highest scientific rigour.

There may be other aspects of particular nonrandomised studies that might affect the results of such studies and their comparability with different studies of the same type. If these aspects are likely to be important, they should also be identified.

Categorise studies

Nonrandomised studies include:

- classical observational designs such as
  – cohort studies (with concurrent controls)
  – case-control studies

- quasi-experimental designs such as
    - 'before and after' studies
    - case series with historical controls
    - a comparison of the results of two or more single-arm studies.

Single-arm studies may be extracted from randomised trials when there is no common reference on which to construct an indirect comparison.

See Appendix 10 for definitions of each type of study.

Assess quality of studies

Classical community-based epidemiological designs, such as controlled cohort and case-control studies, can be used to estimate the comparative clinical performance of therapy if randomised trials are not available. However, it has been repeatedly shown that such studies are subject to a range of biases that frequently lead to overestimation of the true benefit of the treatment given to the intervention group. Consequently, claims about comparative clinical performance that are based solely on data from such sources will be treated with some scepticism.

Data from the other types of quasi-experimental nonrandomised designs (eg 'before and after' studies, case series with historical controls, comparisons of results of two or more single-arm studies) are subject to major and (often) nonquantifiable biases. Consequently, claims about comparative clinical performance that are based solely on data from these types of analyses will be treated with scepticism.

Some criteria that should be used to assess the quality of nonrandomised studies are provided in Appendix 10. However, these are for general guidance only and might have to be adapted to particular situations. The interpretation of the results of such studies is difficult, and expert epidemiological guidance will be helpful if data of this type are central to the submission.

Tabulate responses

Where there is more than one study of the same type, it is more efficient to present the assessments in a table.

B(ii).4 Characteristics of the nonrandomised studies

> **Information requests**
> - Adapt the guidance given in Part II, Subsection B.4, including the suggested tables, to describe the characteristics of each included comparable nonrandomised study.
> - Indicate when and where each included comparable nonrandomised study was conducted.
> - Compare these aspects of the studies and assess any important differences.

The description of the characteristics of each nonrandomised study should facilitate their comparison across the studies. For studies deemed comparable for the submission, it is particularly important to assess the comparability of the patients included in the studies and the dose regimens used for the proposed drug and, as relevant, for the main comparator.

Similarly, assess how far apart in time and place the studies were conducted. This is necessary because changes in medical practice and patient characteristics might mean that nominally similar therapies may not be comparable when the studies have been conducted at different times or in different geographical regions.

B(ii).5 Outcome measures of the nonrandomised studies

> **Information requests**
> - Adapt the guidance given in Part II, Subsection B.5, including the suggested tables, to present definitions of the patient-relevant outcomes measures, their natural units of measurement and the duration of follow-up when the outcomes were assessed in each included comparable nonrandomised study.
> - Compare and assess any important differences in the outcomes measured across the nonrandomised studies.

When presenting definitions of the study outcomes, the distinctions between primary and secondary outcomes and between primary and secondary analyses are less important in a comparison involving nonrandomised studies.

B(ii).6 Results of the comparison involving nonrandomised studies

> **Information request**
> - Present the results of all patient-relevant outcomes measured, together with their respective 95% confidence intervals.

In general, the results will be in the form of a proportion, a difference in proportions, an odds ratio, or a relative risk. Occasionally, the results will be in the form of a difference in some other response variable (eg forced expiratory volume).

B(ii).7 Extended assessment of comparative harms

The presentation of a wider basis of comparative harms is relevant for a comparison involving nonrandomised studies (see Part II, Subsection B.7).

B(ii).8 Interpretation of the clinical evidence

Information requests
- Discuss the results and the interpretation of the comparison involving nonrandomised studies cautiously.

- Based on the results of the clinical evaluation, state the category from Part II, Subsection B.8 that best describes the proposed drug.

Discuss the results and interpretation of the comparison involving nonrandomised studies cautiously, because of the inability to minimise important biases such as selection bias.

Section C(i)
Translating the clinical evaluation: Guidance in relation to indirect comparisons based on randomised trials or nonrandomised studies

The purpose of this section is to provide guidance on any premodelling studies that might be useful for submissions relying on either indirect comparisons of randomised trials (see Section B(i)) or nonrandomised studies (see Section B(ii)).
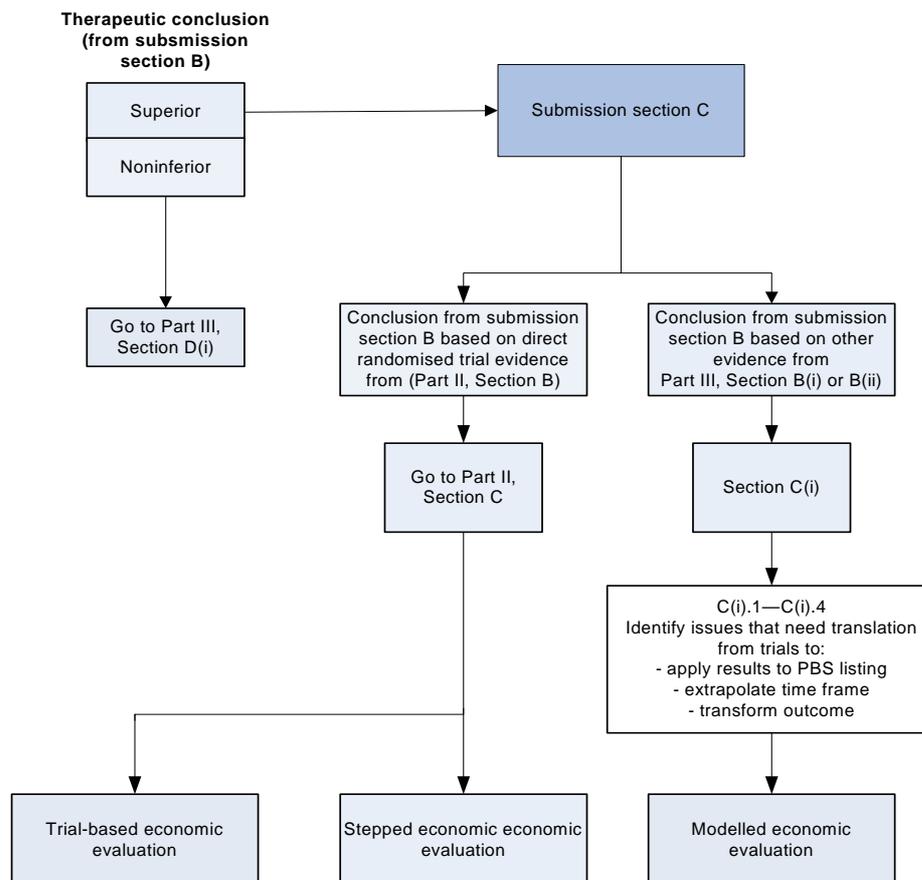
Figure C(i).1   Key information requests for submission section C of a major submission to PBAC with clinical data from an indirect comparison of randomised trials (Section B(i)) or from nonrandomised studies (Section B(ii))

C(i).1–C(i).4   Relevant premodelling studies

> **Information requests**
>
> - Following the format requested in Part II, Section C, present any relevant premodelling studies used to translate the clinical evaluation to the economic evaluation reflecting the population and circumstances of use for the proposed PBS listing.
>
> - Provide copies of all sources of data in an attachment or a technical document (cross-referenced from the main body of the submission) and electronic copies of all computer-based analyses.

Although not all the guidance given in Part II, Section C can be applied to clinical evaluations based on indirect or nonrandomised comparisons, the intention of presenting additional premodelling studies to translate the results to an economic evaluation, presented in submission section C, may still be relevant. That is:

- identify the issue (see Part II, Section C.1)
- present a focused analytical plan (see Part II, Section C.2)
- present the results of the premodelling study (see Part II, Section C.3)
- identify the relationship between the premodelling study and the economic evaluation (see Part II, Section C.4).

If any premodelling studies are performed in this way, the three steps to enhance transparency requested in Subsections D.1 and D.5 may also apply to the economic evaluation for these types of studies.

However, the guidance given in Subsection C.2 on translating the clinical evaluation to the economic evaluation does not usually apply for these types of studies. For example, in these circumstances, there is no basis to guide an assessment of variation in the comparative treatment effect, an extrapolation of comparative time-to-event data or a transformation of a comparative treatment effect on surrogate outcomes to a comparative treatment effect on final outcomes. As a result, in these circumstances, the resulting economic evaluations are generally either modelled without reference to supporting premodelling studies or presented as cost-minimisation analyses.

In presenting the economic evaluation for indirect comparisons of randomised trials in Subsection D.5, also provide the separate incremental cost-effectiveness ratios of the proposed drug against the common reference and of the main comparator against the common reference, together with the results applying the 95% confidence interval of the respective incremental treatment effects. This enables PBAC to confirm that, if the main comparator is therapeutically superior to the common reference and of acceptable cost-effectiveness, an assessment can be made as to whether a similar conclusion can be drawn for the proposed drug.

Sources of information and electronic calculations

Separately provide copies of the original sources of all data (beyond those already presented in response to Section B(i) or B(ii)) in an attachment or technical document.

Cross-reference the extraction of data from each source to the level of the page, table or figure number of the source document.

Also, to enable independent verification of each analysis, provide an electronic copy of any computer-based calculations of the analysis (see Part I, Subsection 6.2).

Section D(i)
Economic evaluation for the main indication: Presenting a cost- minimisation approach

Introduction

The purpose of this section is to present an economic evaluation of substituting the proposed drug for the main comparator in the context of the listing requested. As already described in Subsection B.8 and shown in Figures D.1 and D(i).1, the economic evaluation of the proposed drug initially depends on whether the therapeutic conclusion shows:

- the proposed drug is therapeutically superior to the main comparator, or
- the proposed drug is noninferior (equivalent) to the main comparator.

If the proposed drug has been shown to be therapeutically superior to the main comparator, presentation of the economic evaluation according to Part II, Section D is appropriate. However, if the proposed drug has been shown to be noninferior (equivalent) to the main comparator, cost-minimisation analysis is appropriate (or cost analysis under limited circumstances where the proposed drug is noninferior to the main comparator, but has a superior safety profile that generates cost offsets from reduced use of health care resources to manage adverse reactions).

Cost-minimisation analysis

A cost-minimisation analysis applies when the proposed drug is demonstrated to be no worse (noninferior) therapeutically than other drugs at the same or a lower price. Assuming PBAC accepts the alternative therapies as providing acceptable outcomes in terms of both effectiveness and safety for their cost, a new treatment that offers these outcomes at a lower cost is preferable.

Cost analysis

A cost analysis compares costs only and so is strictly defined as a partial rather than a full economic evaluation, because it does not quantitatively assess comparative costs in a ratio over comparative effectiveness. Although less preferred than a full economic evaluation, cost analyses have sometimes been presented and found to be acceptable if the proposed drug is demonstrated to be no worse in terms of effectiveness but to have a superior safety profile compared with the main comparator.
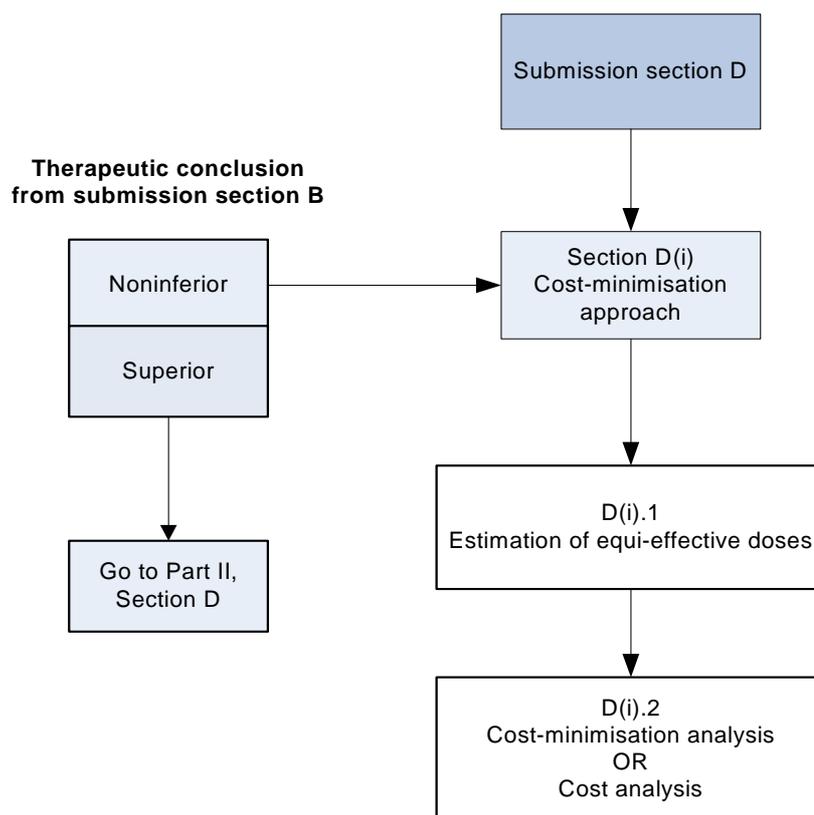
Figure D(i).1   Key information requests for submission section D of a major submission to PBAC in which the is a therapeutic conclusion from section B is noninferior

D(i).1 Estimation of the equi-effective doses

> **Information requests**
> - Calculate the equi-effective doses using the best available evidence from the hierarchy of evidence shown in this section.
> - Address issues that might affect the calculation, such as any plateauing of the dose-response curves and/or a 'ceiling effect'.

Calculation of equi-effective doses

For both types of economic analysis, it is necessary to estimate the equi-effective doses as a first step in estimating the comparative costs.

Calculate equi-effective doses at 'steady state'. In other words, the dose of each drug should be the average dose used by the remaining participants after dose titrations are complete and after excluding participants who discontinue the drug (note that this is similar to the method used to calculate doses from Level 5 evidence). 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/study, the weighted average dose is calculated using the number of participants still on the drug at steady state as the weighting factor. There is no

justification for weighting the doses between trials/studies by the duration of therapy in the trial/study as well as by the number of participants.

It is accepted that, in circumstances where a sponsor does not have access to the primary data from a trial/study, the calculations would be limited to the way the doses are reported in the published report. For example, the average doses might have to be weighted by the number of participants enrolled rather than the number of participants at steady state.

Use one of the following formats as a guide to report the conclusion on the equi-effective dose calculations:

- for doses set by fixed protocols: 'proposed drug 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 drug X mg and main comparator Y mg are equi-effective'.

Hierarchy of evidence

The following hierarchy provides a guide to the preferred approach to calculating equi-effective doses depending on the data available (Level 1 = best).

Level 1: **Direct randomised trials where doses of both drugs are titrated against a response or where doses of both drugs are fixed if the drugs are given in regular clinical practice according to a fixed protocol used in the trials**

This source of evidence is most preferred because it maximises both internal validity by directly measuring effectiveness in a scientifically rigorous study design and external validity by examining dosing practices that reflect regular clinical practice. The design allows the equi-effective doses to emerge from the different dose-response curves reflecting different potencies.

The principle of full follow-up is addressed below under the presentation of the calculations of the equi-effective doses.

Level 2: **Direct randomised trials where doses of one or both drugs are arbitrarily fixed in a way that does not reflect regular clinical practice**

This source of evidence is less preferred than the Level 1 evidence above, because the drugs might not have reached the same point on their respective dose-response curves if the doses are fixed. Present dose-response data for the two drugs 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 both drugs might be better than fixing the dose of just one drug, because the latter introduces a clearly unbalanced approach. Note also that calculating the average dose from a trial in which subjects are randomised to different doses of the same drug 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 drug 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.

Level 3:   **Indirect comparisons of two or more sets of randomised trials involving one or more common reference**

This source of evidence is less preferred than Levels 1 and 2 because indirect comparisons (see Section B(i)) are generally less preferred than direct randomised trials.

Level 4:   **Nonrandomised studies where both dose and effect are measured**

Similarly, this source of evidence is less preferred than the previous three levels for the reasons that indirect comparisons (see Section B(ii)) are generally less preferred than direct or indirect comparisons from randomised trials.

Level 5:   **Nonrandomised studies (including market research data) where dose, but not effect, is measured**

This source of evidence is the least preferred because, whereas the other levels concurrently measure health outcomes to form the basis of a judgment about equi-effectiveness, at this level, different approaches might have to be justified in different circumstances. If doses can be calculated directly from Medicare Australia's Authorities Database, then this would be preferable to market research data (eg IMS or Foresearch), which require extrapolation from sampled data. Market research data are limited to general practitioner prescribing, so ad hoc surveys might be needed for drugs extensively prescribed by specialists. An accurate estimate of the extent of specialist prescribing can be determined by prescriber profiles of PBS drugs. Market research data might also be needed where the same form and strength of drug is used at different doses for more than one indication.

If presenting data from Levels 1 to 4, indicate whether these data are consistent with those recommended in each drug's TGA-approved product information in relation to:

- the doses (and fixed dose regimens where relevant) used
- the methods of titration (eg frequency of titration steps, any thresholds of outcomes used to guide a change in dose, extent of dose variation and duration of titration period).

The defined daily dose from the World Health Organization does not fit in the above hierarchy, but can provide supporting information.

Issues that affect the equi-effective dose calculation

Determining equi-effective doses has proven a difficult issue for several drugs proposed for listing, but it applies primarily in the context of a cost-minimisation analysis. On occasion, this might delay the listing of a product, because a disagreement on equi-effective doses has to be addressed in a resubmission. This is unsatisfactory for both the PBS and the sponsor.

Determining equi-effective doses is unlikely to be difficult where a standard recommended dose is followed with very little variation in doses.

Determining equi-effective doses is difficult when one or both drugs are at the plateau of their dose-response curves. In this circumstance, a large change in comparative dose makes a large difference in comparative cost, but little difference in comparative response.

A related consideration is the likelihood of a 'ceiling effect', in which one but not the other of the drugs has reached the top of its dose-response curve. Where there is evidence to suggest that this has occurred, further consideration needs to be given to whether the drugs are truly equi-effective.

D(i).2 Presentation of a cost-minimisation analysis or a cost analysis

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Information requests

- Present a cost-minimisation analysis (based on equi-effective doses) OR a cost analysis (reflecting management of adverse reactions) .

- Provide copies of all sources of data in an attachment or a technical document (cross-referenced from the main body of the submission) and electronic copies of all computer-based analyses.

Cost-minimisation analysis based on determining equi-effective doses

When the proposed drug is regarded as therapeutically noninferior to its main comparator in terms of both effectiveness and safety, the appropriate type of economic evaluation is a cost-minimisation analysis. That is, the difference between the proposed drug and the main comparator is reduced to a comparison of costs. Effectively, this means that the proposed drug is unlikely to be granted a price advantage over the main comparator and any restrictions applying to the main comparator and any other already-listed drugs within the reference group of the main comparator would apply to the proposed drug, consistent with the position outlined in Appendix 2.

Such a submission need only present an abbreviated submission section D, except where there are differences in the costs of prescribing or administering the two alternatives. Take particular care to justify any decision to model a therapeutic difference due to a factor that is excluded in the trials. Only rarely has a model been accepted that contradicts a conclusion from the evidence of randomised trials that fail to detect a statistically significant therapeutic advantage when designed to do so.

If the conclusion of noninferiority is not also supported by clinical data that enable a judgment regarding equi-effective doses, the submission will be difficult to evaluate. See Subsection D(i).1 for the preferred approach to calculating equi-effective doses.

No other cost consequences

If no other cost consequence is anticipated, consult the Pharmaceutical Benefits Pricing Authority Secretariat, as necessary, for the calculation of drug prices from equi-effective doses.

Cost consequences related to the provision of resources

Listing a therapeutically noninferior drug might have cost consequences related to its differing mode of administration. These have sometimes arisen if the proposed drug and its main comparator are available in different forms (eg tablets, injections, implants and infusions). If this applies in a submission, identify the types of other resources affected, estimate the extent to which the quantity of each type of resource provided would change (in its natural units of measurement) following a listing, and multiply by the appropriate unit costs. Aggregate this with the drug cost impact based on the equi-effective doses to estimate the net cost impact within the cost-minimisation analysis. See also the *Manual of Resource Items and their Associated Costs*.

Cost analysis to reflect cost consequences related to management of adverse reactions

If the proposed drug is demonstrated to be no worse in terms of effectiveness but to have a superior safety profile compared with the main comparator, a price advantage for the proposed drug over its main comparator could rely solely on a reduction in the costs of managing adverse reactions due to the more favourable safety profile.

The generally preferred approach would be to compare also the improved health outcomes due to this safety advantage with the associated incremental costs in a cost-consequence, cost-effectiveness or cost-utility analysis (see Part II, Subsection D.1). However, cost analyses have sometimes been presented and found to be acceptable in these circumstances. The cost analysis could be presented to quantify a claim that the costs offsets from the reduction in resources provided to treat the adverse events avoided are sufficient to reduce the incremental cost to zero or a negative value. In a cost analysis, the extent of the health impact would not be assessed other than to estimate the extent to which the identified types of other resources are reduced. The associated costs would be aggregated with the drug cost impact based on the equi-effective doses to estimate the net cost impact. See also the *Manual of Resource Items and their Associated Costs*. The economic claim could be that, at the price requested, the overall cost of therapy with the proposed drug is the same or less than the overall cost of therapy with the main comparator.

Sources of information and electronic calculations

Separately provide copies of the original sources of all data (beyond those already presented in response to Section B(i)/B(ii))) or expert opinion used in the model in an attachment or technical document. Cross-reference the extraction of data from each source to the level of the page, table or figure number of the source document.

Also, to enable independent verification of each analysis, provide an electronic copy of any computer-based calculations of the analysis (see Part I, Subsection 6.2).

Section E(i)
Estimated extent of use and financial implications: Market-share approach

Introduction

Utilisation and financial estimates can be developed from either an epidemiological or market-share basis. The introduction to Part II, Section E provides some advice on when each approach may be preferred or when presenting both approaches may be informative. Information requests for a stepwise presentation of the epidemiological base are presented in the remainder of Part II, Section E. Requests for the same stepwise presentation of the market-share base are provided in Subsections E(i).1–E(i).6, below and shown in Figure D(i).1. Appendix 9 shows further derails of the steps in each process and the relationship between the epidemiological and market share approaches.

The market and market growth rate

A market-share base might be preferred to generate the utilisation and financial estimates if (in response to Part II, Section B.8) the submission concludes that, overall, the proposed drug is no worse than (ie noninferior to) its main comparator(s). This decision parallels the cost-minimisation approach that would be taken in submission section D (see Section D(i)). The market-share approach first estimates the extent of the current market represented by the main indication and consequently the share likely to be taken by the proposed drug.

Compared with the epidemiological approach, the market-share approach allows an abbreviated presentation of information, where justified as being appropriate or to provide an alternative way of generating estimates to compare with the epidemiological basis.

The key issue with estimates built on the market-share basis is whether the current market or the current market growth rate is expected to increase as a result of listing the proposed drug on the PBS. If not, a drug listed on a cost-minimisation basis would usually have a negligible impact on the net financial cost to the PBS, and this simplifies the information to be provided in submission section E to support that expectation. Exceptions to this simplification include:

- substitution for PBS drugs other than those included in the reference group against which the proposed drug is to be listed on a cost-minimisation basis and thus where a price differential might be expected

- situations in which the proposed drug has a price advantage that is justified in response to submission section D by relying on cost offsets from reductions in the use of non-PBS resources to achieve listing on a cost-minimisation basis

- situations in which a cost analysis is presented in response to submission section D where a price advantage for the proposed drug is justified from reductions in the use of non-PBS resources due to a more favourable safety profile.

In each of these three circumstances, or if the proposed drug is likely to increase the market or to increase the rate of growth of the market, it is informative to estimate the extent to which listing the proposed drug is likely to increase the overall market for the group of drugs (or the extent to which the proposed drug is likely to increase the current growth rate of the overall market).

The market-share approach should rely on drug utilisation data or studies for currently available drugs likely to be substituted by the proposed drug to generate estimates of expected utilisation and costs.

Therapeutic conclusion from submission section B

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│     Noninferior     │──────────────────────►┌──────────────────────────┐
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│      Superior       │                       └──────────────────────────┘
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│  Epidemiological    │                        │   Market-share approach  │
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│     Section E       │                        │        sources           │
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                                               │          E(i).2          │
                                               │ Use and costs of proposed│
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                                               │    further details)      │
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                                               │          E(i).3          │
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                                               │ Financial implications   │
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Figure E(i).1   Key information requests for submission section E of a major submission to PBAC using the market share approach for estimating the extent of use and financial implications

Excel workbook

The standardised Excel 2003 workbook described in Part II, Section E is not designed for the market-share approach. However, the general approach could be adapted as follows.

- The first spreadsheet, relating to Subsection E(i).1, summarises all the background information, primary (not calculated) variables and assumptions essential to the calculation of results presented.

- The second spreadsheet, relating to Subsection E(i).2, calculates the results for the current market, the projected extent of uptake of the proposed drug and the change in the numbers of patients treated where appropriate.

- The third spreadsheet, relating to Subsection E(i).3, calculates the results for the extent of substitution of current drugs.

- The fourth spreadsheet, relating to Subsection E(i).4, calculates the net financial implications for the PBS/RPBS and summarises any sensitivity analyses addressing uncertainty discussed in Subsection E(i).6.

- Subsequent spreadsheets relating to Subsection E(i).5 can be used as necessary.

In some circumstances, a simpler approach might be appropriate, especially if the current market size or market growth rate is not expected to change as a result of listing the proposed drug.

E(i).1 Justification of the selection of sources of data

The guidance in Part I, Subsection E.1 is relevant here. The main sources of relevant data for the market-share approach are the PBS data including those supplied by Medicare Australia and data for under-co-payment use of PBS-listed drugs by general beneficiaries, which can be estimated from several sources.

E(i).2 Estimation of use and costs of the proposed drug

Information requests
- Indicate whether the market or the market growth rate will increase as a result of listing the proposed drug.

- Estimate the number of packs dispensed for each form and strength of the proposed drug in each year over five years (disaggregated into proportions for PBS and RPBS, and by beneficiary type).

- Estimate the number of patients likely to take the proposed drug.

- Estimate the costs for each form and strength of the proposed drug (and the aggregated cost for the proposed drug) in each year over five years.

- Present all calculations and results in an Excel workbook similar to the one provided for the epidemiological approach.

Number of packs dispensed and patients treated

Estimate the number of packs dispensed in the most recent 12 months of the current relevant PBS market. Base this estimate on Medicare Australia data, supplemented as appropriate with data from other sources to estimate the contribution of usage by general patients whose co-payment equals the cost of the drug and so does not attract a direct PBS subsidy (under-co-payment usage).

Estimate the rate of growth in this market over the next five years from listing and present this in periods of one year (or more frequent if needed for the calculations). This should be based on historical trends in the market, adjusted for known influences on the market other than the listing of the proposed drug.

Estimate the rate of substitution in this market by the proposed drug in each year over five years. If more than one rate of substitution is expected across the market, break down the overall PBS market into segments of the market, one for each different rate of substitution. If the rate of substitution across the market also varies by year, a further breakdown into years might be required.

Estimate the proportion of each other PBS item substituted as the reduction in the rate of its use in the context of the growth of the overall PBS market.

Estimate the rate in each year over five years of any additional growth in the overall market due to listing the proposed drug as the proportion of use of drug beyond the use that substitutes for other PBS-listed drugs. From this information, back-calculate the numbers of extra patients to be treated in each year over five years unless this rate is zero for each year over five years. Also estimate the number of packs of the proposed drug dispensed for each year over five years.

Disaggregate these estimates into each form and strength of the proposed drug.

Divide each into proportions for the PBS and the RPBS, each divided into proportions by beneficiary type.

Costs over five years

In this way, estimate the costs of each form and strength of the proposed drug in each year over five years, multiplying by the following unit costs for each form and strength and then for the proposed drug overall, each by the following unit costs:

- dispensed price for maximum quantity (DPMQ)
- DPMQ, each with appropriate patient co-payment removed.

For these calculations, use constant prices, make no allowance for inflation and use a zero discount rate.

E(i).3 Estimation of changes in use and cost of other drugs

> **Information request**
> - Estimate the aggregated costs of each form and strength of each affected drug (and then the aggregated cost for all affected drugs) in each year over five years.

Similarly, also estimate the number of packs of other affected PBS items each year over five years, each disaggregated into each form and strength, with each of those divided into proportions for RPBS and PBS, and each of those divided into proportions by beneficiary type.

Thus also estimate the costs of each form and strength of each affected other PBS drug in each year over five years, multiplying by the following unit costs for each form and strength and then for the affected drugs overall, each by the following unit costs:

- DPMQ
- DPMQ, each with appropriate patient co-payment removed.

For these calculations, use constant prices, make no allowance for inflation and use a zero discount rate.

E(i).4 Estimated financial implications for the PBS/RPBS or the NIP

> **Information request**
> - Estimate the net financial implications for the PBS and the RPBS (or the NIP) in each year over five years.

Estimate the net financial implications in each year over five years, calculated by subtracting the net implications of costs estimated in Subsection E(i).3 from the costs estimated in Subsection E(i).2.

E(i).5 Estimated financial implications for government health budgets

> **Information requests**
> - Estimate the extent of net change in the number of prescriptions processed by Medicare Australia for payment (and, where appropriate, the net change in the number of authorisations by Medicare Australia) in each year over five years.
> - Estimate the net financial implications for Medicare Australia in each year over five years.
> - Estimate the net financial implications for each affected MBS item in each year over five years.
> - Estimate the net financial implications for government health budgets in each year over five years.

Responding to this section is informative where any increase in the rate of growth in the overall market due to listing the proposed drug is expected to impact on the costs for

Medicare Australia by increasing the numbers of prescriptions processed and/or the numbers of authorisations required.

Also, where any increase in the rate of growth in the overall market due to listing the proposed drug is expected to increase the frequency of accessing MBS services and/or there is a net impact on the costs of administration; that is, if a cost-minimisation analysis or cost analysis is presented in submission section D (see Section D(i)) involving MBS services. In these situations, estimate the costs to the MBS in each year over five years for each type of MBS item affected and then to the MBS overall, calculated by multiplying by the appropriate unit costs for each MBS item identified: (a) the schedule fee; and (b) the appropriate benefit (ie with the appropriate patient co-payment removed to thus estimate the net financial implications to the Australian Government health care budget of the changes in each year over five years).

E(i).6 Identification, estimation and reduction of uncertainty

The guidance in Part I, Subsection E.6 is relevant here. The main uncertainties with the market-share approach are the projected growth rate in the market (overall and in relation to particular drugs within it), the extent of any change in the growth rate as a result of listing the proposed drug and the extent of substitution rate(s).

PART IV

INFORMATION REQUESTS FOR SPECIFIC PRODUCT TYPES

Product type 1   Fixed combination products

Introduction

This section applies to a submission for a fixed combination of active component products seeking subsidisation under the PBS and the National Immunisation Program (NIP). It applies both to a combination of products in a single dosage form and to individual dosage forms in a composite packaging.

However, this section does not apply to drugs that — for specific indications — are almost invariably used together in fixed dose combinations for clinical reasons, such as oral contraceptives, hormone replacement therapy and *Helicobacter pylori* eradication regimens.

The labelling of the combination product should clearly identify the component generic products.

PT1.1 Matters to consider for fixed combination products

Information requests

- Comply with all information requests in Parts I–III of these guidelines, where applicable.

- Provide information as part of the response to Part II, Subsection A.2 to show that the combination product has been approved by the TGA, or is recommended for approval by the TGA, and meets all clinical criteria required by the TGA. Confirm that any requested restriction is consistent with any restriction for each component of the combination product.

- For each component of the combination product, provide information as part of the response to Part II, Subsection A.3 to show that:

    – it is (preferably) listed on the PBS or funded on the NIP

    – the doses are consistent with the doses of the combination product.

- Also as part of the response to Part II, Subsection A.3, show that listing the combination product would not result in:

    – inappropriate dosing of either component (eg the combination product should not contain components for which individual dose titration is preferable)

    – unnecessary proliferation of products or dose forms.

- As part of the response to Part II, Subsection A.4, identify the main comparator products and explain the reasons for the selection of these comparators.

- Provide data as part of submission section B to show additive (not necessarily synergistic) beneficial effectiveness of the components.

Identifying the main comparators

More than one comparison should usually be presented for a combination product, such as a combination of the following:

- the combination product against its components given concomitantly as the basis for a cost-minimisation recommendation (this need not apply where the combination product consists of the individual dosage forms in a composite packaging)

- the combination product (or its components given concomitantly) against each of the component products given alone as the basis for establishing at least an additive beneficial effectiveness (or the basis to establish no loss of beneficial effectiveness of the components in the case of fixed combination vaccine products; see Part IV, Product type 3), thus involving at least two comparisons depending on the number of components in the fixed combination product

- the combination product against the therapy that prescribers would most replace in practice, should this be expected to vary from the current concomitant use of the individual components.

Pricing of fixed dose combination products

If the request for listing is on a cost-minimisation basis against the component products, the pricing of a combination product would normally be no greater than the sum of its individual components (at the current price to pharmacist level for PBS products or at the Commonwealth price for NIP products), usually calculated on a per milligram basis.

Where the combination product(s) are expected to substitute for two or more strengths of the component products, the price to pharmacist should reflect the sum of the individual components as a function of the expected proportions of substitution.

Support any request for a price advantage with evidence of acceptable cost-effectiveness via improved health outcomes or acceptable cost offsets.

Effectiveness and cost-effectiveness

A demonstrated health outcome advantage with acceptable cost-effectiveness will provide support for listing.

An additive effect of the combination could be demonstrated with reference to:

- the same surrogate outcome, such as blood pressure or forced expiratory volume

- in the case of fixed combination vaccine products, no loss of beneficial effectiveness of the components across different diseases or strains of pathogens (see Part IV, Product type 3).

Where advantages in patient convenience resulting in improved health outcomes or cost offsets to the Australian Government health budget (the PBS, the NIP or the Medicare Benefits Scheme — MBS) or the patient are claimed, they should be demonstrated.

Where improved compliance is used as an argument for improved health outcomes, data should be provided.

Product type 2   Nutritional products

Introduction

This section applies to submissions for nutritional products seeking subsidisation under the PBS. It includes requests for general additional information relating to nutritional products, and additional information for specific medical conditions. This section also provides additional guidance for identifying the main comparator in relation to nutritional products.

These additional requests for information are not exhaustive, but seek to clarify the particular needs of PBAC and its Nutritional Products Working Party (NPWP), which advises PBAC on submissions for nutritional products.

PT2.1 General requests for additional information

Information requests

- Comply with all information requests in Parts I–III of these guidelines, where applicable.

- As part of the information included in response to Part II, Subsection A.1:

  – provide a list of all ingredients in the product proposed for listing, including, in the case of a product for allergy or intolerance, the origins of the ingredients

  – confirm that the proposed product complies with the latest published draft *Australia New Zealand Food Standards Code — Standard 2.9.5: Food for Special Medical Purposes*

  – justify the requested maximum quantity and repeats for the proposed product

  – present a table(s) comparing the nutrient contents of the proposed product with those defined in relation to the recommended dietary intakes (RDIs)

  – present a table comparing the contents of the proposed product with the nutritional needs of the patients who would be eligible to receive it, referring to the standard amount of the key nutrient

  – identify (i) where the proposed product is used in conjunction with other foods; and (ii) where this is the case, the percentage of nutrients provided by the proposed product as proportions of a strict dietary regimen (examples of different circumstances for specific medical conditions are provided in Subsection PT2.2).

- As part of the information included in response to Part II, Subsection A.3, 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.

- As part of the information included in response to Part II, Subsection A.4, include a description of the main comparator product(s).

Response to Part II, Subsection A.1

Subsection A.1 of a major submission includes details about the proposed drug and its expected use on the PBS. For nutritional products, information should be provided about all the ingredients. In the case of products that will be used to overcome allergies or food intolerances, this should include information on the origin of the ingredients.

The *Australia New Zealand Food Standards Code — Standard 2.9.5: Food for Special Medical Purposes* (under development)[21] sets out the requirements under these standards for foods that have medical purposes. Part II, Subsection A.1 of the submission should confirm that these requirements have been met.

Maximum quantity and repeats

The requested maximum quantity and repeats for the proposed product should be justified based on the understanding that this is 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 reverse proportion to the amount of regular foods tolerated.

Tables of RDIs and nutritional needs of patients

Australian RDIs are listed in *Nutrient Reference Values for Australia and New Zealand.*[22]

The tables of nutritional contents should allow an assessment to be made of whether the proposed product and its main comparator product(s) provide the required amount of key nutrient for patients for whom the proposed product is intended. This assessment should include (as applicable) the following age ranges:

- infants younger than one year

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[21]

http://www.foodstandards.gov.au/standardsdevelopment/proposals/proposalp242foodsforspecialmedicalpurposes/index.cfm

[22] http://www.nhmrc.gov.au/publications/_files/n35.pdf

- children 1–2 years
- children 2–5 years
- children 5–10 years
- older children 10–15 years
- adolescents 15–20 years
- adults (older than 20 years).

The age used should be the mid-point of the age range. For the nonadult age ranges, the nutrient calculations should be compared for a child whose weight is on the 50th percentile for weight using accepted growth charts.[23] For the adult age range, pregnancy and lactation tables should also be included for the product, unless the product is unsuitable for pregnant or lactating women.

Comparison of proposed product against nutritional needs of patients

For the comparison of the composition of the proposed product against 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 *Australian New Zealand Food Standards Code — Standard 2.9.1: Infant Formula Products*.[24]

Response to Part II, Subsection A.4

The description of the main comparator products(s) should be based on a relevant amount of nutrient in relation to the RDI, rather than to the total product volume. As an example, for an amino acid formula, this description for comparative purposes should be based on a stated protein equivalent, not 100 g of the comparator products.

Response to Part II, Section B

Section B of a major submission for a nutritional product should include comparative randomised trial or other study data, as that described in Part II, Subsections B.1–B.8, or Part III, Section B(i) or B(ii), as appropriate. 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 submission section B.

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[23] For example, http://www.who.int/childgrowth/standards/en/ and http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm .
[24] http://www.foodstandards.gov.au/thecode/foodstandardscode.cfm

PT2.2   Additional information requested for specific medical conditions

> **Information requests**
>
> A submission for the PBS to subsidise a product for use in the management of one of the following conditions should provide the additional information requested in this section in response to Part II, Subsection A.1:
>
> * multifood allergy
>
> * monosaccharide intolerance
>
> * weaning from total parenteral nutrition (TPN) to formula
>
> * patients requiring ketogenic diets
>
> * infant formula products, such as a formula used in infants younger than 12 months.

Multifood allergy

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

Monosaccharide intolerance

Confirm that the formula of the proposed product will supply the initial protein, energy, fatty acid, vitamin and mineral requirements for the patient, noting that such a child, at least initially, may need to obtain 100% of the RDI of the identified nutrients, which may be elevated to permit catch-up growth, via the product. These needs will change as recovery occurs.

Weaning from total parenteral nutrition (TPN) to formula

Confirm that the formula of the proposed product will supply incremental increases in protein, energy, fatty acid, vitamin and mineral requirements until full 100% RDI nutrient intake is achieved enterally. Formula can be gradually reduced as foods are introduced.

Patients requiring ketogenic diets

Confirm that the formula of the proposed product will supply the patient's protein, vitamin and mineral requirements. For this to occur, the formula should be multi-ingredient and individually calculated, and a fat source will need to be added (such as Calogen or Liquigen oil emulsions), together with a small prescribed amount of carbohydrates. Patients who can eat foods would need less or no formula after about four years of age.

Infant formula products, such as a formula used in infants younger than 12 months

Present a table comparing the proposed product with the requirements of the *Australian New Zealand Food Standards Code — Standard 2.9.1: Infant Formula Products* (see Subsection PT2.1) 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.

PT2.3 Additional guidance for identifying the main comparator

In theory, and consistent with other types of products proposed for subsidy on the PBS, the main comparator for a nutritional product is the therapy that prescribers would most replace in practice. In some cases, comparisons with more than one comparator will be necessary or will provide the NPWP and PBAC with sufficient information on which to base their recommendations.

The information in the following sections will help sponsors of nutritional products to select the appropriate main comparator product(s).

Existing products with similar mechanisms of action

If the proposed product is in a class that contains other, already-listed dietary supplements with the same or similar mechanism of action, the main comparator would usually be the product in the class that is prescribed on the PBS for the largest number of patients in the appropriate age group. A comparison with a more appropriate form (similar in mechanism of action), not necessarily subsidised on the PBS but available internationally, might provide the NPWP and 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 it has a new or additional mechanism of action), the main comparator would usually be the product that is prescribed on the PBS to treat that indication for the largest number of patients in the appropriate age group. If there is no similarly listed PBS product, a comparison with any other alternative product for which data exist might help the NPWP and PBAC in making an assessment of the proposed product's clinical effectiveness and safety. However, such a comparison would not necessarily inform the economic factors involved in considering the proposed product.

No currently listed products

If no currently listed product is available, the main comparator would usually be standard medical management (this could include special dietary restrictions). This should be clearly and consistently defined in both the submission and the comparative randomised trials.

Product type 3   Vaccine products

Introduction

This section applies to submissions for vaccines seeking listing under the PBS or seeking funding under the NIP.

These additional requests for information are not exhaustive but are to clarify the needs of PBAC when applying the general approach of these guidelines to the specific circumstances of vaccines. They are not an alternative set of requests, so comply with all information requests in Parts I–III of these guidelines where applicable.

The order of this section follows the order of the main submission sections of these guidelines.

PT3.1   Details of the proposed vaccine and its intended use on the PBS or NIP (submission section A)

Pharmacological class and action (Part II, Subsection A.1)

Information requests

- Provide the following information:
  - number, identification and amounts of antigens (components) in the proposed vaccine
  - formulation of the proposed vaccine
  - any information about any expectation of a limited initial supply, where relevant.
- Present other relevant characteristics, such as the disease to be prevented by the vaccine, and the defining characteristics of the vaccine, which include:
  - whether the immunising agent is live, attenuated or killed, whether it is absorbed or non-absorbed, and whether it is viral or bacterial
  - a description of any cold storage requirements that might apply to its distribution
  - a description of the external dimensions of the vaccine packed for storage.

Section IV, Product type 1 gives details of the additional information requirements of submissions containing fixed combination vaccine products. As mentioned in Subsection PT1.1, 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.

Indications and requested restrictions (Part II, Subsection A.2)

Information requests

- Indicate whether the submission is for listing on the PBS or funding under NIP, with a rationale.

- Explain and justify any restrictions on subsidised use of the proposed vaccine to certain populations, seasons, geographical distributions and ethnic groups.

- Describe any requested PBS restriction or NIP scheduling in relation to the TGA-approved indication and also the *Australian Immunisation Handbook*, with an explanation and justification for any discrepancies. Where the relevant indication or part of the handbook is not finalised, refer to the latest draft version and any other relevant advice about any anticipated changes to the draft.

- If a catch-up program is also requested, define and justify its duration from commencement of the overall funding arrangement and its extent in terms of extra targeted population groups.

- Explain the relationship between the proposed vaccine and vaccines currently available on the NIP (or the PBS, as relevant) in terms of both their antigen content and their dosage schedules (see also additional requests below in relation to Part II, Subsection A.4).

PBS listing/NIP funding

Several factors affect whether vaccines will be listed on the PBS or be funded under the NIP. A vaccine should generally be proposed for funding under the NIP where there is expected to be an additional health benefit to the community beyond the individuals vaccinated, which would be improved by maximising coverage rates of the proposed vaccine in the identified individuals.

More specific considerations favouring a submission for NIP funding include the following:

- The target for the proposed vaccine is a broader population in which there is either no need to assess risk factors for the disease in each individual, or the assessment of risk factors at an individual level is straightforward (eg age, sex, ethnicity, geography).

- There is a reason to maximise population coverage of the proposed vaccine because the proposed vaccine reduces one or more of:

  – the proportion of susceptible individuals

  – carriage of the pathogen(s) affected by the vaccine

  – transmission of the infection (including nosocomial infections or reducing the rate or extent of spread of infections in other institutional settings, such as child care centres, schools or nursing homes).

Integral to these specific considerations are as follows:

- The proposed vaccine protects against a new infection or reactivation of an existing infection.

- The efficacy of the proposed vaccine is sufficient to achieve one or more of the reductions identified in the second bullet point, above (eg reductions in the proportion

of susceptible individuals, carriage of the pathogen affected by the vaccine, or transmission of the infection).

- The disease is sufficiently severe or prevalent in an unimmunised population to justify maximising the use of the proposed vaccine in order to achieve its full community health benefit.

- The proposed vaccine needs only to be delivered as a single dose or a few doses.

An additional factor that might be considered in supporting a request for funding under the NIP is the existence of claimed advantages of increasing herd immunity, particularly where those advantages are supported by clinical evidence (see additional requests below in relation to Part II, Subsection D.3 for the presentation of such advantages and evidence).

PBS listing might be favoured when the proposed vaccine is 'discretionary' for the majority of the population (eg to vaccinate an individual against a disease that is not sufficiently prevalent in Australia to justify maximising the use of the proposed vaccine), or the assessment of risk factors is less straightforward (eg an assessment of immune system status is required).

A vaccine may be simultaneously listed on the PBS and funded under the NIP for different indications.

Restrictions

Given that the target for the proposed vaccine is a broad population, a restriction under the NIP should involve a straightforward assessment of risk factors at an individual level (eg age, sex, ethnicity, geography). The usual aim is to vaccinate all eligible individuals once they reach the age range specified for the eligible population, which results in an ongoing primary program. Where a more complex assessment of risk factors for the disease in each individual is required, a restriction under the PBS would be more appropriate.

Catch-up program

A catch-up program provides coverage of individuals who could benefit from vaccination at the introduction of a new program, but who are older than the age range specified for efficient delivery of the ongoing primary vaccination program. A catch-up program might also provide for a faster onset of any herd immunity generated by the vaccine (see Subsection PT3.4 below). A catch-up program may be considered appropriate by the Australian Technical Advisory Group on Immunisation (ATAGI).

Describe the arrangements for any requested catch-up program(s) and compare them with those of the requested ongoing primary vaccination program. Justify the selection of the requested age range(s) of eligible individuals within these programs (and any other characteristics of the eligible individuals) and the requested duration(s) of the programs (and any other features of the programs). See also Subsection PT3.4 below.

Relationship with other listed vaccines

A new vaccine program funded under the NIP should integrate with current programs as much as possible to maximise coverage and efficient delivery of the overall vaccination schedule.

Treatment details (Part II, Subsection A.3)

> **Information requests**
>
> - Specify the proposed schedule of administration of the vaccine, including details of doses 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).
>
> - Where appropriate, discuss whether a vaccination course that begins with the proposed vaccine can be completed with a competing vaccine (or vice versa).
>
> - Identify and justify any differences from treatment recommendations in the TGA-approved product information or the *Australian Immunisation Handbook* (or the latest draft version of either document where these are not finalised).
>
> - Specify any new or additional requirements that are likely to have an impact on the financial implications of listing the proposed vaccine.
>
> - Indicate when such programmatic requirements are expected to extend to also include other particular delivery systems (which might vary across states and territories), such as through clinics, community centres and schools.
>
> - Specify whether the proposed vaccine is to be available as a substitute for existing products or is to be added to current arrangements for either the NIP or the PBS.

The *Australian Immunisation Handbook* is published every two or three years by the National Health and Medical Research Council following its preparation by ATAGI.[25] 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.

Main comparator (Part II, Subsection A.4)

> **Information requests**
>
> - Define the main comparator in terms of the current approach to preventing the disease to be prevented by the proposed vaccine that is likely to be most replaced in practice.
>
> - Where the defined main comparator is an alternative vaccine, identify differences between the vaccines (use a table, if appropriate).

If there is an alternative vaccine available on the NIP or PBS, this will usually be the main comparator. If an alternative vaccine is not currently funded, the advice of the department (see page iv) may be sought. If there is currently no vaccine available, the main comparator would usually be standard medical management.

Where the main comparator is an alternative vaccine, present a table if this would assist in comparing the content and characteristics of the vaccines (eg the antigens attenuated by the vaccines, the strength of the vaccines, the scheduling of doses, the routes of administration and the fit with the current vaccine schedule). If a table comparing vaccine content and characteristics is presented, and if the trials presented in submission section B use other vaccines, consider including those other vaccines in the comparative table.

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[25] *The Australian Immunisation Handbook*, 8th edition (2003). National Health and Medical Research Council, Canberra, 2003.
http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/handbook03

PT3.2 Clinical evaluation for the main indication (submission section B)

Assessing noninferiority between a vaccine combination product and its components (Part II, Section B, or equivalent)

> **Information request**
> - 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.

As discussed in Subsection PT1.1, the components of vaccine combination products should have an additive (not necessarily synergistic) beneficial effectiveness — for vaccines that combine antigens, this means that there should be no loss of beneficial effectiveness of each of the components. For example, if there is any reduction in titres for any components of the proposed combination vaccine product compared with its individual component products, the noninferiority assessment would be whether this would be expected to reduce the overall vaccine effectiveness to a clinically important extent. Appropriate evidence comparing the fixed combination vaccine product with each of its individual components would usually be required as part of the response to Part II, Subsections B.1–B.8, or Part III, Section B(i) or B(ii). Further guidance on assessing noninferiority is given in Appendix 5.

Outcome measures (Part II, Subsection B.5 or equivalent)

> **Information request**
> - Provide any regulatory standards for immunogenicity outcomes that would inform the interpretation of the clinical importance of these surrogate outcomes in relation to directly patient-relevant final outcomes.

The interpretation of immunogenicity outcomes is particularly important in the context of a conclusion of therapeutic superiority, or if they are the primary outcomes of the trials.

Assessment of comparative harms (Part II, Subsections B.6 and B.7 or equivalent)

> **Information requests**
> - As vaccines are generally given to a 'well' population, describe potential harms adequately, including, as part of the information included in response to Subsection B.6, how adverse events were ascertained in the trials.
> - Provide any information on adverse reactions that might have arisen following any launch of the proposed vaccine in other markets as part of the information included in response to Subsection B.7.

The assessment of comparative harms should extend beyond those temporally associated with the administration of the vaccine to those that might emerge some time after the vaccine course is completed. This might include the consequences of possibly delaying rather than preventing the disease, in addition to adverse reactions to the vaccine.

PT3.3 Translating the clinical evaluation to the listing requested for inclusion in the economic evaluation (submission section C)

Information requests

- As appropriate, apply the clinical evaluation to any different population identified in the request for listing, including for a catch-up program.

- Establish and describe the basis to transform immunogenicity outcomes reported in the clinical evaluation to patient-relevant outcomes where such outcomes are the primary outcomes of the trials or where the outcomes are otherwise important to the submission.

- Provide any regulatory standards for immunogenicity outcomes that would inform the transformation of these surrogate outcomes.

Applying the clinical evaluation to any different population

This may be necessary if the trials recruited participants who were older or younger than the requested target populations. For example, justify any claims that the extent of vaccine effectiveness is similar for individuals in both the primary and catch-up populations.

Immunogenicity outcomes

Additional advice on translating immunogenicity outcomes to patient-relevant outcomes is found in Subsections C.1 and C.2), for reference if appropriate for a vaccine submission. For the proposed vaccine, transforming an immunogenicity outcome from a vaccine trial usually requires two separate analyses that:

- show that a threshold level of antibody response predicts a particular extent of protection and thus a subsequent magnitude of reduction in cases of the disease presenting in each of one or more manifestations

- assess whether there is any limit to the duration of this predicted effect or waning of the effect over time.

Although any relevant regulatory standards for immunogenicity outcomes should be provided, they might not always satisfy the requirements needed to map the direction and magnitude of a change in the surrogate immunogenicity outcome to the duration, magnitude and severity of one or more changes to subsequent clinical outcomes for inclusion in an economic evaluation.

PT3.4 Economic evaluation for the main indication (submission section D)

Type of economic evaluation (Part II, Subsection D.2)

Information request

- In the context of a conclusion of therapeutic superiority, provide a cost-utility analysis (or cost-effectiveness analysis). Provide a cost-benefit analysis as a supplementary analysis only.

Consistent with Part II, Section D and Appendix 7, a cost-utility analysis is preferred to a cost-benefit analysis for the economic evaluation in the context of a conclusion of therapeutic superiority. A cost-benefit analysis might be potentially useful as a supplement to a cost-utility analysis to estimate the value of the consequences of the proposed vaccine that might not be captured by other means (eg changes to injection frequency and adverse reactions). When valuing outcomes, Appendix 6 gives further guidance on utility valuation and Appendix 7 gives further guidance on monetary valuation as a supplementary analysis.

Refer to Appendix 8 if production changes (nonhealth outcomes) are claimed in a supplementary analysis.

Population and circumstances of use reflected in the economic evaluation (Part II, Subsection D.2)

Information requests

- Present and assess the appropriateness of available evidence to estimate the epidemiology of the disease in the Australian population and any subgroup as identified by the restrictions requested in response to Subsection A.2.

- Where catch-up programs are requested, use sensitivity analyses presented in response to Subsection D.6 to examine the sensitivity of the model's base case to the marginal costs and benefits of different options of adding a catch-up program, and then:

  – extending the catch-up population

  – lengthening the duration of the catch-up program.

The base case of the modelled evaluation should be for the primary population. When assessing the appropriateness of available evidence for estimating the prevalence of the disease in Australia, possible sources of epidemiological evidence include routine surveillance data, seroprevalence studies and surveys.

Structure and rationale of the economic evaluation (Part II, Subsection D.3)

Information requests

- State whether a static or a dynamic model is used to estimate the epidemiological impact of the program involving the proposed vaccine.

- State whether a joint analysis has been considered and include this where appropriate.

- Justify the duration of the model.

- Explain and justify the approach taken in the mathematical modelling of consequences, such as any waning or limited duration of vaccine effectiveness or herd immunity implications.

Type of model

The type of model used (static or dynamic) should be stated. Static models are those in which the force of infection (probability per unit time that a susceptible person acquires infection) is constant over time. These are usually structured as decision analysis models or Markov models. Static models ignore herd immunity effects (see below).

Dynamic models are those in which the force of infection depends on the number of infectious individuals in the population at each time point, and this number would be expected to decline following immunisation. Dynamic models allow herd immunity and age shift to be assessed, and should be considered when the force of infection is likely to change following immunisation (ie if the proposed vaccine blocks transmission of infection and coverage is extensive), and when the risk or severity of the disease depends on age.

In situations where a small proportion of the population is to be immunised, either through low coverage or targeted immunisation, or the proposed vaccine does not prevent circulation of the pathogen, herd immunity effects would be expected to be negligible and so a static model would be more appropriate.

Joint analysis

In an analysis of all affected vaccinations, a joint analysis refers to whether the cost of delivery or coverage rate across multiple vaccinations is likely to be affected by a new proposed strategy. For example, this might apply when the proposed vaccine contains multiple components and could change the number of needles to be injected at one or more steps in the vaccination schedule.

Duration of a model

The duration of a model should be justified, because the cost-effectiveness ratio for vaccination programs generally reaches a plateau after a length of time, and the time span of a model should not be limited to a time before a plateau is reached. Presenting model traces of key variables, such as the incremental cost-effectiveness ratio over time, would assist in assessing the impact of varying the time horizon of the model (see also Subsection D.5).

Modelling of consequences

Two sources of uncertainty that usually have an important impact on the results of an economic evaluation of a vaccine in a new disease area are the extent of duration of effectiveness before any waning of effect, and the extent of any herd immunity.

Variables in the economic evaluation (Part II, Subsection D.4)

> **Information requests**
> - Include additional program costs where these are expected to change with the introduction of the proposed vaccine.
> - Present a systematic basis to support the evidence or assumptions used for all variables expected to impact on overall vaccine effectiveness.

Additional program costs

The description of the additional program costs that may change should include, for example, the costs of additional Australian Childhood Immunisation Register (ACIR) payments if additional encounters are required to give the proposed vaccine. There might also be changes for the delivery of the proposed vaccine through clinics, community centres and schools. If initiation of one or more specific enhancements of a surveillance program is requested or is advised by the ATAGI as being an essential component of

funding the proposed vaccine under the NIP, also include the costs of the resources for such a program. The advice of the department, particularly the Immunisation Section, should be sought (see page iv).

Systematic basis

The systematic basis to support variables should include any waning or limited duration of vaccine effectiveness (such as any surveillance studies on the need for booster doses) and/or herd immunity implications (such as observational studies). The quality of these nonrandomised studies for extrapolation purposes should be presented and assessed separately as described in Subsection C.2.

Sensitivity analyses (Part II, Subsection D.6)

Information request

- Due to the likely number of uncertain parameters, present multivariate sensitivity analyses in addition to univariate sensitivity analyses.

As models of vaccines might be sensitive to the discount rate used for calculating the net present value of health outcomes, sensitivity analyses varying this rate should be presented together with any arguments seeking to justify a rate other than the requested annual rate of 5% in Subsection D.4.

PT3.5 Estimated extent of use and financial implications (submission section E)

Estimated financial implications for the NIP

Where appropriate, the costs presented in submission section E should estimate costs using the Commonwealth price that applies to vaccines funded under the NIP, rather than the dispensed price for maximum quantity with appropriate patient co-payments removed that applies to vaccines listed on the PBS.

Estimated extent of use and cost of the proposed vaccine (Part II, Subsection E.2)

Information requests

- Where the proposed vaccine is to replace an existing product, present estimates of extent of use based on data from current estimates of vaccinated cohorts.

- Where the proposed vaccine is indicated for a new disease, present estimates of extent of use based on standard population estimates, with further modification as necessary if restricted to specific target populations.

- Where a program for a catch-up cohort is requested, explain and justify the approach used to estimate the extent of use and cost of the proposed vaccine in the program.

- Consistent with the additional requests for information (above) in response to Subsection D.2, present these estimates for a catch-up cohort as a series of marginal

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> analyses examining the impacts of various options for the size and duration of the catch-up program.

Estimates of use as a result of NIP funding should also include allowance for estimates of wastage and usage beyond the target population. The advice of the department, particularly the Immunisation Section, should be sought (see page iv). Where an epidemiological approach is needed to modify the estimates of extent of use based on standard population estimates to estimate use in a specific target population, see also additional requests above for information in response to Subsection D.2 for possible sources of epidemiological evidence.

Estimated financial implications for government health budgets (Part II, Subsection E.5)

> **Information request**
> - Include costs of administration through the NIP or PBS as appropriate, including delivery through general practice.

In addition to the costs of administration, cost consequences to government budgets beyond the health sector (such as clinics, community centres and schools) could also be identified and estimated for separate presentation in response to this section. These cost consequences might vary across states and territories.

APPENDIXES

Appendix 1 Relevant factors influencing decision making by PBAC

This appendix provides lists of quantitative and qualitative factors that are relevant to decision making by PBAC. Section 4.5 in Part 1 outlines how each of these factors might have an influence on a decision to list a proposed drug on the PBS.

Table A1.1   Factors that are more readily quantified

Relevant factor	Description
Comparative cost-effectiveness	• Presented as cost-minimisation analysis or incremental cost-effectiveness ratios (including incremental cost-utility ratios). • Includes a consideration of comparative costs, including the full spectrum of cost offsets (Part II, Section D and Part III, Section D(i)).
Comparative health gain	• Presented as both effectiveness and toxicity (Part II, Subsections B.6 and B.7 and equivalent subsections in Part III, Sections B(i) and B(ii), and the denominator of the incremental cost-effectiveness ratio or incremental cost-utility ratio in Part II, Subsection D.5). • This is assessed in terms of both magnitude of effect and clinical importance of effect.
Patient affordability in the absence of PBS subsidy	• Presented as cost/patient/course for acute or self-limited therapy, or cost/patient/year for chronic or continuing therapy (Part II, Subsection D.5). • Calculations for episodic therapy are more difficult.
Financial implications for the PBS	• Presented as the projected annual net cost to the PBS/RPBS (Part II, Subsection E.3 and Part III, Section E(i)).
Financial implications for government health budgets	• Presented as the projected annual net cost/year (Part II, Subsection E.4 and Part III, Section E(i)).

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Table A1.2   Examples of factors that are less readily quantified

Relevant factor	Description
Uncertainty	Discussed in: • Part II, Subsections B.3–B.6, relating to the direct randomised trial evidence • Part III, Section B(i), relating to an indirect comparison of two or more sets of randomised trials involving one or more common references • Part III, Section B(ii), relating to the nonrandomised study evidence • Part II, Subsections C.1 and C.2, relating to translating the direct randomised trials to the listing requested • Part III, Section C(i) in relation to translating an indirect comparison of randomised trials or nonrandomised studies to the listing requested • Part II, Subsections D.4–D.7, relating to the economic evaluation • Part III, Section D(i), relating to cost minimisation • Part II, Section E and Part III, Section E(i) relating to the utilisation and financial estimates. • Appendixes 6 and 7, relating to the plausibility of the valuation of health outcomes The extent and nature of assumptions compared with the extent and nature of data-sourced evidence are important considerations. The presence of uncertainty increases the hesitation involved in making the decision, increasing the likelihood that a risk averse decision will be made from the perspective of the PBS.
Equity	Affordable access is a central policy principle of the PBS (Part II, Subsection F.3) and is considered alongside the economic evaluation. There are many implicit equity and ethical assumptions in the use of quality-adjusted life-years gained; for example, age and socioeconomic and geographical status (Part II, Section D). This means that these assumptions might also need to be reconsidered alongside the economic evaluation on a case-by-case basis.
Presence of effective alternatives	This distinguishes between: • an active comparator or placebo for add-on therapy • a placebo for no active intervention. It also helps to define the clinical need for the proposed drug (see Part II, Subsection A.5).
Severity of medical condition treated	This depends on any restriction requested in Part II, Subsection A.2. The emphasis here is only on the nature and extent of disease as it is currently managed (as described in Part II, Subsection A.2).

Relevant factor	Description
Ability to target therapy with the proposed drug precisely and effectively to patients likely to benefit most	If the proposed drug appears not to be acceptably cost-effective across the broader population, it might become acceptably cost-effective in patients likely to benefit more than the average (assuming costs of drug therapy do not increase proportionally).
	This aspect is usually discussed in Part II, Subsection A.2 (and can influence the choice of comparator in Part II, Subsection A.5).
	Claims of benefits greater than the average result from the ITT analysis should be supported by appropriate trial evidence (see Part II, Subsection C.1).
Development of resistance	This applies predominantly to antimicrobial agents (see Part II, Subsection F.3).
	PBAC complies with the government-endorsed prudent use principles proposed by the JETACAR 1999 report[26] and liaises with the Expert Advisory Group on Antimicrobial Resistance for specific advice on the likely extent of the development of resistance for a new antimicrobial agent and appropriate management strategies that might be applied through a PBS listing.

ITT = intention to treat; PBS = Pharmaceutical Benefits Scheme

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[26] http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pubs-jetacar-cnt.htm/$FILE/jetacar.pdf

Appendix 2 Improving the alignment between TGA registrations and PBS restrictions

A2.1 Purpose of this appendix

This appendix was previously published as a separate policy statement by PBAC in 2002. The statement was developed in response to requests for clarification over the alignment of PBS restrictions with TGA registrations. It also addresses the implications of extensions to TGA-approved indications occurring after an earlier listing on the PBS, including the implications for earlier PBAC conclusions on comparative therapeutic performance and therefore sometimes for pricing. The statement is incorporated into the PBAC Guidelines as background information to help in the preparation of a submission in any of these circumstances.

A2.2 Background

1. Under current arrangements, applications to PBAC are accepted only for specific indications that are in accordance with the Australian registration (or proposed registration) on the Australian Register of Therapeutic Goods. However, there are circumstances where inconsistencies have developed between TGA registration and final PBS listing.

2. A particular area of controversy is where a drug in a therapeutic group is granted TGA registration for an additional indication and PBAC, because it considers there is a class effect (that is, all drugs in the group have similar safety and efficacy and produce similar health outcomes), has not always isolated the indication for PBS subsidy purposes to the drug in question. This has extended PBS subsidy for the indication to other products in the group that may not have registration approval for the indication — although sponsors should only promote their drugs in line with the Product Information document approved by the TGA.

3. The application of class effect reasoning has evolved from the inherently comparative nature of the considerations of PBAC, and is a common description in the therapeutics literature. Class effects occur when it becomes clear after a review of the comparative effectiveness and safety of drugs from the same pharmacological class that they achieve basically the same clinical effects. The conclusion of a class effect has occurred in many therapeutic areas, including hypercholesterolaemia, hypertension, peptic ulcer disease and arthritis.

A2.3 Discussion

4. The extension of PBS subsidy of a product for an indication beyond its registration approval has the following problems:

    • It produces a lack of alignment between TGA registration approvals and PBS subsidy approvals. Where there is PBS subsidy for an indication, there is a

reduced incentive in these circumstances for the sponsors of the other drugs to go back to the TGA to seek registration for the new indication. Although this results in cost savings for the other companies concerned, there is policy inconsistency if one arm of government provides subsidy approval in specific situations where another arm of government has not given registration approval. The overall result can be seen as undermining TGA registration processes.

- That some products receive subsidy under the PBS for indications for which they do not have registration approval is undesirable from a legal policy perspective and could result in significant criticism. The criticism would be based on the fact that a PBS subsidy is being made available for the use of a drug for an unregistered indication when persons importing, manufacturing or supplying the drug for that indication could be committing an offence.

- Particular companies may engage in considerable research effort and expense to obtain registration approval for a particular indication. It can be seen as unreasonable that other companies 'piggy back' on their subsequent PBS subsidy approval for the indication without the need for a registration approval for their products. This is notwithstanding the fact that the company making the application may also itself in other circumstances gain the benefit of such 'piggy backing'.

A2.4 Preferred approach

5.   The preferred approach of PBAC is not to extend PBS restrictions to individual products beyond the TGA registration approval. This approach removes the previous policy inconsistency outlined above, and the associated problems that it creates.

6.   Under this approach, sponsor(s) obtaining listing approval may obtain a better return for the research effort and expense incurred in obtaining registration approval. If other sponsors want to compete on equal ground, they would need to seek TGA registration to be granted the same indication and then seek subsidy approval. This would cost additional funds and put them at a market disadvantage in the meantime.

A2.5 Unrestricted listings

7.   This preferred approach applies for all the products that are listed in the PBS Schedule for specific indications (including as 'restricted benefit' or 'authority required'). It does not, however, apply to the area of unrestricted PBS subsidy approvals.

A2.6 Prospectivity/retrospectivity of the preferred approach

8.   Currently, the PBS cannot align with the TGA-approved indication for an unrestricted drug because the PBS Schedule does not state any purpose (indication) to which the subsidy is limited (restricted). It would be a major exercise to rewrite the entire schedule to specify the TGA-approved indications for unrestricted drugs.

9.   This would make the schedule much longer, restrictive and complex, and thus less acceptable to doctors. Importantly, it would raise concerns for patients who had legitimately been subsidised for an unrestricted drug being no longer eligible because the indication is outside the TGA-approved indications. The only way those concerns could be addressed would be through grandfathering clauses — for existing patients unrestricted listings would apply and for new patients a restricted listing.

10.   Retrospective application of this preferred approach in any circumstances is not considered desirable because it will mean that situations will arise where patients who are stabilised on particular drugs would have to be taken off them and put on alternatives if PBS subsidy is to be retained.

A2.7 Pricing issues

11.   Where applicable, consideration will need to be given to whether a new or changed restriction changes any previous PBAC recommendation that listing should be on a cost-minimisation basis (ie on the basis of achieving equivalent health outcomes). This will provide a satisfactory basis for the Pharmaceutical Benefits Pricing Authority (PBPA) to determine the flow-on consequences of any change in the application of the cost-minimisation policy — in particular, whether a price advantage was justified for the new indication over other indications for the products. For PBAC to consider whether to change its previous recommendation, relating to listing on a cost-minimisation basis, adequate supporting evidence will, of course, need to be provided by the sponsor.

12.   Where a price advantage is granted for the product receiving listing exclusivity, and the product concerned is subject to the Therapeutic Group Premium (TGP) arrangements, the question arises as to whether it can remain in those arrangements. Inclusion within these arrangements gives the company the flexibility to apply TGPs payable by patients where the company is not satisfied with the price received from the Commonwealth for PBS reimbursement purposes.

13.   It is considered that, where the product receiving listing exclusivity was granted a price advantage for a new restriction, it could no longer be said to be equivalent, in terms of health outcomes, to other products in the therapeutic group, and would therefore need to be taken out of the TGP arrangements for that group.

Appendix 3   Grandfathering

'Grandfathering' refers to the provision of PBS-subsidised therapy with a drug to patients who were receiving treatment with the drug before its listing on the PBS and for which a restriction involving previous authorisation is required by the PBS. This appendix is relevant to Part II, Section A.2.

Information requests

- If the submission includes a request for grandfathering, propose wording to include its intention in the requested restriction.

- Justify the request for grandfathering, including by providing estimates of the likely numbers of patients using the proposed drug, the sources of those patients and the source of the estimates.

Requests for grandfathering arise in the case of patients who started therapy before implementation of a PBS listing and for whom it is not advisable, on clinical or other grounds, to have a break in therapy in order to demonstrate eligibility for PBS subsidy. However, these patients should, as far as possible, be required to meet the same eligibility criteria that are applied to subsequent patients. This would ensure that, as far as possible, the terms of the restriction and acceptable cost-effectiveness are adhered to while not denying patients who meet the criteria access to ongoing treatment on a subsidised basis.

Patients seeking grandfathering for a PBS-subsidised treatment can come from a number of sources, each with different levels of control by the sponsor. These sources include:

- open-label long-term continuation trials that follow on from preregistration clinical trials (eg institutional ethics committees may require that patients involved in such studies continue to receive treatment, at the sponsors' expense, until such time as the item might become subsidised through the PBS)

- the Special Access Scheme (which stops once a drug is registered)

- postregistration clinical trials, compassionate use programs and patient familiarisation programs

- public hospital supply

- private prescription.

The main concern is to maximise the likelihood that patients to be grandfathered can demonstrate that they met the PBS eligibility criteria at the time therapy with the drug was started. The information that will maximise this likelihood includes:

- whether a narrower restriction than the likely TGA-approved indication will be requested

- the nature of the investigations that would contribute to a decision about PBS eligibility under the restriction

- the thresholds for these investigations to determine PBS eligibility that are proposed and subsequently accepted.

As more information becomes available on these aspects before PBS listing, it is important to maximise the likelihood that the necessary information is recorded in relation to each new patient at the start of therapy.

Grandfathering is particularly unlikely to be granted for patients starting the proposed drug between the date of any PBAC recommendation involving the relevant restriction and the date that the recommendation is implemented on the PBS, unless those patients can demonstrate that they have met the PBS eligibility criteria at the time therapy with the drug was started. This is because, as part of the PBAC recommendation, the essential elements of the restriction are determined and can be made more widely known. Therefore, it should be possible for these elements of the restriction to be complied with, as far as possible, and the details of this compliance recorded for each such patient in the interim period leading up to implementation of the listing. Subsequently, when initial PBS subsidy is sought, the necessary information can be supplied to Medicare Australia as part of the authorisation process to confirm that the PBS eligibility criteria had already been met.

Appendix 4   Expert opinion

This appendix outlines the situations in which expert opinion can be used, and explains how expert opinion should be collated and presented in a submission.

A4.1 Uses of expert opinion

Expert opinion is not a substitute for sound scientific evidence. Therefore, it is considered where there are no observed data available, or where such data addressing the matter for which expert opinion has been sought are unlikely to become available in the near future. Observed data may come from randomised trials or nonrandomised studies, including from drug usage evaluations (DUEs), cross-sectional studies or case studies (see also the discussion of adjustment of resource provision estimates in Part II, Subsection C.2). Expert opinion can also supplement observed data, for example to review the likely representativeness to the national level of a DUE conducted in a single locality or in another country. Such supplementation will help the interpretation of observed data, and therefore reduce its uncertainty.

Expert opinion can be useful in several aspects of preparing submissions to PBAC; for example, to help:

- define the clinical need for the proposed drug and thus the context of its use by defining the drug's place in treatment in terms of the main indication(s) based on what should be recommended (see Part II, Subsection A.2), and the main comparator(s) and clinical management algorithms based on what is likely to change (see Part II, Subsection A.5)

- interpret the clinical importance and patient relevance of the outcome measures reported in the trials (see Part II, Subsections B.5 and B.8)

- modify the patterns of resource use and, very rarely, the clinical outcomes measured in randomised trials conducted in different settings, such as in other countries (see Part II, Subsection C.2)

- predict which resources would be used and how often each would be used to manage outcomes reported in the randomised trials, but not followed up (see Part II, Subsection C.2)

- identify the proportion of patients with the medical condition who would meet the eligibility criteria established by the requested restriction (see Part II, Subsection E.2)

- predict the proportion of patients within this eligible population who would take the proposed drug (see Part II, Subsection E.2)

- predict the rates of uptake of the proposed drug (see Part II, Subsection E.2)

- predict the extents of substitutions, increases and decreases of other PBS-listed drugs (see Part II, Subsection E.3).

A4.3 Presenting expert opinion

> **Information requests**
> - Present expert opinion as a technical document or an attachment to the main submission, with clear cross-references to the relevant sections of the main body of the submission.
> - Justify the need for expert opinion.

If expert opinion is included, its use should be justified in the introduction of the section involved. Include a clear rationale for, and the aims of, eliciting the expert opinion. Where expert opinion is used to fill in a gap in information, describe the nature of this gap clearly and indicate the steps that have been taken to address the gap, such as a literature search.

A4.4 Describing the collection and collation of expert opinion

> **Information requests**
> - Describe and justify the approach chosen to elicit expert opinion.
> - Describe the methods used to obtain and collate the opinions, and summarise the opinions together with the extent of any variability in the opinions (see Table A4.1).
> - Indicate how the opinions have been used in the main body of the submission and justify the approach used in the sensitivity analysis (see Part II, Subsections D.6 and E.6) to reflect any variability in the opinions obtained.

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. Expert opinion may be presented as qualitative or quasi-quantitative information.

There are many approaches to addressing information gaps. The choice of the preferred approach might be influenced by the availability of existing surveys, small numbers of prescribers with appropriate expertise, and resource limitations, such as time. Options for primary collection of opinions include interviews, focus groups, self-administered questionnaires and telephone surveys. If the survey is to determine what changes a prescriber might make to their prescribing behaviour, ensure that the hypothetical future scenario is clearly detailed.

When summarising the opinions and their variability, interpret the findings and discuss the limitations and biases of the method chosen. 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. Where expert opinion is used to modify estimates from randomised trials or nonrandomised studies, particularly estimates reported in Part II, Subsections B.6 or C.2 or any other input into the economic evaluation in Part II, Subsection D.4, compare the results and justify the modification. Present a summary table that compares multiple sources or multiple variables. Table A4.1 provides guidance on the details that should be included.

Table A4.1   Methods to collect and collate expert opinion

Information to be provided	Notes
The criteria for selecting the experts	Prefer: - a random or comprehensive set of prescribers likely to prescribe the proposed drug, OR - the appropriate medical specialty group.
The number of experts approached[a]	
The 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 conflict(s) 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.
The 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, it might help to ask the experts to define the comparative clinical place of the proposed drug and the main comparator based on this background information. Including the experts' definitions in the technical document or attachment would allow an assessment of the consistency of the background information with the evidence provided in the submission.
The method used to collect the opinions	For example, were the experts approached individually or was a meeting convened? Was any incentive used to maximise responses?
The medium used to collect the opinions	For example, was information gathered by direct interview, telephone interview or self-administered questionnaire?
The 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 - the extent to which each question is open or closed. To allow an independent assessment to be made, include in the technical document (or as an attached copy) the questionnaire or an outline of the interview questions.
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.

Information to be provided	Notes
The 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, and, if not: (i) the approach used to finalise the estimates, and (ii) the approach used to present the variability in the opinions.	 For example, the majority opinion or a Delphi technique could be applied; for quantitative results, point estimates (such as the mean, median or the mode) could be presented. For example, present the range of opinions including common and outlying views expressed; 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 also ask the reason 'why' (eg explain why would you do this, explain why is this important). Conveying these reasons alongside expert opinion-based estimates might help improve their acceptability, particularly if a small group of experts has been approached. 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 5   Assessment of noninferiority

A5.1 Introduction

Noninferiority means that, in terms of effectiveness, the proposed drug is no worse than its main comparator. It is used to support a claim of equivalence because it is not adequate to demonstrate the *absence* of a statistically significant difference between the treatments to claim equivalence; such a lack of a significant difference might occur when the trials are too small to demonstrate a real difference in the effects of the interventions. The appropriate comparison to present is the point estimate of the difference with its 95% confidence interval. This allows PBAC to assess whether the confidence interval contains the minimal clinically important difference (see Figure B.2 in Part II, Subsection B.8).

Thus, a submission should support any conclusion for therapeutic noninferiority with the information contained in its submission sections as referred to below.

A5.2 Dose information

As part of the information provided in submission section B (Subsection B.4 or equivalent), ensure that the dosing relativity used in the trials is appropriate. Any conclusion of noninferiority should be accompanied by a determination of equi-effective doses. (Section D(i).1 of Part III has further information on equi-effective doses.)

A5.3 Noninferiority threshold

As part of the information provided in submission section B ((Subsection B.5 or equivalent), explain and justify on clinical or other grounds the value of the noninferiority threshold difference in treatment effect between the proposed drug and its main comparator. Show how a difference greater than this nominated noninferiority threshold difference would be clinically important. A specifically designed noninferiority direct randomised trial would have specified a noninferiority threshold in its power calculation and so might have provided one or more grounds to justify this threshold as a prespecified minimal clinically important difference (MCID). Demonstrate that a systematic approach has been taken in the search for relevant and appropriate references to support the nominated threshold and provide the supporting citations, including any references to one or more regulatory agencies that might have provided guidance on any such thresholds in medical conditions similar to the proposed main indication.

If the basis of the clinical evaluation is an indirect comparison of randomised trials and the nominated noninferiority threshold relates to an absolute comparison (eg absolute risk difference or weighted mean difference) rather than a relative comparison (eg relative risk or odds ratio), discuss the issues raised by relying on an indirect comparison of the difference between absolute treatment effects rather than on an indirect comparison of the ratio of relative treatment effects (see Part III, Section B(i).6 for further background on these issues).

A5.4 Method of analysis

Also as part of the information provided in submission section B (Part II, Subsection B.5, or equivalent), indicate whether the analysis of each trial was conducted on a per protocol basis (which is appropriate for an analysis in support of a conclusion of noninferiority, because it helps examine any impact on the conclusions of losses to follow-up or poor compliance), as well as the standard intention-to-treat (ITT) basis (which is the generally preferred basis for an analysis; see Part II, Subsection B.2).

If one or more specifically designed noninferiority direct randomised trials are available, also describe the primary analysis of noninferiority in detail for each such trial, including the prespecified noninferiority threshold (or MCID) used in the power calculation and whether the preferred per protocol basis rather than the intention-to-treat basis was used in the context of this noninferiority analysis. Comment on any differences in the prespecified noninferiority thresholds across these trials and with the nominated noninferiority threshold.

For any direct randomised trial that was not designed as a noninferiority trial, also describe its primary analysis in detail, including the prespecified MCID used in the power calculation.

A5.5 Presenting an assessment of noninferiority

Assessing noninferiority based on an indirect comparison of randomised trials

As part of the information provided in response to Part II, Subsection B.6, present the results of each comparative analysis using, where possible, both the per protocol and the ITT basis of each trial with their 95%0 confidence intervals in a way that allows for direct comparison with the nominated noninferiority threshold justified in response to Part II, Section B.5. Comment on any differences between the results for the per protocol and ITT populations. Where there is more than one trial reporting the same outcome, statistically combine these results using the random effects method and, where possible, both the per protocol and the ITT basis. Report each result with its 95% confidence interval in a way that similarly allows a comparison with the nominated noninferiority threshold (see Figure B.2 in Part II, Subsection B.8). Comment on any differences between the results for the per protocol and ITT populations. If the per protocol basis differs across trials, justify the approach to resolve this in the meta-analysis.

If one or more specifically designed noninferiority direct randomised trials are available, also report the results and stated conclusion of the primary analysis of noninferiority for each such trial. Report whether the entire 95% confidence interval of the treatment effect between the two drugs is more favourable to the proposed drug than the prespecified noninferiority threshold corresponding to the proposed drug being less effective. If so, there is statistical support to the conclusion of noninferiority based on an appropriate prespecified trial design.

If the primary analysis of a specifically designed noninferiority direct randomised trial does not present the 95% confidence interval and/or adopt a per protocol population basis for the analysis and/or compare this interval with the noninferiority threshold justified in response to Part II, Subsection B.5, then present the results, where possible, using both the per protocol and the ITT basis of each trial with their 95% confidence intervals in a

way that allows for direct comparison with this threshold for noninferiority. Discuss whether these results might influence the conclusion of the primary analysis of the trial.

For any direct randomised trial that was not designed as a noninferiority trial, also report the results of the primary analysis as prespecified. Report whether the entire 95% confidence interval of the treatment effect between the two drugs is more favourable to the proposed drug than the prespecified MCID corresponding to the proposed drug being less effective. If so, there is post hoc statistical support to the conclusion of noninferiority. Investigate whether the conclusion of noninferiority is impacted by a comparison of an analysis conducted on a per protocol basis and/or whether the 95% confidence intervals compared with the noninferiority threshold justified in response to Part II, Subsection B.5 would modify this conclusion and report these investigations.

Supplementary analyses might be helpful to support conclusions of noninferiority that have to rely on primary outcome analyses that were not adequately powered to assess noninferiority. Base these supplementary treatment comparisons on the results for secondary outcomes that are known to be most responsive to change.

Assessing noninferiority based on an indirect comparison of randomised trials

The general approach described above for direct randomised trials needs to be adapted for an indirect comparison of randomised trials in response to Part III, Subsection B(i).6. Report the point estimates for the indirect relative treatment effect with their 95% confidence intervals in a way that allows for direct comparison with the nominated noninferiority threshold for inferiority justified in response to Part III, Subsection B(i).5. Report whether the entire 95% confidence interval of the treatment effect between the two drugs is more favourable to the proposed drug than this noninferiority threshold corresponding to the proposed drug being less effective. If so, there is indirect statistical support to the conclusion of noninferiority.

Where possible (and appropriate noting that there is no basis for a prespecified noninferiority design for an indirect comparison of randomised trials), provide additional investigations and supplementary analyses as described above for direct randomised trials.

A5.6 Assessing comparative harms in the context of noninferiority

As part of the information provided in submission section B (Part II, Subsection B.7 or equivalent), examine whether the extended assessment of comparative harms also supports a conclusion of noninferiority.

A5.7 Interpretation of the clinical evidence

As part of the information provided in submission section B (in response to Part II, Subsection B.8 or equivalent), discuss any results to support a conclusion for noninferiority in the context of the similarity or otherwise of the mechanism of action(s) of the proposed drug and the main comparator in order to assess whether this conclusion is supported by a 'class effects' argument (see also Appendix 2).

Appendix 6   Utility valuation of health outcomes

A6.1 Use of health-related QALYs gained and cost-utility analysis

The QALY (quality-adjusted life-year) is a measure of adjusted survival time where the adjustment is by means of health-related quality-of-life preference weights derived for specific health states. Expected survival time in each of these health states is adjusted using the preference weights and then summed across the duration of survival to generate expected QALYs gained. The use of preference weights distinguishes QALYs from other quality-of-life measures.

The QALY has become widespread as a measure of health outcome in the economic evaluation of health care interventions. The key characteristics of the QALY are as follows:

- It combines extension of life and quality of life in a single index that allows comparison across health interventions.

- The utility weight index measures strength of preference on a cardinal index anchored on a 0 to 1 interval of death to full (perfect) health, with equal intervals measured in such a way as to have equal value and an allowance for the existence of health states perceived to be worse than death (ie < 0).

- The utility weights that underpin the QALY measure are based on a sample of individual preferences. These preferences are obtained in a way that involves a trade-off between quality and quantity of life. This provides some validity to the QALY as representing societal trade-offs and therefore social values.

The implication of using this scale is that one year of life in full health is counted as one QALY. Even though one year of life in normal health is less than one QALY, this does not necessarily mean that all incremental QALY gains are numerically smaller than incremental life-year gains. This is because incremental QALY gains can also encompass the possibility of improving quality of life, and such improvements can happen for a long period before any improvement in survival happens.

Theoretically, at least, the QALY provides a measure of health outcomes that is comparable across health care interventions. This form of analysis should therefore be considered whenever it is appropriate to the outcomes of the proposed drug. However, many concerns over the estimation of QALYs have been documented.

Guidance on when a cost-utility analysis should be presented is provided in Part II, Subsection D.1.

Other relevant factors (see Part II, Subsection F.3 and Appendix 1) should be considered alongside, not within, a cost-utility analysis. These include prognosis, severity, age, distributional effect, context (eg emergency or prevention) and other equity and ethical issues that are ignored in measurement using a multi-attribute utility instrument (MAUI). Therefore, a submission should draw these issues to the attention of PBAC where this is thought important and relevant.

A6.2 Obtaining utility weights

Several approaches to obtaining utility weights are discussed in these guidelines:

- using a MAUI in a direct randomised trial

- creating scenarios to indirectly elicit utility weights

- directly eliciting utility weights in a randomised trial

- obtaining a sample of patients matched to trial participants and eligible patients and using a MAUI

- mapping results of other quality-of-life instruments to the utility weight anchors of a 0 to 1 interval of death to full (perfect) health

- reporting utility weights from published sources.

The generally preferred method of measuring QALYs is by the repeated application of a valid, reliable and responsive MAUI questionnaire to participants in a randomised double-blind trial, together with the application of an appropriate scoring algorithm (see Part II, Subsections B.5 and B.6).

However, it is recognised pragmatically that such instruments are not routinely included as an outcome measure in many trials, so it is anticipated that there will be a lag time before this preference can be met routinely. It is also recognised that in many cases it will be necessary to attach utility weights to health states that are not observed within a trial; for example, because they are the result of events that occur outside the trial timeframe. Accordingly, guidance is also provided on alternative approaches (see Subsections A6.4 and A6.5 of this appendix). In some circumstances, it is possible that an alternative approach would be preferred to the use of a trial-based MAUI (see Subsection A6.4 of this appendix).

Post-trial transformation to estimate preference weights ('utilities')

Preference weights are preferably generated directly from a trial using MAUIs or may subsequently be elicited with the aid of scenarios. Several other approaches have been presented in major submissions, and are discussed and assessed briefly below in Subsection A6.5 of this appendix. MAUIs and scenario-based elicitation of preference weights are further assessed in Subsections A6.3 and A6.4 of this appendix, respectively.

MAUIs (multi-attribute utility instruments)

MAUIs have three defining elements:

(a) A generic health-related quality-of-life instrument. Those recommended in Part II, Subsection B.5 have been assessed according to the criteria for such instruments identified. This element of a MAUI is a descriptive system (a questionnaire containing a set of items or statements with multiple response categories) that provides a description of the health-related quality of life of each respondent.

(b) A scaling technique, such as time trade-off (TTO) or standard gamble (SG). This is used to derive preference-based rankings for a sample of the health states covered by the descriptive system.

(c)   A model, which is used to extrapolate from this sample to generate cardinal weights for all health states covered by the descriptive system (that is, to develop a preference-based scoring algorithm for the MAUI). Both mathematical and statistical models have been used to provide utility weights for any health state that can be described by the instrument in terms of its dimensions and levels. For these utility weights to be meaningful for an economic evaluation, the scaling technique must reflect the trade-offs that individuals are willing to make between health outcomes.

Together, these elements generate the unique advantage of trial-based measurement with a MAUI, which is that the direct observation of the actual health states experienced in the trial can be used to generate utility weights in an acceptable way using utility scores of the health states that have been generated in a separate population-based study. Therefore, it is the combination of these three elements that enables acceptable post-trial transformations to estimate utility weights (see Subsection A6.3 of this appendix).

A6.3 Trial-based utility valuation of health outcomes

Measurement of QALYs using a trial-based MAUI

For MAUIs, the measurement of the health state happens in the trial itself, which enables more accurate and unbiased measurement of the health states as experienced by the patients receiving the relevant treatments. The valuation step is then inferred using an acceptable scoring algorithm, which means that the valuation is conceptually and practically separated from the assessment of the particular disease or treatment, and therefore not subject to bias.

To maximise comparability across submissions, it would be ideal to request that a single 'off-the-shelf' MAUI be used in randomised trials across all submissions presenting a cost-utility analysis. Inter alia, criteria to guide the selection of such an instrument would be that it is valid, reliable and responsive, and that it uses an acceptable scoring algorithm and an acceptable preference elicitation technique. However, in practice, no single MAUI has demonstrated unequivocal superiority against all the others and no single MAUI has been universally accepted. There is also debate about whether generic MAUIs are sufficient to capture all important disease-specific factors that might be relevant for particular disease pathways and treatments. The advantages and disadvantages of trial-based MAUIs are discussed further below.

Advantages of relying on trial-based MAUI data

Trial-based MUAI data has the following advantages:

(a)   It promotes comparability across cost-utility analyses.

(b)   It minimises bias by eliminating the need for an analyst intermediary.

(c)   It can appropriately minimise observer bias by assessing the subjective outcome of health-related quality of life under appropriate blinded conditions.

(d)   It minimises the information asymmetry of the health state being assessed because the trial participant is directly measuring the health-related quality of life of the health state as it is being experienced.

(e)   It applies the scoring algorithm of the general population (which can minimise a source of uncertainty if this was elicited in an Australian population or possibly from socioeconomically similar countries with similar life expectancy) to take responses from the MAUI questionnaires to generate utility weights using an acceptable technique. In other words, the utility scores in the scoring algorithm have been elicited separately from the reporting of the responses in the trial context for each MAUI. The utility weights are calculated by a validated linkage between the response from the MAUI questionnaire in the trial and the utility score inferred for that response from respondents in the general population using the scoring algorithm.

(f)   As a direct translation, it minimises the number of steps between the direct trial-based measurement of health-related quality of life and its valuation.

(g)   It estimates some of the distribution and heterogeneity variation of health states in a population.

(h)   It maintains a fixed period of assessment to which the MAUI applies.

(i)   Repeatedly applying the MAUI during the trial allows for direct conversion into the net present value of the future flow of realised QALYs gained and incremental QALYs gained and might provide a basis for extrapolation beyond the horizon of the trial.

(j)   It provides a benchmark against which to compare any more specific elicitation of preferences presented as supplementary evidence (eg using a scenario-based approach; see Subsection A6.4 of this appendix).

(k)   It provides advantages for sponsors and analysts in terms of time and cost to assess the appropriateness of using an acceptable 'off-the-shelf' MAUI in a trial.

(l)   It provides efficiency advantages for respondents and analysts because no MAUI developed so far takes more than about five to eight minutes to complete when self-administered (and less when using computer-based, interviewer-administered questionnaires) and because analysis of the each of the main MAUIs is well-developed.

(m)   The main MAUIs have been developed with the objective of having international applicability, so it is anticipated that this preference for trial-based MAUI utility weights will have increasing relevance over time to the multinational trial programs for new drugs.

(n)   It is possible to conduct an independent and peer-reviewed verification of any preferred MAUI — including its reliability, validity and responsiveness, the clinical importance of any differences detected by the instrument, and other desirable psychometric properties.

(o)   The use of a consistent MAUI would allow replication (and potentially meta-analysis) of results across similar direct randomised trials conducted between the proposed drug and its main comparator.

Disadvantages of relying on trial-based MAUI data

Trial-based MAUI data has the following disadvantages:

(a)   The MAUI might be relatively insensitive to the patient-relevant outcomes affected by the proposed drug, particularly if its main treatment effects or the impacts of the medical condition do not fall within the domains examined by the MAUI. This interpretation of the results needs to be assessed against the possibility of a true negative (ie that the proposed drug has no overall perceptible incremental effect on utility; see also Subsection A6.4 of this appendix). The MAUI should therefore be demonstrated not to fit the context of the proposed drug and the medical condition by comparing the results from the MAUI with an accepted nonutility quality-of-life instrument, such as the SF-36.

(b)   It is unlikely that, in the near future, a randomised trial would be designed to have the MAUI as its primary outcome. The trial might therefore be underpowered to detect a difference using the MAUI. As with all secondary outcomes, the results of the MAUI would need to be assessed with reference to the conclusion from the primary analysis of the trial.

(c)   Trial participants might not be directly representative of the population for whom listing is requested, although an assessment of the distribution and heterogeneity of the results of this outcome might provide a basis for applying them to the targeted population.

Trial-based direct elicitation of utility weights

Conceivably, direct methods might be used within a trial to ask patients to value their current health state at baseline (or over a recent period of time at baseline) and at one or more time points during the trial follow-up (or over a recent period of time at each time point). Advantages (a)–(d), (f) and (h) listed above would also apply to trial-based direct elicitation of utility weights.

The main disadvantage for direct elicitation in the trial setting is the time horizon assumption for TTO or SG (ie the trial participant is required to answer a hypothetical question assuming that he or she remains in the current health state for the rest of his or her life expectancy). In a scenario-based setting, the entire framework is hypothetical, so there is less risk of any distortion arising from the respondent first having to conceptualise what it might mean to remain in the current health state for a prolonged period.

This approach might also raise potentially important issues to do with adjusting utility weights for groups of patients in certain disease groups (eg quadriplegics) and with different adaptations. The defined range of a utility scale is full health (1) to death (0), but people with cancer and other diseases adapt (or adjust up) their estimate of utility closer towards 1 — such people's 'normal health' might be considerably less than 1, but they adapt up to 1. This potentially biases against the allocation of further health resources

(so-called 'double jeopardy'). Some groups, when making the adjustment, could also eliminate their capacity to benefit.

Presenting trial-based direct elicitation and results

If utility weights have been directly elicited in a randomised trial, provide details of the method used and justify the selection of the approach taken (eg SG or TTO; interview-based and/or computer-based). The same considerations for the design of the preference elicitation task apply in this context as in a scenario-based approach (see Subsection A6.4 of this appendix). Report and assess the results as for MAUIs, above.

A6.4 Scenario-based utility valuation of health outcomes

Background

As discussed in Subsections A6.2 and A6.3 of this appendix, obtaining utility weights using a MAUI within the context of a randomised double-blinded trial is the preferred method. This section of this appendix presents a less preferred alternative, because there is an expected lag time before most major submissions would be able to report utility weights on this basis. Furthermore, given that most randomised trials are designed overseas, few randomised trials would be conducted primarily to ensure that useful economic information is generated from this preferred source of evidence for PBAC and similar decision makers.

A submission might seek to justify the inclusion of a scenario-based approach to valuing health states in utility weights as supplementing trial-based utility weights. Alongside this justification for providing these supplementary estimates, present both sets of methods and results and comment on the interpretation of the results compared to each other. As with the interpretation of the results of any measure of health outcomes, any claim for an improved sensitivity in quantifying the utility weight of smaller advantages needs to be assessed against the possibility of a true negative (ie that the proposed drug has no overall perceptible incremental effect on utility; see also Subsection A6.3 of this appendix). Document the evidence that supports any claim that any difference in results between trial-based utility weights and scenario-based utility weights is attributable to the special characteristic of the health state and not some idiosyncrasy in the utility measurement procedures that have been adopted. This would help justify any apparent diminution in comparability across submissions that provided trial-based utility weights. Similarly, if using a scenario-based utility valuation to capture the impacts of health outcomes only occurring beyond the horizon of the trial, document the evidence that supports any claim that the scenario-based utility weights reflect the trial-based utility weights (eg by including one or more health states captured and valued within the trial as part of the scenario-based utility valuation study).

Other situations where a scenario-based approach might supplement trial-based utility weights include those in which:

- the health states are associated with quantitatively important anticipated factors (in which one or more elements of the health state are anticipated rather than experienced, so that concepts such as anxiety, risk aversion, fear, hope or dread might be captured) or nonhealth outcome factors such as convenience

- the health outcomes are significantly affected by prognosis.

If the introduction of the proposed drug is expected to induce a succession of changing health states that have a significant interactive effect on utility and the composite utility is not equal to the sum (in which a profile of health states would need to be valued), then this suggests that the QALYs approach is unlikely to be suitable and an alternative and technically more complex approach might be more appropriate, such as a healthy-year equivalents approach.

A submission might need to present a scenario-based approach to valuing health states as utility weights in the absence of any trial-based utility weights. In this situation, the main objective of achieving a comparable approach across submissions is diminished. Furthermore, many of the issues in interpreting scenario-based utility weights in the absence of trial-based utility weights are similar in nature to the issues in interpreting any results of nonrandomised studies in the absence of a direct randomised trial. In particular, it is difficult to minimise the many sources of analyst bias that are intrinsic to this approach (including in the unblinded nature of the construction and presentation of the scenarios, the design of the methods to elicit values and the analysis and interpretation of the results, which are all conducted after the trial results are known).

A particular source of potential biases can be identified with post-trial scenario-based approaches to valuing health outcomes. This is because there is a justifiable preference for eliciting these values from individual respondents drawn from the general population (because they might better reflect the perspective of society overall as representing the balance of taxpayers and patients) rather than of patients alone (who are likely to recognise that they would be the beneficiaries of any new subsidised intervention). However, this inevitably leads to an information asymmetry for the respondent in relation to each specific post-trial scenario in a scenario-based utility study. Seeking to address this information asymmetry by loading more information into the scenarios raises the problem that respondents might manage this burden by unknown filter mechanisms used subconsciously when assimilating the information provided about the scenarios.

On the other hand, giving insufficient descriptions of the scenarios raises the problem that respondents might manage the gaps by unknown extrapolations, also used subconsciously, when assimilating the information provided about the scenarios. It is likely that both assimilation processes are operating simultaneously whenever a respondent is interpreting the presentation of scenarios. It would therefore be expected that their responses would be sensitive to the construction and presentation of the background and scenarios by the analyst. However, any examination of the sensitivity of the results to these sources of bias would be limited by the number of scenario variations that can be examined for any one respondent or in any one study. In contrast, these sources of bias can be more successfully minimised by the trial-based MAUI approach outlined in Subsection A6.2 of this appendix, which separates the scoring of each health state by the fully informed but appropriately blinded patient who is actually experiencing it from the previous generation of the valuation of that health state by members of the general population (thereby avoiding the need for a further analyst to act as an intermediary after the trial).

The post-trial scenario construction process has a number of implications. The scenario-based approach runs the risk of presenting 'extremes' of health states for valuation rather than reflecting the distribution. Given the limited number of health states presented for valuation, there is rarely a basis to examine this source of uncertainty in sensitivity analyses. Using a MAUI in the context of a randomised trial (see Part II, Subsection B.5)

avoids this problem. Furthermore, a key implication of analyst bias is the potential for the scenario-based approach to focus on particular symptoms and attributes, which would not necessarily be the way that a person experiencing the health state would perceive it. This leads to a distortion along the lines that 'nothing seems as important as when you are asked to think about it'.

Presenting the methods of generating scenarios and of presenting them to respondents

If preference weights in utility units have been derived with the use of hypothetical health state scenarios, provide details of the methods used in the utility study as part of the information provided in Part II, Subsection C.1. Provide data and references that support the validity and reliability of these methods.

Describe the approach taken to construct the scenarios. The scenarios should be developed rigorously, including by demonstrating that consideration has been given to the following:

- Describe the basis of the derivation of the health state scenarios for the survey. Discuss the relationship between these scenarios and the quantified estimates supporting the therapeutic conclusions presented in submission section B or modified in submission section C. Given the inherently subjective nature of this process, report any attempt to minimise selection bias in the process and its impact. A more convincing case would be based on a randomised trial that measured health-related quality of life frequently with one or more valid and reliable generic instruments, and the construction of the scenarios is justified and compared with the detailed quality-of-life information from the trial results using these instruments.

- Explain the derivation of the descriptions in each scenario. Discuss the approaches taken to reflect the experience of patients experiencing these health states in the text of the scenarios. For example, describe the derivation of the health state scenarios and weighting and whether they were derived directly using one or more facilitated focus groups (such a group should include Australians — users of the proposed drug and people with some experience of the medical condition, as well as medical experts). In particular, explain how the five to nine attributes (see guidance in relation to text below) were selected for inclusion in each scenario from the range of patient experiences. Discuss the need for, and implications of, choosing a proxy (eg a carer, a family member or a health care professional) in place of patients for this step.

- Examine whether the description of each scenario was understandable to Australian respondents. For example, report whether initial scenarios developed were piloted using in-depth interviews on all aspects of the respondents' thoughts and comments before undertaking the full survey. If a pilot study was conducted, advise whether it identified any issues and how these were addressed before the scenarios were used in the utility study.

- Report any assessment of the scenarios developed in terms of validity, reliability, responsiveness to change, and clinical importance. Report any assessment of the duration of the period covered in each scenario compared with the duration assumed in the choice-based preference elicitation task (see below).

- Clearly distinguish between elements in the scenarios relating to health and elements not relating to health (such as convenience of use, increased availability of options and any other externality). If nonhealth elements are included, ensure that elicited

preferences can be presented separately as health elements alone and [XX as?]health elements combined with other elements. The base case should be based on health elements alone. Use sensitivity analyses to examine the impact of including any other elements.

The text used to describe each health state scenario is crucial as the means to convey the basis of the utility weight elicited. Demonstrate that consideration has been given to the following:

- Respondents to scenarios are likely to be subject to cognitive overload when the number of attributes or aspects of the health state increases beyond five to nine.

- Each scenario should adopt the patient's perspective, such that respondents are to imagine that they are in the health state described. The scenarios may be presented in the first or third person.

- Each scenario should be a single static health state rather than a profile of two or more different health states.

- The 'ex post' perspective (in which the health state is as experienced with a full diagnosis without considering the risk of a future event) is preferred in the description of scenarios to ensure that all relevant and important aspects are included explicitly and that all irrelevant aspects are excluded (eg the process of diagnosis and a range of possible prognoses). Provide a justification to support the use of an 'ex ante' perspective in any health state scenario. A possible example is the use of a drug that is intended to prevent a future harmful event.

- As the scenarios are to be presented to individuals with limited technical knowledge, use simple language and a logical sequence of presentation of material to allow all respondents to understand the background and the scenarios. Avoid technical terms and unnecessary words.

- Minimise the possibility of framing and labelling effects in which apparently small changes in wording of the scenario can produce substantial shifts in response. A possible way of doing this is to provide more background context, but because each scenario is essentially a subjective matter, it is difficult to anticipate where problems could arise in any particular context. Report the results of any pilot testing for obvious framing and labelling effects (such as the use of emotive disease labels such as 'cancer' or 'neurological disorder' in the health state description) in the design and implementation of the scenario. An exception to the above example might be where an ex ante perspective is justified.

- To minimise sponsor bias, the pharmaceutical company should not be named during the survey. To focus on the health state, it would be preferable not to identify the treatment or the nature of the treatment. A justification should be provided if the treatment is to be identified in order to assess some nonhealth outcome aspect of therapy.

- Consider including questions to confirm the respondents' comprehension of the background information and scenarios provided, and report the results of such a validation exercise.

- Justify the number of scenarios to be presented for valuation. The burden on respondents represents an upper limit, which is influenced by the complexity of the information presented and the number of attributes, as well as the number of scenarios. If the number of scenarios to be valued is less than this upper limit, consider including one or more extra scenarios that capture any important variation in

the description of one or more health states to be valued. These extra scenarios would enable the presentation of sensitivity analyses of the impact of the description of the scenarios valued for the base case. An important limitation of the scenario-based approach to valuation is that sensitivity analysis of this important source of uncertainty is rarely presented.

Provide a copy of the information provided to the respondents as an attachment to the submission. Include in these materials any background information, the text of all health state scenarios, any questions used to confirm comprehension and the questions used to elicit preference weights ('utilities'). Also provide a copy of any computer program used to facilitate the presentation of information and the elicitation of utility weights.

Outline the methodology adopted in implementing the survey instrument. Demonstrate that consideration has been given to the following:

- Face-to-face interviews are preferred to facilitate comprehension of the background information provided, the description of the scenarios and the questions asked. Provide a justification to support the use of telephone interviews or posted self-administered questionnaires.

- The respondent should be asked questions throughout the background narrative to keep them involved and to ensure understanding.

- Interviewers should be carefully trained to read material at an appropriate pace, and to use conversational inflection, pauses and eye contact in the appropriate manner.

- Material should be provided in a logical sequence and illustrated where appropriate with pictures, graphs or diagrams. Include display items to enhance understanding and to increase interest.

Comment on how the study addressed the controversy of whose utility weights are elicited (eg a patient, a proxy for the patient, such as a care-giver, or a member of the general population) discussed in the background above. The possibly unattainable ideal is that these utility weights are elicited from a representative cross-sectional sample of the Australian general population that is fully informed of all health implications of each health state scenario presented.

If respondents are not from the general population, this approach might also raise potentially important issues to do with adjusting utility weights for groups of patients in certain disease groups (so-called 'double jeopardy', see Subsection A6.3 of this appendix for further explanation). Therefore, for health states reflecting a chronic medical condition, also comment on whether the approach taken reflects adaptation of patients to the experience of the health state, and the implications this has for relating the valuation to the duration of the health state.

Elicitation, statistical analysis, reporting of results and interpretation of scenario-based utility valuation of health outcomes

Anchor the utility weights elicited on a 0–1 ratio scale of death to full (perfect) health. Elicit these weights using a choice-based preference elicitation task, which makes explicit that a choice or trade-off has to be made and therefore allows for the strength of preference to be revealed. Justify the method chosen and provide details of the method used. The method chosen may be one of the following:

- Standard gamble (SG): this method has the more direct theoretical foundation.

- Time trade-off (TTO): this is a direct measurement tool designed specifically for use in health care evaluation. It is more appropriate for use by respondents who have difficulty in understanding probabilities. It is particularly useful in studies that compare alternatives in which TTO is the major clinical factor. The utility weight is based on how much quantity of life people are prepared to give up for additional quality of life.

   Each of these scaling techniques is confounded: TTO by time preference and SG by risk attitude. As both SG and TTO relative values are consistent in the direction of expected bias compared to each other and comparison of the two techniques indicates that they provide similar results, either can be used as a scaling technique in a submission.

- The use of a MAUI to generate utility weights from a scenario is discouraged. This would not be a preference elicitation task, but rather a 'mapping' from one scenario to another, MAUI-based, scenario. If the scenario captures only a few domains covered by the MAUI, the respondent is forced to guess from the information provided what response should be given for the other domains covered by the MAUI. On the other hand, if the scenario is constructed to capture all domains, the analyst's control of the scenario descriptions is so influential that the descriptive words chosen can tend to lead the respondent towards particular responses in each domain. In an extreme case, the analyst could effectively nominate the utility weight yielded by this approach based on his or her own expert opinion and then align the text of the scenario descriptions to the text of the MAUI questions.

- Other methods for eliciting preferences, such as discrete choice experiments or other conjoint analysis methods, are still in development and thus any guidance here is preliminary. There are five main stages that characterise these types of study:

  - *Determine the attributes*: if based on one or more submitted randomised trials, the attributes should reflect the different components of the trial arms. If they are not defined on this basis, then literature reviews, patient group discussions and individual patient interviews will need to be used to solicit the attributes. These attributes should be important to the patients. If cost is used as an attribute, the technique can generate willingness-to-pay (WTP) under certain circumstances (see Subsection A7.2 of Appendix 7). In order to ensure that the analysis is being used to value health states rather than to value the treatments, it is important to exclude any other description or process aspect of the treatment.

  - *Define the characteristic levels*: justify the use of cardinal, ordinal or categorical scales. The levels should be realistic, be capable of being traded off, and capture all relevant outcomes.

  - *Choose the scenarios to be presented in the stated preference experiment*: justify the presentation of the scenarios to ensure that they are realistic (for example, ensure that the defined period of time for each scenario is consistent for both the proposed drug and the main comparator) and that they make sense to the respondent (see guidance on constructing the scenarios above in this section of this appendix). The number of scenarios will increase with the number of attributes and attribute levels, and it is generally not feasible to present all combinations of scenarios in a questionnaire. Use an appropriate experimental design, typically a fractional factorial design based on orthogonality, to choose the subset of scenarios to be presented in the experiment. Describe and justify the basis for generating the experimental design, including details of any software

used. Provide the full experimental design in an attachment to the submission, including a list of all scenarios developed.

– *Establish preferences using discrete choices*: present each respondent with a series of pairs or groups of options (choice sets) among the scenarios and request that a selection be made defining which is the most preferred. Ranking and rating exercises have been used in conjoint analysis; however, the use of discrete choice experiments is preferred, because they are more consistent with the choice-based nature of SG and TTO, and have a more established basis in economic theory and statistical analysis.

– *Analyse data*: analyse the responses from the scenarios using regression techniques. Typically, a multinomial logit analysis is used because the dependent variable is a discrete random variable. Justify the modelling approach, including consideration of treatment of repeated observations and heterogeneity (eg use of mixed logit). Report on the extent to which the model explains the variation in preference selection. Explore the impact of possible confounding factors.

Claimed advantages of conjoint analysis include the ability to describe health state changes in terms of comparisons across the attributes, the duration of these changes and the probability of these changes occurring. Although the techniques of conjoint analysis are developing, they are still not yet sufficiently acceptable to have direct influence on PBAC decision making on their own. They are claimed to also explicitly consider nonhealth elements (in which case, results should be presented with and without including those elements). However, it is not clear that there is an acceptable framework outside the QALY framework in which to consider these claimed advantages in a comparable way across submissions

Ensure that the sample size is large enough to measure population variance. The power of the study should be tested and between-group correlations should be demonstrated.

Present the results of the utility study as part of the information provided in response to Subsection C.2. Report the results as the point estimate of the mean utility of each health state scenario with its 95% confidence interval. In discussing these results, provide an overall assessment of the approach adopted to elicit preference weights from the hypothetical scenarios. Consider particularly:

- whether the methods by which the health state scenarios were constructed allow all the critical changes in quality of life associated with the intervention to be captured and presented in such a way that they are accurately perceived by the respondents

- whether the methods by which the health state scenarios were derived and constructed are likely to lead to bias in the valuation of health-related quality of life associated with the intervention, for example, by focusing on some aspects of health-related quality of life (eg example physical functioning) while excluding or minimising the impact of others (eg mental or social health).

From these results presented in Subsection C.2, identify and justify the estimates to be used as variables in the economic evaluation presented in Subsection D.5 for the base case and Subsection D.6 for the sensitivity analyses.

A6.5 Other methods for obtaining utilities

The following methods have all been presented in submissions to PBAC. Each raises a series of concerns, as detailed below.

Mapping of generic and disease-specific scales

In contrast with MAUIs, although other generic and disease-specific scales may be based on sophisticated psychometric techniques for instrument construction, none of those scales is capable of representing individual preferences on a scale of 0 = death and 1 = 'full health', and so none can be used to calculate QALYs without some transformation. Despite this, a number of attempts have been made to 'map' from scores reported in randomised trials using generic or disease-specific quality-of-life measures into utility weights, which are then used to construct QALYs. Approaches vary from a simple intuitive mapping to the use of statistical techniques. For example, responses on a visual analogue scale of 0 to 100 to the question asking respondents to rate their health today have been divided by 100 and (wrongly) claimed to therefore measure utility weights on a 0 to 1 scale. Another example is the use of regression to 'map' an association between two sets of responses from a survey of respondents, each completing both the quality-of-life instrument and a MAUI or other acceptable technique of eliciting preference weights. This regression 'map' is then used to transform into 'utilities' the responses to the quality-of-life instrument reported by respondents in another trial.

These are not well-established procedures. Where statistical techniques have been used, tests of reliability might include the predictive value of the technique across a range of quality-of-life values and changes in quality of life within, and differences between, respondents in the relevant medical condition. Where this approach is adopted, extensive sensitive analysis around the estimates generated should be undertaken to examine the sensitivity of results of the economic evaluation to this variable. Where such 'mapping' is presented, special attention needs to be given to establishing that the results generated are plausible and unbiased, particularly where the preference weight estimates generated have a substantial impact on the results of the economic evaluation.

It is difficult to illustrate the assessment of plausibility and bias in these circumstances. An approach that does not 'map' to an adequate utility instrument (ie that satisfies characteristics (b) and (c) of QALYs shown above) would not meet an essential prerequisite in estimating a preference weight index. An approach that is not based on a study that concomitantly measured the quality-of-life measure and such an index would also not meet an essential prerequisite to generate an association. Other issues to assess include the difficulties of 'mapping' ordinal (ranking) scales to the cardinal utility scale, the presence of floor and ceiling effects in most quality-of-life measures, and whether an acceptable range of important dimensions are adequately captured (the latter two have been assessed as acceptable for the MAUIs recommended in Subsection B.5). A more structural approach might be taken to map specific dimensions of a generic quality-of-life instrument to corresponding dimensions of a multi-attribute utility instrument (possibly best exemplified by the mapping of the SF-36 to the SF-6D), but this involves a much greater amount of developmental research work.

Population matching studies

Another alternative occasionally used involves recruiting a separate sample of patients with characteristics similar to those in the randomised trials and for whom listing is requested. These matched patients then complete a MAUI reflecting their current health state (as a surrogate for a trial participant directly completing the MAUI), which is then used to estimate utility weights for the economic evaluation.

This population-matching approach is also subject to multiple sources of bias and thus uncertainty, particularly related to how similar the sampled patients are to those in the economic evaluation and the inability to blind the sampled patients from the objectives of the study. This can be context-specific; for example, if there are important symptomatic drug toxicities, it might be particularly important to ensure that the sampled patients are exposed to the drug and its toxicities at the time the MAUI is completed.

This approach might be strengthened by getting the sampled patients to complete another quality-of-life instrument that was completed in the trials, and using the results of this concurrent instrument to more closely match a subset of sampled patients with trial participants and with the population for whom listing is requested. It can also be used to develop sample-based statistics of variance around the utility weights, which can be used in the sensitivity analysis of the economic evaluation.

Preference weights ('utilities') sourced from the literature

'Off-the-shelf' utility estimates may sometimes be available from the literature, and have been most often used when seeking to examine the impact of quality-adjusting a survival claim estimated in terms of life-years gained. As for any presentation of secondary (or even tertiary) data or analysis, the validity of the utility estimate depends on the methods used to elicit the estimate. Accordingly, present and assess the results against the preferred characteristics of a primary utility study, including:

- how the studies were identified (eg systematic search preferred to selective reporting)
- how representative the health state in each identified study is of the health state in the presented economic evaluation (including in dimensions of the type and severity of symptoms and the duration of the health state)
- how the health state was captured (eg MAUI versus scenario-based)
- how the preference was elicited (eg SG or TTO)
- what sample was chosen to respond to the MAUI questionnaire or scenario (eg members of the general public, patients, care givers, 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.

A particular difficulty in interpretation has occurred when a cost-utility analysis relies on combining utility weights across different sources for different health states within an economic evaluation, particularly across different sources that used different methods.

Appendix 7   Monetary valuation of health outcomes

A7.1 Preference for cost-utility analyses over cost-benefit analyses

Cost-benefit analyses are not preferred by PBAC because they are not likely to be helpful to most PBAC deliberations. The reasons for this are as follows:

- Cost-benefit analysis is typically applied in the context of a fixed decision rule, which does not incorporate the breadth of equity and ethical considerations that are relevant to PBAC decision making (see also Appendix 1).

- The use of willingness to pay (WTP) to elicit monetary valuation for a cost-benefit analysis, which will be influenced by an individual's income and assets, is inconsistent with the principles of PBAC as a subsidy program to ensure equity of access.

- There remain considerable problems with interpreting WTP responses in the context of the Australian health care system where individuals do not typically face market prices. It could be argued further that the PBS, which uses fixed levels of co-payment and safety nets to achieve its objective in minimising low income as a barrier to accessing drugs listed on the PBS, removes price signals even more than other elements in the Australian health care system.

- The methods for deriving monetary valuations of health gains presented to date have not satisfactorily minimised the hypothetical nature of the responses elicited or the incentives for the respondents to provide values that reflect a desire to have the PBS subsidy proceed in the full knowledge that the respondent will not directly incur this cost. Although it is theoretically possible to improve the realism of the scenarios and of the questions asked to elicit plausible monetary values (see Subsection A7.2 of this appendix), there remains a residual uncertainty in aligning the provision of resources valued in monetary units with welfare outcomes, which are apparently valued in the same monetary units.

- Cost-benefit analyses typically assign preference weights including to other welfare changes beyond the primary focus of PBAC on health outcomes (these include production changes and process changes), which have tended to reflect the construction of the scenario or attribute used to elicit the monetary valuation rather than to reflect the weights assigned by PBAC when considering a fuller range of other relevant factors, particularly equity.

- For the above reasons, there is unlikely to be a consistent exchange rate between monetary valuation and the utility weight that is the preferred basis for assessing strength of preference (see Subsection A6.1 of Appendix 6). Therefore, considering these two approaches to valuing outcomes in parallel would predictably result in inconsistent decisions across submissions. This is undesirable.

- Although it is possible to use utility-based instruments in randomised trials to estimate the strength of preference for different health outcomes (see Subsection B.5), this is not yet practical for monetary-based instruments. Therefore, the advantages outlined in Subsection A6.3 of Appendix 6 for trial-based utility weights cannot be generated for monetary valuation. There are therefore disadvantages in common

between scenario-based utility valuation (see Subsection A6.4 of Appendix 6) and scenario-based monetary valuation (see Subsection A7.2 of this appendix).

Given the above reasoning, monetary valuation of health outcomes is allowed but is considered to be supplementary to utility valuation. Therefore, if both a cost-utility analysis and a cost-benefit analysis are presented in a submission, discuss the differences in the results and any differences in conclusions. In the absence of a cost-utility analysis, discuss why only a cost-benefit analysis is thought to be informative and why a cost-utility analysis is not possible. For example, consideration of such analyses might be justified in some situations to provide informative insights to the perception of the respondents to the clinical performance of a proposed drug; however, such analyses should be interpreted cautiously in the absence of a worthwhile gain in health outcomes. Further guidance is provided in Subsection A7.2 of this appendix.

A7.2 Scenario-based monetary valuation of health outcomes

Background

Monetary valuation of health outcomes is typically scenario based. The issues raised in Subsection A6.4 of Appendix 6 regarding the use of scenarios as a basis for eliciting the strength of preference in a utility metric largely overlap with their use as a basis for eliciting the strength of preference in a monetary metric. It is conceivable that monetary valuation could be elicited in the context of a randomised double-blind trial, but the practicalities of addressing the issues raised below suggest that this will not occur in the near future.

This appendix seeks to identify those areas where monetary valuation might be informative in situations where utility valuation is problematic. Situations identified to date have tended to arise due to concerns over the lack of sensitivity of utility valuation to perceived increments in health outcomes. These have included short-term changes in health outcomes, differences in health outcomes that are too small to be detected with utility-based instruments, and differences across adverse reaction profiles for two drugs that are otherwise similar in terms of comparative effectiveness. An alternative metric might be justified in these circumstances, because underlying the quality-adjusted life-year (QALY) approach is the fact that survival duration is the metric, and there might be health gains that are valued, but that are not sufficient for individuals to trade off survival. However, this reduces comparability across submissions, because it introduces a new valuation system that is not necessarily interpreted the same way in the valuation step by the respondent as utility valuation, and also brings in other aspects, whether implicit or not, beyond valuing health outcomes.

A submission seeking to supplement a utility valuation of health outcomes with a monetary valuation of health outcomes should provide a justification for doing so. Alongside this justification for providing these supplementary estimates, present both sets of methods and results and comment on the interpretation of the results compared with each other. As with the interpretation of the results of any measure of health outcomes, any claim for an improved sensitivity in quantifying the utility weight of smaller advantages needs to be assessed against the possibility of a true negative (ie that the proposed drug has no overall perceptible incremental effect on strength of preference; see also Subsections A6.3 and A6.4 of Appendix 6). Document the evidence that supports any claim that any difference in results between utility-based valuation and monetary-

based valuation is attributable to the special characteristic of the health state and not some idiosyncrasy in the utility measurement procedures that have been adopted. This would help justify any apparent diminution in comparability across submissions that provide utility weights.

A submission that provides monetary valuations of health outcomes without corresponding utility valuations would be more difficult to assess in terms of comparability across submissions.

Consistent with the request in Section D and Subsection A6.4 of Appendix 6, a submission that seeks to provide a monetary valuation of any attribute other than health outcomes (eg a production change; see Appendix 8) should do so separately from the valuation of health outcomes. This can be done by providing a supplementary economic evaluation that adds the additional information to the base case economic evaluation. A request in a submission for PBAC to consider a nonhealth outcome or process attribute (such as convenience of use, increased availability of options and any other externality) would need to be judged on its merits, which would be informed by the direction and extent of the impact of its inclusion on the base case economic evaluation. This distinction is therefore important both to promote consistency of decision making based primarily on health outcomes and to allow flexibility to consider other factors that PBAC might accept as relevant.

Presenting the methods of generating scenarios and presenting them to respondents

If preference weights in monetary units have been derived with the use of hypothetical health state scenarios, provide details of the methods used in the study as part of the information provided in Subsection C.1. Provide data and references that support the validity and reliability of these methods. Refer to the text under the corresponding subheading of Subsection A6.4 of Appendix 6 to identify the information to be provided, including a clear description of the attributes that are compared between the proposed drug and its main comparator. Additional information specific to monetary valuations includes the following:

- Describe the attributes in each scenario in a way that matches the policy question and the underlying theoretical construct to be addressed in the contingent market.

- Whenever a probability of any type is included for an attribute in a scenario, examine more than one level of probability when eliciting monetary values in order to assess the degree of understanding (eg that a greater probability of benefit yields a greater monetary value of WTP).

- Where scenarios are developed as changes in health states rather than as the health states themselves, describe the likelihood, extent and duration of each change.

Elicitation, statistical analysis, reporting of results and interpretation of scenario-based monetary valuation of health outcomes

The most commonly used method is contingent valuation (CV) to elicit willingness to pay (WTP). If a CV study is included in a submission, provide a justification for its inclusion, including why it would be informative for PBAC decision making.

The submission should outline the methodology adopted in designing and implementing the CV survey instrument. Demonstrate that consideration has been given to the following:

- The contingent (hypothetical) market should be a simple out-of-pocket payment to elicit the individual's strength of preference by considering the question of spending their private income to estimate the value of the change in health states being presented. Ensure that respondents understand the nature of the payment vehicle and that their responses are interpreted appropriately. The average WTP across respondents from this valuation might not necessarily be the WTP that society overall has for subsidising drugs to improve health outcomes for the population as a whole, but it is not clear that changing the hypothetical market to reflect a societal question of funding a public subsidy program would be meaningful to respondents. This market should also be described in simple language, eliminating unnecessary words and avoiding technical jargon.

- The initial WTP elicitation instrument describing the contingent market should be piloted alongside the piloting of the background information and the scenarios. Report any issues arising and how they were addressed before the full study began.

- Discuss the choice between a discrete choice format or an open-ended questionnaire format (with prompts or a payment card) to elicit responses. The closed-bid discrete choice format with randomly selected bids presented to each respondent and only one bid per respondent is more theoretically valid and less subject to bias than the other methods. Other issues to consider include the sample size required for the statistical analysis to infer the mean WTP from discrete choices and the increased likelihood of nonresponse or protest response from open-ended questions. Justify the range of values used in the discrete choices or the prompts or payment cards. When conducting the survey, randomly allocate the selection of the order of discrete choices across respondents or the selection from the range of values in prompts and cards.

- To ensure some consistency within the timeframes across different WTP studies, frame the questions in one of two ways:

  – as a one-off payment but constrained to within any one year, by invoking each respondent's annual (rather than lifetime) income

  – as a regular yearly payment, with the value derived for 'this year' only, not for a 'hypothetical' year.

- Remind respondents of their budget constraints for their WTP throughout the survey.

- When conducting the survey, adopt a random ordering of questions across respondents.

- WTP studies should be conducted in a comparative sense and respondents should be made aware of any close substitutes. This would help to make clear the extent of incremental improvement in health across the alternatives.

- WTP is expected to be correlated to ability to pay. Indicate whether ability to pay has been assessed according to personal or household income (and, if the latter, whether this is adjusted for household size) and whether it has been assessed according to current income or also reflects assets that could be realised to make payments. Sociodemographic characteristics of respondents should be collected and included in the analysis.

From the above information, indicate the steps that have been taken to minimise the following sources of bias in the WTP survey:

- *hypothetical bias*: the respondent responds to a perception that the survey is hypothetical with hypothetical and therefore meaningless answers

- *strategic bias*: the respondent varies the WTP from the 'true' WTP in order to increase the chances of getting a preferred decision by influencing the decision maker

- *interviewer bias*: face-to-face or telephone interviews run the risk that valuation will be influenced (purposefully or accidentally) by the interviewer

- *starting-point bias*: the initial prompt or bid in the bidding approach will anchor the respondent towards the starting bid, narrowing the distribution around the mean (portraying greater consensus than truly exists) and causing a loss in efficiency

- *'yea-saying' bias*: the respondent will agree with amounts as offered by interviewer

- *range bias*: the elicitation procedure presents a range of potential WTP amounts that influences the WTP amount given by respondents

- *sponsor bias*: knowledge of the identity of the sponsor affects responses; minimised by not naming the sponsor of the survey or the manufacturer of the drug.

The validity of the WTP depends on minimising sources of bias in order to reveal the true strength of preference in monetary terms.

Some preliminary guidance in relation to other stated preference methods, such as discrete choice experiments and conjoint analysis, is presented under the corresponding subheading in Subsection A6.4 of Appendix 6. The methodological guidance on those methods should be considered in addition to the general guidance given above in this section for valuing discrete health states. In addition, discrete choice experiments might also be used to calculate monetary measures of the composite of incremental health outcomes from the proposed drug as a comparison of the alternative profiles of health outcomes over defined periods of time resulting from the proposed drug and the main comparator. If so, justify the presentation of these profiles of health states to ensure that they realistically and accurately reflect the choice context (for example, allowing for a 'status quo' or an 'opt out' option where appropriate for the presentation of the alternative profiles in each choice set) and that they make sense to the respondent (see general guidance on constructing the scenarios).

The statistical analysis, interpretation and reporting of data

Present the results of the scenario-based monetary valuation study as part of the information provided in response to Subsection C.2. Report mean WTP values on a net present value basis for each health state and then the overall aggregate with their 95% confidence intervals, interquartile range and full range.

Assess the results of the WTP survey as follows:

- Present WTP values without adjustment for income. Also report WTP disaggregated across income group. Where the mean ability to pay in the survey differs from the national average, comment on the interpretation of the results.

- Present the results both in an unadjusted fashion and with outliers removed. Discuss any difference in these results.

- Report the response rate. Comment on the implications of the response rate and other potential sources of selection bias for the interpretability of the results of the survey.

- Report the proportions of zero and very high bids. If either or both of these are greater than 10%, discuss the possible reasons for these proportions and their implications. Ask respondents to explain their reasons for responding with a zero bid.

- Conduct regression analyses to assess the factors that might explain the WTP values given. Variables to examine include an 'interviewer' variable, a 'question order' variable, a 'prompt' variable (of the range of starting values in the prompt), and an 'income' variable.

- Assess whether the results make economic sense (ie that WTP increases with the size of both health gains increases and ability to pay increases).

WTP values are context specific, so values should only be used and applied to the specific circumstances for which they were obtained. WTP values are interpreted as an upper limit to true valuation. From these results presented in Subsection C.2, identify and justify the estimates to be used as variables in the economic evaluation presented in Subsection D.5 for the base case and Subsection D.7 for the sensitivity analyses.

Appendix 8 — Including nonhealth care resources and nonhealth outcomes in a supplementary analysis

This appendix provides additional guidance on the preparation of supplementary analyses of an economic evaluation to incorporate changes in nonhealth care resources and/or nonhealth outcomes that would be attributable to the listing of the proposed drug (see Subsection D.1).

A8.1 Identifying, measuring and valuing nonhealth care resources

Occasionally, because of the medical condition under treatment or the age of the patients, consideration of direct nonhealth care costs such as social services (home help, day care, meals on wheels, private travel to access health care, etc) might be relevant.

If incorporation of nonhealth care resources is relevant for a supplementary analysis, adapt the general principles as detailed in Subsection D.4 and the *Manual of Resource Items and their Associated Costs* for health care resources to generate and present these variables. In brief, the resources should be identified and defined. An appropriate unit of measurement should be identified and the extent of change in the provision of the resources should be estimated. Present and justify an appropriate unit cost to estimate the value of the resources.

A8.2 Identifying, measuring and valuing nonhealth outcomes

Occasionally, listing a proposed drug might generate worthwhile impacts that are not captured as health outcomes, such as the value of information to the patient generated by an additional diagnostic test that does not change management of a medical condition.

If incorporation of changes in nonhealth outcomes (including economic outcomes) is relevant for a supplementary analysis, adapt the general principles outlined in Subsection D.4 for health outcomes, including by reference to Subsection A7.2 of Appendix 7, as appropriate. In brief, the outcome should be identified and defined. An appropriate unit of measurement should be identified and the extent of change in the outcome should be estimated. Present and justify an appropriate valuation of the outcome.

Production changes

A production change is the value estimated in monetary units of the potential working time gained or lost measured in time units (days, weeks, years etc), which is realised as productive activity. It may also include realising the productive change of the potential impaired working time gained or lost by a sick patient continuing to work (measured in similar time units together with a measure of any associated change in the extent of impairment). Production changes have been called indirect economic outcomes in recognition of the fact that subsequent decisions had to be made to realise the time gained

as productive activity to the advantage of the rest of society rather than as any other activity.

Provide a strong justification if production changes are combined with surrogate outcome indicators in an economic evaluation because this combination is generally inappropriate.

If production changes are to be included in a cost-utility analysis, adopt a method that 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 to the individual receiving the proposed drug. These health-related changes are therefore already appropriately included in the denominator of the cost-utility ratio.

Unlike direct health benefits, the economic benefit to society through patients' return to, or maintenance of, productive capacity is both difficult and controversial to estimate accurately. This is because the available methods and their application remain unresolved. Therefore, although changes in production as an outcome of therapy may be included in supplementary analyses in submissions to PBAC, they should not be included in the base-case analysis.

There are several difficulties in estimating the net present value of production changes. These estimates are underpinned by three assumptions:

- for short-term absence, production will be made up on the 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 otherwise unemployed.

Where estimation of production changes can be justified in the submission, address each of the three underlying 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 due to returning to health from an episode of illness depends on demonstrating that:

- the worker returns to work

- 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 (Note: if the worker is highly productive, the incentives to replace him or her are stronger.)

- no temporary replacement from outside has been employed (namely, that there is full employment).

As in this example, the **marginal** increase in society's production due to the return of healthy workers to the workplace is overestimated if the human capital method is used; that is, the workers' time regained is simply multiplied by the labour market value of the average worker (usually estimated by the average wage). It is not always likely to be zero either, but some proportion in between. Provide and justify the best estimate of the true proportion based on firm evidence.

Addressing the four questions in the example above would therefore help to convert the potential working time gained or lost reported in time units into production gains or losses

reported in monetary units. The friction method has been advocated as a method that provides a basis to help make this type of conversion. Although there is no evidence that it has yet been applied in Australia, it is theoretically preferable to the human capital method for this reason. However, in the example provided above, it only offers a basis for addressing the last two of the four questions and only does so by proposing an indirect estimate at the national level rather than a direct estimate at the patient level. The friction method therefore still generates an upper estimate compared with an approach that could address all four of the questions above. Other evidence needs to be provided to address the first two questions, because not all healthy workers would choose to deploy the time gain to return to contributing to societal production. In the example above, recognising that this choice exists is important because deploying the time gain for some other purpose, such as a leisure activity, is an intrinsic part of valuing the improved health as a gain in utility weights rather than valuing it as a production gain to society in monetary terms.

Any evidence to support an estimate of the proportion of people who choose to return to contributing to societal production would also need to account for the influence of incentives provided through various types of sickness benefit payments provided by social security systems and employers, which vary across countries. This might hinder the translation of overseas evidence to Australia.

Answering all four questions satisfactorily in the example above would therefore help minimise double-counting across the denominator and the numerator of an incremental cost-utility ratio, because it would more accurately estimate the extent of production gains to society beyond the gains valued by the population benefiting with improved health. Valued in monetary terms, these production gains would represent a more suitable estimate for inclusion in the numerator of this ratio.

The above example is intended to illustrate the application of the three more general reasons. A similar approach would be needed in other contexts, such as a drug that prevents future episodes of illness, or a drug that might improve production capacity in individuals who, without the proposed drug, would otherwise stay at work, although unwell, and therefore perform at less than full production capacity.

Present the results of the economic evaluation excluding the production changes in the base case. Assess the impact of including these changes in a supplementary analysis. This separation allows PBAC to consider the impact of their inclusion on the direction and extent of change on the base case.

At the same time, PBAC can weigh up, as another relevant factor, the inevitable equity implications of varying the base case to include an element that explicitly favours those who make a greater contribution to production. Inclusion of production gains favours those interventions that improve the health of people who are able and choose to return to contributing to societal production.

The present value of production changes should be calculated. This means that where production gains are anticipated over a number of time periods (beyond one year) these should also be discounted. Discounting future costs and benefits is a standard feature of economic evaluation. Costs or benefits are discounted at an annual rate of 5%.

A8.3 Resources and outcomes to be excluded

Costs should be limited to those associated with the medical condition under treatment. In other words, do not include as consequences in the economic evaluation other unrelated medical conditions that, in the fullness of time, are likely to afflict patients who live longer as a result of effective treatment that they receive now.

Appendix 9   Developing utilisation and financial estimates

As discussed in Part II, Section E and Part III, Section E(i), there are two broad approaches (epidemiological and market share) to developing utilisation and financial estimates. The two approaches are not mutually exclusive and Figure A9.1 shows the relationship between them.
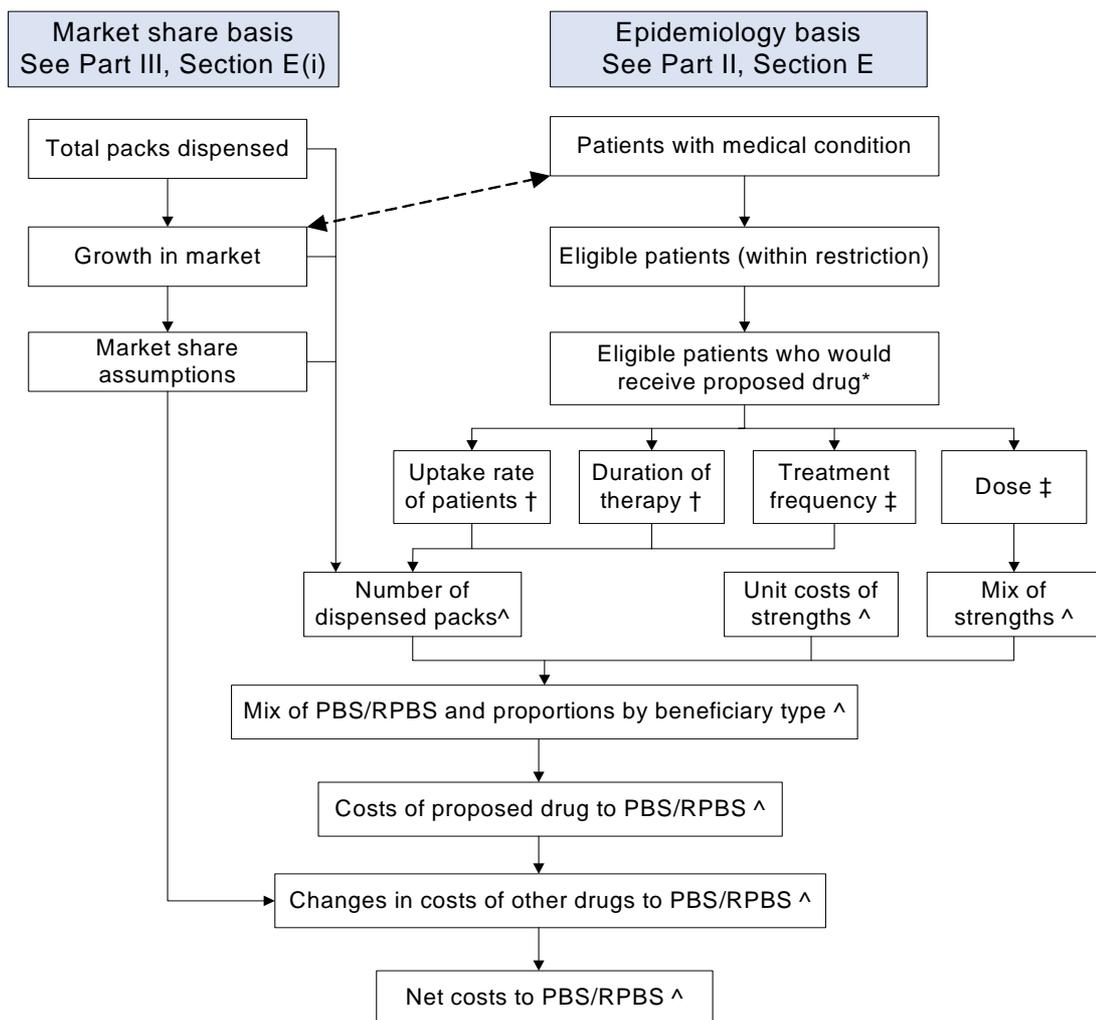
* Monitored by Medicare Australia's Authorities Database/Medicare Australia's data of processed prescriptions (which are incomplete for some drugs, eg most section 100 drugs)/other databases
† Partly monitored by market research/prescribing databases
‡ Monitored by market research/prescribing databases
^Monitored by Medicare Australia's data of processed prescriptions (which is incomplete for some drugs, eg section 100 drugs)

Figure A9.1   Development of utilisation and financial estimates (submission section E): relationship between the epidemiology and market share approaches

Appendix 10 Measures taken by the investigators to minimise bias in nonrandomised studies

This appendix is relevant to Part III, Section B(ii). It is designed as a useful guide to help PBAC and the sponsor review the scientific rigour of the evidence by assessing the measures taken by the investigators to minimise bias. It is not intended to discourage the presentation of data.

Categorise studies into the study types defined below. Then, for each methodological topic listed for the relevant study type, choose the description that best fits each study. If the submission includes a number of studies of the same type, tabulate the responses. In each case, the methodological descriptions are arranged in a descending order of quality (ie 1 is worst).

As for the assessment of randomised trials in Part II, Section B and Part III, Section B(i), the purpose of these assessments is to provide the sponsor and PBAC with a clear idea of which studies are of greater scientific rigour. There is no minimum standard, but PBAC is most likely to be persuaded by the data of the highest scientific rigour. Submissions should therefore be particularly careful to justify using the results of studies with less scientific rigour in an economic evaluation in place of trials with greater scientific rigour.

There may be other aspects of particular nonrandomised studies that might affect the results of such studies and their comparability with different studies of the same type. If these aspects are likely to be important, they should also be identified.

Note: In each case, if there is insufficient information available to classify the study, assign it to category 1.

A10.1 Classical observational designs

Controlled cohort studies

In this study type, assignment of the groups of individuals to treatment is not random. However, individuals receiving the proposed drug are followed forward in time from their first exposure and control individuals are followed forward in time from their enrolment in the study. Cohort studies can be concurrent or historical. In the former, the study is planned and conducted prospectively. In the latter, existing records are used to define treatment status and determine the outcomes.

Possibility of confounding

It is important that there are no substantial differences at the baseline between treated and control participants in respect of factors that could influence the outcome(s) being studied. Identify which of the following best describes the differences in baseline factors:

1. There were significant differences in baseline factors between treated and control participants that have been shown to influence the study outcome(s), and these were not adjusted for in the main analysis.

2. There were significant differences in baseline factors between treated and control participants that might have influenced the study outcome(s), and these were not adjusted for in the main analysis.

3. There were no differences in baseline factors between treated and control participants that might have influenced the study outcome(s); or any differences were adjusted for in the main analysis.

Adequacy of follow-up

It is important that an attempt is made to summarise the study outcomes for all participants who were included in the study. Identify which of the following best describes the adequacy of follow-up in the study:

1. There were significant numbers of drop-outs with no assessment of study outcome(s) in the participants who dropped out, and drop-out rates differed between treated and control groups.

2. There were some drop-outs with no assessment of study outcome(s) in the participants who dropped out, and drop-out rates were (approximately) equivalent in treated and control groups.

3. Study outcome(s) were assessed in all or nearly all treated and control participants.

Blinding of outcomes assessment

It is important that the observer responsible for measuring the study outcome is unaware of whether the participant belongs to the treated or control group. Identify which of the following best describes the blinding of outcomes assessment:

1. There was no attempt to blind the observer(s) to the treatment or control status of the study participants, or any attempt made was inadequate to keep the observer(s) fully blind to the treatment or control status of the study participants.

2. The observer(s) were kept fully blinded to the treatment or control status of the study participants.

Case-control studies

In this study type, participants are defined by the presence (cases) or absence (controls) of the study outcome, and their prior use of the proposed drug is compared.

Selection of cases

It is most important that cases are selected independently of their treatment status. Identify which of the following best describes the selection of cases:

1.   The process of referral and selection of cases was likely to have been influenced by the participants' prior use of the drug and knowledge of the association between use of the drug and study outcome (eg a woman of child-bearing age with a painful swollen leg is more likely to be referred for investigation if she has been using an oral contraceptive).

2.   The process of referral or selection of cases was not influenced by the participants' prior use of the drug or knowledge of the association between use of the drug and study outcome.

Selection of controls

The purpose of the control group is to provide an estimate of the odds of exposure in participants who are free from the disease in question in the source population. Identify which of the following best describes the selection of controls:

1.   The controls were not drawn from the same source population as the cases.

2.   The controls were drawn from the same source population as the cases (community controls).

Possibility of confounding

It is important that there are no substantial differences between cases and controls in respect of factors that could influence the outcome being studied, other than the risk of exposure to the drug. Identify which of the following best describes the comparability of cases and controls:

1.   There were significant differences in factors between cases and controls that have been shown to influence the study outcome, and these were not adjusted for in the main analysis.

2.   There were differences in factors between cases and controls that might have influenced the study outcome, and these were not adjusted for in the main analysis.

3.   There were no differences in factors between cases and controls that might have influenced the study outcome, or any differences were adjusted for in the main analysis.

Possibility of measurement bias

It is important that assessment of treatment status (or exposure) is made in an unbiased way. Identify which of the following best describes the assessment of treatment status:

1.   The measurement of previous drug use (or exposure) was made using an unstructured interview or questionnaire by an observer who was aware of the case or control status of the participants.

2. The measurement of prior drug use (or exposure) was made using a structured interview or questionnaire by an observer who was aware of the case or control status of the participants.

3. The measurement of prior drug use (or exposure) was made using a structured interview or questionnaire by an observer who was unaware of the case or control status of the participants, or the definition of exposure preceded the outcome (eg based on a computerised prescription record, as in a case-control study 'nested' in a larger cohort).

A10.2 Quasi-experimental designs

'Before and after' studies

In this type of study, participants are observed before and after an intervention (eg a new drug) is introduced. It is really only possible to use this design if the manifestations of the illness being treated are both chronic and reversible. Typically this will be an opportunistic study, rather than planned. In addition to the sources of bias that affect the previously mentioned observational designs, this study type has particular problems related to time (or order) effects, resulting from the participants being observed over a period, and the lack of a contemporaneous control group. There may be changes in disease severity, symptomatology or resource use that occur independently of any treatment, and it is impossible to assess these properly without a contemporaneous control group. It is highly likely that participants would be switched to the new therapy because they have not been doing well on the old therapy, and thus their symptoms would tend to be most severe at the time of switching. Regression to the mean will make the new drug seem better than the old one, in terms of both apparent treatment responses and resource provision.

Selection of participants

1. The participants were selected retrospectively from case notes, and the investigators were probably aware of the responses to the old treatment at the time of selection.

2. The study was planned, prospective data collection was undertaken in both study periods, and selection of the participants was made without knowledge of the treatment responses.

Possibility of confounding

1. There were within-participant differences in factors between the two study periods that were likely to influence the study outcome(s), and these were not adjusted for in the main analysis.

2. There were no within-participant differences in factors between the two study periods that were likely to influence the study outcome(s), or any differences were adjusted for in the main analysis.

Adequacy of follow-up

1. Drop-out rates differed between the 'before' and 'after' study periods, with no assessment of study outcome(s) in the participants who dropped out.

2. There were no drop-outs in either study period (this implies prospective data collection in both periods), or study outcome(s) were assessed in all participants who were commenced on treatment.

Blinding of outcomes assessment

1. The observer(s) responsible for outcome assessment were aware of which treatment the study participants had been receiving.

2. The observer(s) responsible for outcome assessment were kept fully blinded to the treatment being received by the study participants.

Case-series with historical controls

Typically, this type of study is carried out by a clinical department that has introduced a new management procedure and wishes to compare the results with those of patients treated previously in the department using the old management procedure. Therefore, this type of study shares the same problems of order effects as 'before and after' studies but does not involve the same individuals in both arms.

Selection of participants

1. The participants were selected retrospectively from case notes, and the investigators were probably aware of the responses to the old treatment at the time of selection.

2. The study was planned, prospective data collection was undertaken in both study periods, and selection of the participants was made without knowledge of the treatment responses.

Possibility of confounding

1. There were differences in factors between participants in the two study periods that were likely to influence the study outcome(s), and these were not adjusted for in the main analysis.

2. There were no differences in factors between participants in the two study periods that were likely to influence the study outcome(s), or any differences were adjusted for in the main analysis.

Adequacy of follow-up

1. Drop-out rates differed between the two study periods, with no assessment of study outcome(s) in the participants who dropped out.

2. There were no drop-outs in either study period, or study outcome(s) were assessed in all participants who were commenced on treatment.

Blinding of outcomes assessment

1. The observer(s) responsible for outcome assessment were aware of which treatment the study participants had been receiving.

2. The observer(s) responsible for outcome assessment were kept fully blinded to the treatment being received by the study participants.

Comparison of the results of two or more single-arm studies

In addition to all the problems noted earlier with 'before and after' studies or case-series with historical controls, this approach has the added disadvantage that the outcome assessments were made by different investigators in different settings. It is not possible to compare the results of such studies with any confidence. Assess comparisons involving single arms extracted from randomised trials (when compared without a common reference) as comparisons of the results of two or more single-arm studies.

Selection of participants

1. In the studies for either or both alternatives, the participants were selected retrospectively from case notes, and the investigators were probably aware of the responses to the old treatment at the time of selection.

2. The studies for both alternatives were planned, prospective data collection was undertaken for all consecutive patients in the study period, and selection of the participants was made without knowledge of the treatment responses.

Possibility of confounding

1. There were differences in factors between participants in the study populations for the two alternatives that were likely to influence the study outcome(s), and these were not adjusted for in the main analysis.

2. There were no differences in factors between participants in the study populations for the two alternatives that were likely to influence the study outcome(s), or any differences were adjusted for in the main analysis.

Adequacy of follow-up

1. Drop-out rates differed between the studies for the two alternatives, with no assessment of study outcome(s) in the participants who dropped out.

2. There were no drop-outs in the studies for either alternative, or study outcome(s) were assessed in all participants who were commenced on treatment.

Blinding of outcomes assessment

1. In the studies for one or both of the alternatives, the observer(s) responsible for outcome assessment were aware of which treatment the study participants had been receiving.

2. In the studies for both alternatives, the observer(s) responsible for outcome assessment were kept fully blinded to the treatment being received by the study participants.