Guidelines for company submissions for funding consideration of medicines and cell, tissue and gene therapy products

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agency for
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Record of updates

Date	Version	Summary of changes
December 2020	1.0	Publication of initial procedures and guidelines for company submissions to ACE.
March 2022	1.1	Updated to clarify the ERC critique process and include information about process for companies to discuss risk-sharing agreement with ACE for their products, and to revise the MOH Drug Advisory Committee's terms of reference. Minor additions, wording changes and amendments of Figures throughout the document have also been made to improve the clarity of the text.
March 2023	1.2	Minor additions, wording changes and amendments of Figures throughout the document and templates have been made to improve the clarity of the text and streamline processes.
September 2023	1.3	Minor additions and wording changes throughout the document have been made to improve the clarity of the text and streamline processes.
January 2024	1.4	Updated to clarify the pricing resubmission process, re-registering submission intent, pre-submission meetings, ERC's response to the company response template and including a detailed change record for changes made to the evidence submission.
April 2024	1.5	Minor changes regarding submissions for related indications and updated reference links.
October 2024	1.6	Updated to include CTGTP List. Minor additions and wording changes have also been made to improve the clarity of the text and streamline processes.
October 2026	2.0	Updated to incorporate abridged evaluation pathway, clarify the pricing resubmission process, include new guidance on risk-sharing agreements, incorporate the charging procedure previously published as a separate document, clarify literature search requirements, and revise key company response timelines. Revisions have been made to improve clarity of the text. The guide has also been separated into two documents for ease of reference. (A) Procedures for company submissions for funding consideration of medicines and cell, tissue and gene therapy products (B) Guidelines for company submissions for funding consideration of medicines and cell, tissue and gene therapy products

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Abbreviations and acronyms

Term	Definition
ACE	Agency for Care Effectiveness
BIA	budget impact analysis
CDA-AMC	Canada's Drug Agency
CI	confidence interval
CDL	Cancer Drug List
CDS	Cancer Drug Subcommittee
CTGTP	cell, tissue and gene therapy product
CMA	cost-minimisation analysis
CrI	credible interval
CSR	clinical study report
CUA	cost-utility analysis
DAC	Drug Advisory Committee
EMA	European Medicines Agency
ERC	Evidence Review Centre
FDA	Food and Drug Administration
HSA	Health Sciences Authority (Singapore)
HTAC	Health Technology Advisory Council
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
LOA	Letter of Acceptance
LOU	Letter of Undertaking
MAF	Medication Assistance Fund
MAUI	multi-attribute utility instrument
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MOH	Ministry of Health, Singapore
MSAC	Medical Services Advisory Committee (Australia)
NHMRC	National Health and Medical Research Council (Australia)
NICE	National Institute for Health and Care Excellence (England)
NMA	network meta-analysis
NOO	notification of outcome
OR	odds ratio
PAP	patient assistance programme
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
Pharmac	Pharmaceutical Management Agency (New Zealand)
PICO	population, intervention, comparator, outcome
PSA	probabilistic sensitivity analysis
PSM	proposed surrogate measure
PVA	price-volume agreement
RCT	randomised controlled trial
RoB	risk of bias
RR	relative risk

RSA	risk-sharing agreement
SD	standard deviation
SDL	Standard Drug List
QALY	quality-adjusted life year
TCO	target clinical outcome
TGA	Therapeutic Goods Administration (Australia)

Introduction

This document describes guidelines that have been developed to assist companies prepare a submission to ACE to inform funding decisions made by the MOH Drug Advisory Committee (DAC) and, where applicable, the Health Technology Advisory Council (HTAC). They reflect best HTA practice, as far as possible, and seek to maximise the confidence in the clinical claims and value proposal presented in the submission. The company-led submission process and key timelines are outlined in a separate document, **Procedures for company submissions for funding consideration of medicines and cell, tissue and gene therapy products (CTGTPs)**.

The key information that should be included in the submission is highlighted as a checklist in boxes at the start of each section of the guidelines. Further explanation for each information request is provided under the numbered subheadings following these boxes. Companies are encouraged to use the text headings in the guidelines as a template for their submission.

Although the guidelines present the preferred approach to preparing an evidence submission to ACE, they are not prescriptive or mandatory. Alternative approaches are permitted when adequately justified and supported by evidence. Similarly, evidence submissions initially developed for other HTA agencies (e.g. NICE [England], PBAC or MSAC [Australia], or others) can be adapted and contextualised to the Singapore setting, at the company's discretion.

Companies should attempt to include all the key information requested in the guidelines in their submission. Where an information request cannot be addressed or is not relevant, a clear explanation should be provided.

Proposed submission structure

A submission should comprise the following main sections, presented in sequential order (Section 3 is not required for an abridged evaluation):

- **Section 1 – Context**. Describes the proposed medicine or CTGTP, its intended use in Singapore, clinical need for funding and the therapies most likely to be replaced by or added to the medicine or CTGTP in clinical practice.
- **Section 2 – Clinical evaluation**. Provides the best available evidence comparing the clinical performance of the proposed medicine or CTGTP with that of the comparator(s) (preferably from direct randomised trials, or, if these are not available, from other suitable studies). This section should end with a therapeutic conclusion stating whether the proposed medicine or CTGTP is superior, non-inferior or inferior to the comparator.
- **Section 3 – Economic evaluation**. Presents an economic evaluation of the consequences of substituting the proposed medicine or CTGTP for the comparator or in addition to the comparator in local clinical practice for the indication under evaluation. There are two alternative pathways for presenting economic evidence, which are described in the following sections:
  - **3A** – guidance on presenting a cost-utility analysis
  - **3B** – guidance on presenting a cost-minimisation analysis.
- **Section 4 – Utilisation and financial impact**. Includes the expected utilisation of the proposed medicine or CTGTP in Singapore clinical practice and the associated financial impact to the government.

Full and expedited submissions should have an executive summary (**not exceeding 10 pages**) that clearly sets out the key aspects and issues presented in the main body of the submission.

Preparing the submission

The main body of the submission should be concise and **not exceed 150 pages** in length (five pages for abridged submissions). Additional information can be included as appendices or attachments. Any information that is important for the DAC to consider during their funding deliberations should not be included in the appendices. Font size for text in the main body of the submission should not be smaller than size 11. Smaller font sizes may be used in tables.

The information presented in the submission should be **fit for purpose**. When considering a more complex analysis, companies should weigh the additional information requirements and evaluation burden against the additional confidence that such an analysis provides. Where complex methods reduce the confidence in estimates compared with simpler methods, they are unlikely to be accepted.

Companies must ensure that all confidential information in the submission is **highlighted and underlined**.

The submission should be sent to ACE electronically in Microsoft Word. If an economic model is included with the submission, it must be fully executable, and all programming code must be accessible (no locked cells). Companies should also complete the Costing template to estimate the expected utilisation and financial impact of the medicines or CTGTPs under evaluation.

A submission checklist is provided in **Appendix 1** for companies to complete to ensure that all relevant documents are provided to ACE.

Section 1 Context for the submission

Introduction

In Section 1, establish the context for the submission by providing the following information:

- the scope of the evaluation (PICO framework);
- the clinical claim that the submission will address;
- the expected use of the proposed medicine or CTGTP in local clinical practice; and
- the regulatory status of the proposed medicine or CTGTP.

1.1 Defining the evaluation framework and clinical claim

KEY INFORMATION REQUIRED

☐ Tabulate the scope of the evaluation using the PICO framework

☐ Define the clinical claim that the submission aims to address

1.1.1 Rationale for submission

Provide a brief introductory statement outlining the purpose of the submission.

1.1.2 Evaluation framework

In Table 1.1.2, define the scope of the evaluation by presenting the PICO elements - proposed population, intervention, comparator(s), key effectiveness and safety outcome(s) - and the overall clinical claim that the submission aims to address.

Table 1.1.2: Key elements of the evaluation framework

Element	Description
Population	Briefly describe the target health condition and population to be treated
Intervention	State the medicine or CTGTP under evaluation
Comparator(s)	State the comparator(s), which may include proprietary (branded), non-proprietary (generic) medicines and biosimilar products.
Outcomes	Briefly state the key patient-relevant clinical effectiveness and safety outcomes[a]
Clinical claim	State the clinical claim that the submission presents as follows: 'In [population with health condition], [intervention] is worse than/as effective as/more effective than [main comparator] at improving/reducing [outcome(s)]'. Clinical claims can be reported separately for clinical effectiveness and safety outcomes.

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

1.1.3 Target population and health condition

KEY INFORMATION REQUIRED

☐ Describe the target population and health condition in the Singapore setting

☐ Estimate the number of people in Singapore with the health condition

The target population should be in line with the HSA approved indication for the proposed medicine or CTGTP.

A proposal for off-label use of a medicine or CTGTP in an unapproved population should only be presented in exceptional circumstances[i] if there is sufficient evidence to show that **all** of the following criteria are met:

- The off-label use of the medicine or CTGTP is considered to be standard of care for the proposed population in local clinical practice and also in line with international best practice and/or registered indications approved by US FDA or EMA; and
- There is a lack of affordable and cost-effective treatment alternatives to the off-label use of the medicine or CTGTP for the proposed population; and
- There is sufficient evidence available to robustly assess the safety, clinical effectiveness and cost-effectiveness of the off-label use of the medicine or CTGTP in the proposed population.

Provide an overview of the health condition that can be treated by the proposed medicine or CTGTP. Include details of the underlying course of the condition, including diagnosis, symptoms and prognosis (with and without treatment). Describe the effects of the health condition on patients and their carers, if relevant, including the morbidity and premature mortality associated with the condition.

If the medicine or CTGTP is proposed for use in a subgroup(s) of the population with the health condition, indicate whether the usual course of the health condition, or the available therapies for that subgroup(s), differ from that of the whole population with the health condition.

Estimate the annual incidence and prevalence of the health condition, and the number of people in Singapore affected in the total target population (and in any proposed subgroups if applicable), preferably using local data, if available. In all cases where estimates or assumptions are made, please justify your reasoning and clearly state sources used.

Describe the population who would be treated in Singapore with the proposed medicine or CTGTP, including their age, sex, important comorbidities and condition-related characteristics.

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

[i] An example could be consideration of the use of the proposed medicine or CTGTP in a population with a broader age range (e.g. in children) than what is stipulated in the approved indication, if use in the broader population fills an important unmet clinical need or equity consideration and/or constitutes routine clinical practice. Another example could be when the HSA indication is narrower than the indication approved by overseas regulatory agencies and use in line with the overseas indication represents standard of care for that population in Singapore.

1.1.4 Intervention and comparator(s)

KEY INFORMATION REQUIRED

- ☐ Provide a short overview of the proposed medicine or CTGTP
- ☐ Provide justification for the proposed comparator(s)
- ☐ List the HSA-approved indication(s) for the proposed medicine or CTGTP and comparator(s)
- ☐ Indicate whether overseas regulatory approval has been obtained for the proposed medicine or CTGTP and provide US FDA or EMA clinical efficacy and safety reviews, where available
- ☐ Summarise the pharmacological action and dosing requirements of the proposed medicine and its comparator(s)

Intervention

Provide a general description of the proposed medicine or CTGTP.

Describe any specific response criteria or continuation rules (if applicable) associated with the use of the proposed medicine or CTGTP (e.g. in line with the approved indication or clinical practice guidelines). Discuss whether the response criteria can be reasonably achieved and describe any changes required to enable them to be incorporated into routine clinical practice.

Choice of comparator(s)

Select the comparator(s) which represents the current alternative therapy routinely prescribed for the condition in Singapore (i.e. the therapy most likely to be replaced in clinical practice, including non-proprietary or biosimilar medicines) and provide justification. In some instances, ACE may advise companies to also conduct analyses which compare the medicine or CTGTP with the most cost-effective treatment option available. The choice of comparator(s) should not be determined based on expert clinical opinion alone, but supported by evidence from other sources such as current local utilisation patterns and evidence-based clinical practice guidelines.

Comparisons with therapies which are used off-label for the indication under evaluation are permitted only if they constitute routine clinical practice in Singapore, informed by local and/or international clinical practice guidelines, and there is sufficient evidence available to robustly assess their safety, clinical effectiveness and cost-effectiveness in the proposed population.

If other medicines or CTGTPs are expected to be approved by HSA for the target population and could be considered at the same or upcoming DAC meeting, then these medicines or CTGTPs should be considered as relevant comparators.

Where there is more than one comparator, the main comparator should be the therapy that is most likely to be replaced with the proposed medicine or CTGTP. The following general hierarchy is intended to assist in selecting the appropriate main comparator:

a) **An alternate mode of administration.** If the proposed medicine or CTGTP is already routinely used in clinical practice for the target population, but with a different mode of administration (e.g. oral, intravenous, subcutaneous injection) compared to the mode of administration presented in the submission, the main comparator would usually be the current mode of administration most commonly

prescribed.

b) **An existing pharmacological analogue**. If the proposed medicine or CTGTP is in a therapeutic class where pharmacological analogues are already used in clinical practice, the main comparator would usually be the analogue that is prescribed for the largest number of patients in the target population.

c) **New therapeutic class**. If the proposed medicine or CTGTP is in a new therapeutic class but would be used for a target population for which there are other, routinely used therapies, the main comparator would usually be the therapy that is prescribed for the largest number of patients in the target population.

If the proposed medicine or CTGTP is for a target population for which there are no currently available therapies, or it will be used in addition to ("add-on therapy") – rather than replace – a therapy, the comparator would usually be standard clinical management (such as best supportive care, watchful waiting, conservative management or a surgical procedure). The choice of standard clinical management as the main comparator needs to be justified and clearly defined for the Singapore context.

If the intervention and the comparator form part of a treatment sequence in the pathway of care, it may be appropriate to compare alternative treatment sequences.

Different comparators for subgroups

A different comparator(s) for a subgroup(s) of the target population can be considered if:

- the proposed medicine or CTGTP is claimed to be significantly more effective or has significantly less adverse effects than the main alternative comparator therapy in the subgroup (but not in the remainder of the target population); or
- the main comparator used to treat the overall target population cannot be used in the subgroup due to contraindication or intolerance, and therefore, does not constitute an alternative therapy for that subgroup.

Sufficient evidence must be provided justifying the claim for the difference in clinical responses for different populations and therefore for the choice of an alternative comparator.

HSA regulatory approval

State the indication(s) approved by HSA for the proposed medicine or CTGTP as described in the package insert. Any restrictions or contraindications should also be included. If HSA approval has not been finalised, provide the proposed indication and state anticipated timelines for registration.

Provide information on the overseas registration status of the proposed medicine or CTGTP with the US FDA and/or the EMA[ii], including registration conditions or boxed warnings that may apply. Include FDA and/or EMA clinical reviews on efficacy and safety of the medicine or CTGTP as supporting documentation to the submission.

Characteristics and dosing requirements of the intervention and comparator(s)

Present a brief description of the characteristics and dosing requirements of the intervention and the comparator(s) in Table 1.1.4.

[ii] Regulatory information from TGA (Australia) or MHRA (UK) can also be provided as supporting evidence if available.

Table 1.1.4: Characteristics, administration and dosing of the intervention and comparator(s)

	Intervention	Comparator(s)
International non-proprietary name (Brand)		
Available formulation(s), strength(s)		
Therapeutic class		
ATC code[a]		
Pharmacological action		
Route of administration		
HSA-approved dosing regimen		
Average length of treatment course		
Estimated average interval between treatment courses		
Estimated number of treatment courses per patient		
Anticipated care setting		

[a] www.whocc.no/atc_ddd_index

Subsidy/reimbursement status in overseas countries

If the proposed medicine or CTGTP is already subsidised in other countries[iii], provide details of the list and ex-manufacturer prices[iv] in local currencies and the indications covered, whether RSAs are in place, including any restrictions or initiation/continuation clinical eligibility criteria. Indicate if the proposed medicine or CTGTP has been assessed by the respective national HTA agency in each country.

1.2 Clinical management

KEY INFORMATION REQUIRED

- ☐ Present a clinical treatment algorithm for the health condition in line with current clinical practice in Singapore
- ☐ Describe the clinical need addressed by the proposed medicine or CTGTP
- ☐ Include any patient (and/or carer) testimonials, if relevant
- ☐ Describe how the proposed medicine or CTGTP will impact the current treatment algorithm
- ☐ Describe any additional tests, training or services that are required to support the use of the proposed medicine or CTGTP

1.2.1 Clinical treatment algorithm

Present a flowchart that depicts the current clinical treatment algorithm (or pathway) for the health condition in the target Singapore population. The treatment algorithm should be informed by local and international clinical practice guidelines which define current treatment practices in Singapore. A copy of any relevant

[iii] It is preferable to focus this section on countries/jurisdictions in the Asia Pacific (particularly Australia, New Zealand, South Korea and Taiwan), the UK and Canada. Examples from other countries in Europe (such as Belgium or Sweden) or Latin America can be provided as additional information if relevant to the submission.

[iv] Ex-manufacturer price refers to the price before distributor/wholesaler and/or pharmacy mark-ups are applied. It does not take into account confidential price reductions or rebates.

guidelines should be provided as an attachment.

Important characteristics of the target population (and/or subgroup(s)) should be stated. Include all relevant diagnostic criteria and/or tests to identify the target population, where appropriate. Ensure that the treatment algorithm captures all relevant downstream changes to patient management until the expected end of the condition, capturing all treatment options. The healthcare professional(s) who is responsible for prescribing and/or administering the medicine or CTGTP, and the treatment setting (primary care, inpatient/outpatient hospital setting etc.) should also be shown in the algorithm.

1.2.2 Clinical need

Explain the clinical need for the proposed medicine or CTGTP (e.g. how it fills an unmet medical need in the targeted patient group) and describe how it is expected to change current clinical practice (e.g. does the proposed medicine or CTGTP add on, replace or displace the comparator? Does it change existing treatment sequences? etc.). Explain whether it is used as monotherapy or in combination with other treatments.

Indicate where the proposed medicine or CTGTP is most likely to fit into the current treatment algorithm (described in subsection 1.2.1) and explain how it is likely to change the treatment algorithm.

Ensure that the population and the use of the proposed medicine or CTGTP and main comparator(s) in the treatment algorithm are consistent with the elements proposed in the evaluation framework defined in Subsection 1.1.2.

Describe any issues, if relevant, relating to current clinical management (e.g. uncertainty about standard of care, or variations in local practice).

A summary of key themes raised while eliciting patient (and/or carer) testimonials may also be included to substantiate any claims made in this subsection. Present the number of patients, the methods used to select them, the type of condition they have, which hospital they receive care from, how the testimonials were obtained (survey, focus group etc.) and state if any fees were paid to them for their testimonials. The summary should not exceed three pages. Survey questions and individual responses can be provided as an addendum to the submission.

Expert opinion from local clinicians through an advisory panel and/or a well-designed survey should be obtained and presented as qualitative or quantitative (but not statistically analysed) information to validate the treatment algorithm and justify the positioning of the proposed medicine or CTGTP in the Singapore context. Present details (name, specialty, institution) of all clinical experts who informed the algorithm and include copies of administered surveys or hypothetical scenarios that were presented to experts, in addition to their responses, as an attachment.

1.2.3 Administration, assessment and monitoring requirements

Describe how the proposed medicine or CTGTP is used. Describe any changes in requirements needed to support the use of the proposed medicine or CTGTP in clinical practice. This includes any tests or investigations that are necessary to determine initial patient eligibility or continuing eligibility for the proposed medicine or CTGTP; any training or education required by healthcare professionals; treat or monitor for possible adverse reactions; or any specialised capacity or facilities required at the public healthcare institutions (e.g. diagnostic

services).

If the proposed medicine or CTGTP requires a specific skill that is developed through on-the-job training, provide an estimate of the number of patients a healthcare professional would need to treat (as a total number or per year) in order to reach a minimum standard.

1.3 Clinical criteria for MAF or CTGTP listing

KEY INFORMATION REQUIRED

- ☐ Define and justify any restriction(s) in the proposed clinical criteria for funding (i.e. inclusion on the MAF or CTGTP List)

1.3.1 Proposed clinical criteria for inclusion on the MAF or CTGTP List

The proposed clinical criteria for inclusion on the MAF or the CTGTP List seek to limit eligibility of the treatment to specific patient groups in whom it is clinically effective and cost effective. State whether the proposed clinical criteria are consistent with:

i. the (proposed) HSA-approved indication(s);
ii. the target population and health condition that the treatment is being considered for in the submission (as provided in Subsections 1.1.2 and 1.1.3);
iii. the clinical and economic evidence presented in Sections 2 and 3.

Where applicable, discuss the implications that listing on the MAF or CTGTP List is likely to have on another MAF- or CTGTP-listed treatment.

Section 2 Clinical evaluation

Introduction

In Section 2, demonstrate the effectiveness and safety of the proposed medicine or CTGTP in line with the evaluation framework (Subsection 1.1.2) by providing:

- a comprehensive literature search to identify relevant studies;
- an analysis and interpretation of the findings for the whole trial population from each study, including an assessment of the risk of bias affecting the study findings;
- any additional subgroup analyses, meta-analyses and/or indirect treatment comparisons required to estimate the comparative treatment effect of the proposed medicine or CTGTP; and
- an assessment of the applicability of the evidence to the Singapore setting.

Consideration of a comprehensive evidence base is fundamental to the evaluation process. While information from many sources may inform the evaluation, randomised controlled trials (RCTs) directly comparing the proposed medicine or CTGTP with the relevant comparator(s) are considered to provide the most valid evidence of relative efficacy. When RCTs are not available, data from indirect comparisons of randomised trials should be considered, and may be further supplemented by good quality non-randomised studies when relevant.

2.1 Literature search methods

KEY INFORMATION REQUIRED

- ☐ Define the search terms and criteria used to retrieve the most relevant evidence
- ☐ Document the search strategies and the different sources searched

2.1.1 Search strategy

The primary objective of the literature search is to retrieve all relevant studies that compare the proposed medicine or CTGTP with the main comparator(s) for the proposed population. Literature searches should be systematic, transparent, reproducible and updated within four months of the date of evidence submission. Where an earlier systematic literature search has been conducted, a targeted update from the previous search date may be undertaken to identify new relevant evidence, rather than repeating the full search. The methodological standards defined in the *Cochrane Handbook for Systematic Reviews of Interventions*[1] should be followed to generate a high-quality systematic literature search to ensure the accuracy and completeness of the evidence base informing the submission.

Search terms

All search terms should be consistent with the population, intervention and comparator(s) defined in the evaluation framework (Subsection 1.1.2). The search terms used for the population should be broad, to avoid excluding potentially relevant studies, and only need to be applied if the proposed medicine or CTGTP is used for multiple indications. It is not necessary to include search terms for outcomes. Present all search terms in Table 2.1.1a.

Table 2.1.1a: Search terms

Category	Description	Search terms
Study design	[insert description of category]	[e.g. Cochrane Highly Sensitive Search Strategies for identifying randomised trials in MEDLINE, or MeSH terms and text words for non-randomised study designs]
Population	[insert description of category]	[include MeSH terms, text words and synonyms for the target population/health condition]
Intervention	[insert description of category]	[include known proprietary and non-proprietary names, MeSH terms and developmental/provisional medicine or CTGTP names]
Comparator(s)	[insert description of category]	[include known proprietary and non-proprietary names, MeSH terms and developmental/provisional medicine or CTGTP names]

When searching electronic databases, filters should be initially set to only include randomised trials (use *Cochrane Highly Sensitive Search Strategies*[v]). If no direct randomised comparisons are identified, search separately for randomised trials of either the proposed medicine or CTGTP, or the main comparator(s) that would enable an indirect comparison, and present both search strategies. If an indirect comparison is not possible, broaden the search to identify all non-randomised studies (such as cohort studies, case-control studies or quasi-experimental studies) of the proposed medicine or CTGTP, preferably compared with the main comparator(s). In addition, non-randomised studies may provide useful supplementary evidence to randomised trials about long-term outcomes, rare events and populations that are typical of real-world practice. Examples of when non-randomised studies may inform a submission include:

- when randomised trials are not feasible (e.g. when the health condition is rare);
- when it is unethical to conduct randomised trials (i.e. when the treatment effect is extraordinarily large in observational studies and so equipoise is not achieved);
- when the duration of a randomised trial is insufficient to quantify the effect of treatment over the course of the disease;
- when rare adverse events cannot be feasibly captured within the duration of a randomised trial (in this circumstance provide non-randomised data to supplement randomised trial data);
- when eligibility criteria for the trial are very restrictive, and the applicability of the treatment effect to the target population is unknown (in this circumstance provide non-randomised data to supplement randomised trial data).

More information on the hierarchy of preferred study designs is described in the National Health and Medical Research Council (NHMRC) levels of evidence for interventions (see Appendix 2).

Searches in study registries (such as ClinicalTrials.gov) should be simple, highly sensitive, and ideally limited to one search term (e.g. intervention or indication). Due to the varying quality of individual registry entries, it is not advisable to apply additional limitations (e.g. study status or phase).

Evidence sources

The following sources should be prioritised for searching:

- published literature in electronic databases (MEDLINE [via PubMed], EMBASE, International Health Technology Assessment database and the Cochrane Library [which includes the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL)]);
- registers of randomised trials (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform);
- reference lists of all relevant articles that are obtained.

[v] https://training.cochrane.org/handbook/current/chapter-04#section-4-4-7

Present the full search strategy for all databases searched (highlight the primary database used). Summarise the search strategy for each data source in Table 2.1.1b (add rows as needed). Where additional databases are relevant (e.g. PsycINFO for psychology and psychiatry literature), include these in the table.

If relevant evidence is likely to be published in non-journal sources, it may be appropriate to search for grey literature (e.g. institutional reports). Useful sources of grey literature include websites of professional bodies or other organisations relevant to the topic (e.g. US FDA, EMA), OpenGrey, OpenDOAR, Trip Medical Database, and Grey Matters (CDA-AMC)[vi]. This list is not exhaustive, and companies may also choose to search other sources to inform their submission.

To reduce publication and outcome reporting bias, unpublished data (e.g. in clinical study reports [CSRs]) and/or studies that are pending publication should also be identified. Reasons why each trial has not been published, and expected dates of publication (if applicable) should be provided. Copies of all relevant CSRs and pending publications should be provided as an attachment, where available. Sufficient justification should be provided if CSRs are not available.

Table 2.1.1b: Details of search strategy for each source

Source	Date searched	Date span of search	Details of search
MEDLINE (via PubMed)	[insert date]	[insert dates]	State where the complete search strategy (search terms, indexing terms, filters, Boolean operators) has been provided in the submission
EMBASE (e.g. Embase.com)	[insert date]	[insert dates]	State where the complete search strategy (search terms, indexing terms, filters, Boolean operators) has been provided in the submission
Cochrane Library[a]	[insert date]	[insert dates]	State any key differences from the complete search strategy provided for the PubMed/EMBASE search
ClinicalTrials.gov[b]	[insert date]	[insert dates]	State any key differences from the complete search strategy provided for the PubMed/EMBASE search
WHO International Clinical Trials Registry Platform[c]	[insert date]	[insert dates]	State any key differences from the complete search strategy provided for the PubMed/EMBASE search
International HTA database[d]	[insert date]	[insert dates]	State any key differences from the complete search strategy provided for the PubMed/EMBASE search
Other sources[e]	[insert date]	[insert dates]	Not applicable

[a] https://www.cochranelibrary.com/; [b] https://clinicaltrials.gov/; [c] https://www.who.int/ictrp/en/; [d] https://database.inahta.org/;
[e] Report details of supplementary searches, including manual checking of the references in retrieved papers, searches of regulatory dossiers from HSA, US FDA, EMA etc., internal (company) registries, unpublished studies (CSRs) and grey literature.

[vi] OpenGrey: https://www.opengrey.eu/; OpenDOAR: https://v2.sherpa.ac.uk/opendoar/; Trip: https://www.tripdatabase.com/; Grey Matters: https://greymatters.cda-amc.ca

2.2 Identifying and selecting relevant studies

KEY INFORMATION REQUIRED

- ☐ Describe the inclusion and exclusion criteria used to select studies
- ☐ Present search results using a PRISMA flowchart
- ☐ Create a list of relevant included studies
- ☐ Attach copies of included trials
- ☐ Identify trials used in an indirect comparison (if applicable)

2.2.1 Study selection

Describe the inclusion and exclusion criteria used to select studies in Table 2.2.1 (add rows as necessary).

Table 2.2.1: Inclusion/exclusion criteria used in the search strategy

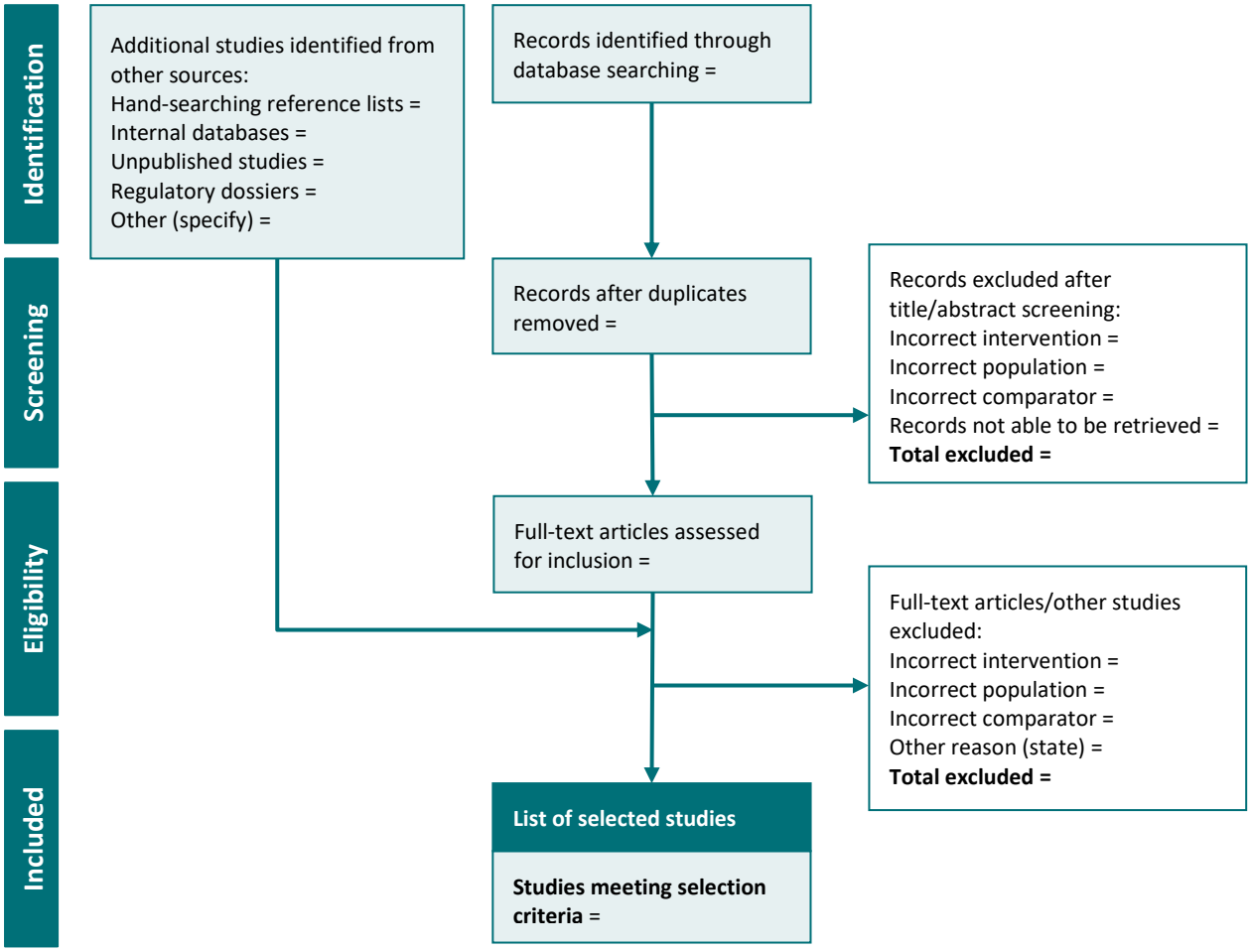
	Inclusion criteria	Exclusion criteria
Population		
Intervention		
Comparator(s)		
Study design		
Language restrictions		

Use a PRISMA flowchart[2,3] (Figure 2.2.1) to indicate the number of studies screened and selected for each search. Extract individual studies from published systematic reviews or meta-analyses and exclude any that do not meet the inclusion criteria.

Direct randomised trials that are selected should form the basis of the submission, where available. If no direct randomised trials are identified that compare the proposed medicine or CTGTP with the main comparator(s), present PRISMA flowcharts separately for the proposed medicine or CTGTP and for the main comparator(s), without excluding studies on the basis of comparator, to enable an indirect comparison of randomised trials. If no randomised trials are identified that would enable an indirect comparison to be conducted, present a third PRISMA flowchart depicting screening for non-randomised studies.

Record all identified studies (with complete references) in an Excel spreadsheet and indicate any excluded studies and the reason for exclusion. Provide the spreadsheet as an attachment.

Figure 2.2.1: PRISMA flowchart showing screening and selection of studies



2.2.2 List of selected studies

Tabulate all selected studies and relevant systematic reviews or meta-analyses that meet the inclusion criteria in Table 2.2.2. Indicate if any studies had sites in Singapore, and the number of local patients included, if applicable.

Table 2.2.2: Studies and associated references used in the submission

Study identifier (ID)	Date of study (start and [expected] completion date)	Status (ongoing/complete)	Source of identification	References
Randomised controlled trials				
Unique (ID) of study used in submission			[e.g. trial registry, electronic database]	• • •
Study 2				
Other studies, such as systematic reviews and non-randomised studies				
Unique (ID) of study used in submission				• • •
Study 2				

Note: add rows and convert to landscape format if required

When data from a single study has been identified in more than one source (e.g. a poster and a published report), or when studies are linked (e.g. an open-label extension to a randomised trial, or one study published across multiple follow-up periods), this should be clearly stated. Ensure that all relevant studies identified outside database searches (e.g. regulatory dossiers, CSRs) are also included.

2.2.3 Ongoing studies

List all ongoing studies (including post-marketing surveillance) of the proposed medicine or CTGTP for the indication under evaluation, and their anticipated date of completion.

2.2.4 Copies of included studies

Provide copies of all included studies (key publications, supplementary data, CSRs) as attachments to the submission. Provide reputable translations of studies that are not published in English.

Where there is more than one report of a randomised trial, provide the published paper(s) and the complete CSR(s). If the results vary between reports of the same randomised trial, discuss and justify these differences. For any included trial identified from a meta-analysis, provide a copy of the individual trial report or publication(s).

2.2.5 Selecting studies for an indirect comparison

If the proposed medicine or CTGTP and the main comparator(s) can be compared using one or more direct randomised trials, an indirect comparison is not required. When direct randomised trials are not available, an indirect comparison of randomised trials should be conducted using established methodology[4,5] (see Subsection 2.6.3).

Justify the exclusion of studies (from Table 2.2.2) that are unsuitable for use in the indirect comparison (e.g. no common reference is available). Factors that may cause heterogeneity across studies should be considered and described, such as study quality, participant characteristics, circumstances of how the medicine or CTGTP is used, management patterns, treatment characteristics, and outcome measures. Do not exclude studies on the basis of heterogeneous characteristics when these are unlikely to modify the treatment effect (or unlikely to affect the assumption of transitivity). Instead, the impact of these studies can be examined by removing them in sensitivity analyses.[vii]

List all indirect comparisons that are possible using the randomised trials within Table 2.2.2. Indirect comparisons using non-randomised studies should be avoided, unless there are no suitable randomised trials available. If there are two or more common reference arms, or if more than one indirect comparison is possible, present a network diagram for each relevant outcome. When a network meta-analysis (NMA) is presented, describe the search strategy required to capture the complete range of studies eligible for the network and any limitations of the search. Any NMAs presented should be based on simple networks (without complex loops and numerous edges[viii]).

[vii] Framework to improve confidence in the results of an indirect comparison (ITC) by justifying trial selections and presenting sensitivity analyses to demonstrate the impact of trial selection on the ITC results is available in *Report of the Indirect Comparisons Working Group to the Pharmaceutical Benefits Advisory Committee: assessing indirect comparisons* (2008). Available at www.pbs.gov.au/info/industry/useful-resources/pbac-feedback

[viii] A loop of evidence exists when two or more direct comparisons contribute to an indirect estimate (e.g. A-B and A-C contribute to B-C – this loop is considered closed if direct evidence exists between B-C, and open when direct evidence for this comparison does not exist). An "edge" in an NMA represents a direct (head-to-head) comparison between pairs of interventions.

Compare the event rates in the common reference groups within trial sets (e.g. A vs C, B vs C). Justify the exclusion of trials with markedly different event rates or treatment effects in the common reference arms, both within the trial sets and across the indirect comparison. Care should be taken when excluding trials because of differences in event rates in the common reference arms when there is evidence of a constant treatment effect across the event rates. Include any excluded trials in a sensitivity analysis (in Subsection 2.6.3).

Present a list of the studies included in the indirect comparison or sensitivity analyses, and the trials excluded from all analyses in Table 2.2.5.

Table 2.2.5: Example table of studies included/excluded in the indirect comparison

Study identifier*	Included/sensitivity analysis/excluded	Justification
Study 1	Included	Not applicable
Study 2	Included	Not applicable
Study 3	Sensitivity analysis	Includes patients with earlier stage of disease than study 1 and study 2
Study 4	Excluded	Common reference arm uses different dosing, reducing likelihood of transitivity

*Study identifier (ID) should be consistent with the IDs in Table 2.2.2.

2.2.6 Selecting non-randomised studies

If no randomised trials are identified, other study designs should be presented, with preference for comparative study designs (such as cohort studies with a concurrent or historical control) over non-comparative studies (such as single arm studies). If no comparative studies are identified, indirect comparisons are preferred over presenting only single arm data, which do not allow for consideration of comparative safety and effectiveness (see Subsection 2.6.3).

If non-randomised evidence is used, the following information should be presented:

- the quality of the source data (for both the proposed intervention and the main comparator);
- the methods for generating an estimate of comparative safety and effectiveness, quantitative estimates of the comparative safety and effectiveness of the proposed intervention, and confidence or credible intervals;
- the uncertainty in the estimates due to data quality or sources of bias, the transitivity of the evidence across the data sources, and applicability of the sources to the Singapore target population; and
- additional evidence or methods to reduce the uncertainty of the results.

2.3 Assessing risk of bias in included studies

KEY INFORMATION REQUIRED

- ☐ Assess risk of bias (internal validity) in the included randomised and non-randomised studies
- ☐ Present the flow of participants through the included randomised trials

Internal validity

The reliability of the results from the included studies will depend on the extent to which potential sources of bias have been avoided in the generation of those results. Information required to assess the risk of bias for randomised trials and non-randomised studies is described below in subsections 2.3.1 to 2.3.4.

2.3.1 Risk of bias assessment for randomised trials

The preferred approach for assessing the risk of bias for randomised trials is described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*[ix].[6] Complete Table 2.3.1 for each included trial (add rows as needed). Provide additional information about the following aspects that may influence an assessment of risk of bias for each trial (state if this information is not relevant or not available):

- **Unmasking**. Discuss whether the proposed intervention or comparator has any effects (such as adverse events) that may result in the participant, the investigator or the outcome assessor 'guessing' the treatment allocation of the participant.
- **Treatment decisions**. Describe how decisions such as either stopping treatment or starting a new or concomitant treatment in response to adverse events, treatment failure or inadequate treatment response were made (including responsible personnel). Discuss whether these decisions could affect the measurement of any of the key outcomes.
- **Testing decisions**. Discuss whether the investigator can request tests that are not part of the protocol or that occur at different times than prescribed in the protocol, and whether these tests may affect the measurement of key outcomes or adverse events.
- **Nature of outcomes**. Regardless of whether the trial is blinded or open-label, discuss whether any of the key outcomes could be affected by a participant's, investigator's or outcome assessor's knowledge of treatment allocation.
- **Missing data**. Discuss the reasons for any loss to follow-up or missing data. Discuss whether the characteristics of the participants who were lost to follow-up are similar to, or different from, those remaining in the trial, and state whether there is a differential loss to follow-up or discontinuation across the arms. Discuss whether missing data are expected to affect the treatment effect, and if the effect is likely to be overestimated or underestimated.

Table 2.3.1: Risk of bias assessment for randomised trials

Bias domain	Study ID	Description	Source	Risk categorisation	Effect of bias
Bias arising from the randomisation process	Study 1	[Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. Describe the method used to conceal the allocation sequence in sufficient detail to allow an assessment of whether intervention allocations could have been foreseen in advance of, or during participant enrolment]	[insert source/page number]	[low risk/high risk/some concerns]	[likely effect the bias may have on the direction of the comparative treatment effect]
	Study 2				
Bias due to deviations from intended interventions	Study 1	[Describe all measures used, if any, to blind trial participants and study personnel from knowing which intervention a participant received. Provide any information relating to whether the intended blinding was effective]	[insert source/page number]	[low risk/high risk/some concern]	[likely effect the bias may have on the direction of the comparative treatment effect]
	Study 2				
Bias in measurement	Study 1	[Describe all measures used, if any, to blind outcome assessors from knowing which intervention a participant received. Provide any information relating to whether the intended	[insert source/page number]	[low risk/high risk/some concern]	[likely effect the bias may have on the direction of the

[ix] https://training.cochrane.org/handbook/current/chapter-08

of the outcome		blinding was effective]			comparative treatment effect]
	Study 2				
Bias due to missing outcome data	Study 1	[Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), and the reasons for attrition/exclusions, where reported]	[insert source/page number]	[low risk/high risk/some concern]	[likely effect the bias may have on the direction of the comparative treatment effect]
	Study 2				
Bias in selection of the reported result	Study 1	[State how the possibility of selective outcome reporting was examined, and what was found]	[insert source/page number]	[low risk/high risk/some concern]	[likely effect the bias may have on the direction of the comparative treatment effect]
	Study 2				
Other sources of bias*	Study 1	[State any important concerns about the study design that are not addressed elsewhere in this table]	[insert source/page number]	[low risk/high risk/some concern]	[likely effect the bias may have on the direction of the comparative treatment effect]
	Study 2				

Note: Adapted from the Cochrane Collaboration's tool for assessing risk of bias RoB 2[6]

* Some examples include use of non-validated or insensitive measurement instruments, selective reporting of subgroups, and inappropriate administration of an intervention

2.3.2 Flow of participants

Present the flow of participants through each stage (enrolment, intervention allocation, follow-up and data analysis) of each randomised trial in Table 2.3.2 (adapt as necessary to record participants who crossed over treatment groups etc.).

Table 2.3.2: Flow of participants through the included randomised trials

Study ID	Intervention arm	No. randomised	Did not receive intervention	Lost to follow-up	Discontinued	Analysed	Median duration of follow-up	Source of information
Study 1	Proposed medicine or CTGTP	*N*	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* months (range)	[Reference]
	Comparator	*N*	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* months (range)	[Reference]
Study 2								

2.3.3 Risk of bias assessment for systematic reviews and meta-analyses

Assess the risk of bias for included individual trials within a systematic review or meta-analysis. Where individual trials are not able to be retrieved and the submission relies on a pooled treatment effect from the published systematic review or meta-analysis, clearly report the risk of bias assessment undertaken by the authors and assess the methodological quality of the systematic review using a validated tool (e.g. AMSTAR2[7]

or ROBIS[8]).

2.3.4 Risk of bias assessment for non-randomised studies

Due to the large variety of non-randomised study designs and their varying susceptibility to different biases, it is complex to assess risk of bias for this type of evidence.

The internal validity of a non-randomised study can be elicited by reference to how the study design or conduct differs from that of a well-designed, double-blind RCT. A risk of bias assessment for a non-randomised study should cover the following types of bias: selection bias (including bias due to confounding), performance bias, detection bias, attrition bias, and reporting bias.

Potential sources of bias include (but are not limited to):

- imbalances in baseline or post-baseline characteristics that are potential confounders;
- treatment switching or imbalances in the use of later-line or concomitant therapies;
- patients who are selected into the study and are already receiving the intervention (or comparator), where these patients are different to those who are not already receiving treatment, or have started then stopped treatment, and where these two groups may have different expected outcomes;
- a definition of the intervention or comparator (doses, duration, setting) that is too broad or ambiguous, and where allocation of intervention status may be influenced by the knowledge of outcomes;
- missing data that affect the estimate of the outcome;
- outcome measures that are subjective, or outcome assessors who are not blinded to treatment allocation;
- timing of measurement of outcomes, or the method of determining outcomes, that differs between study arms;
- reporting of outcomes, time points or subgroups that were not pre-defined in the protocol.

Several risk of bias tools have been developed to identify and report study characteristics that may impact on the comparative treatment effect in non-randomised studies (e.g. ROBINS-I[9] [previously called ACROBAT-NRSI] and RoBANS2[10]). Use the domains defined in a validated tool to describe whether there is a risk of bias for each non-randomised study, and any measures taken to mitigate the risk. Provide references to support the information. While it is not necessary to complete the chosen tool, a risk of bias tool should be attempted for the selected studies, where possible.

2.4 Characteristics of included studies

KEY INFORMATION REQUIRED

- ☐ Present the trial design and eligibility criteria for participants in each study
- ☐ Present the baseline demographic and clinical characteristics of participants and relevant subgroups in each study
- ☐ Provide details of the treatments in each study and for relevant subgroups
- ☐ Describe the primary outcome and important patient-relevant outcomes in each study
- ☐ Define the minimal clinically important difference (MCID) for the primary outcome and key patient-relevant outcomes
- ☐ Specify the non-inferiority margin for the primary outcome, if appropriate

Presenting the characteristics of included studies will enable a comparison across arms and across studies to identify potential confounders or sources of heterogeneity and inform the interpretation of the evidence. The presentation of characteristics of the included studies will vary depending on the type of evidence and the number of studies. For evidence presenting a direct comparison of a medicine or CTGTP with an appropriate comparator, it is preferable to provide study characteristics in a tabulated format (see Section 2.4.1).

The level of detail presented for each study will depend on the number of studies included in the submission. If there are many studies, focus on describing key characteristics in each study, relating to the participants, treatments and settings, that are informative to decision-making. Highlight important differences in the key characteristics, particularly where the differences are likely to have an impact on the treatment effect.

2.4.1 Characteristics of included randomised trials

In Table 2.4.1, describe the trial design and provide details about the eligibility criteria for participants and the treatments administered in each included randomised trial, in line with the requirements of the CONSORT 2010 checklist[x] (items 3 to 5).[11] The table should include the following:

- **Trial design.** A brief description of the trial design (e.g. parallel group, multi-arm parallel, crossover, factorial) including details of randomisation and whether the trial was designed to assess superiority or non-inferiority.
- **Eligibility criteria.** Comprehensive description of the eligibility criteria used to recruit trial participants, including any assessments used to select participants.
- **Settings and locations where the data were collected.** Describe the locations where the trial was conducted, including the country and care setting (if applicable).
- **Trial interventions.** Provide the intended treatment regimens (for intervention and comparators) outlined in the trial protocol. Include administration information (when/how treatments were administered), duration of treatment, continuation or stopping criteria, and titration schedules, if appropriate. Include concomitant medicines or CTGTPs permitted and disallowed during the trial.

[x] https://www.equator-network.org/reporting-guidelines/consort/

Table 2.4.1: Comparative summary of trial design, eligibility criteria and interventions for included randomised trials

Study ID	Study 1	Study 2
Trial design		
Eligibility criteria for participants		
Settings and locations where data were collected		
Trial interventions for each group		

Note: add columns as necessary

2.4.2 Participants

Describe the baseline demographic and clinical characteristics of the participants (e.g. age, sex, disease severity, duration of previous treatments etc.) in each randomised group or study arm in Table 2.4.2. Information should be provided for the whole trial population as well as any subgroups (and their complements) to confirm whether there are imbalances in important prognostic factors or effect modifiers across arms, or between a subgroup and its complement. Where baseline characteristics are unavailable for a subgroup(s), state why and provide any relevant details to reduce the uncertainty related to an imbalance of patient characteristics within the subgroup analysis.

Table 2.4.2: Characteristics of participants in the randomised trials across treatment groups

Baseline characteristic	**Treatment group X (n=)**	**Treatment group Y (n=)**
Study ID (N=)		
Mean (SD) age		
Proportion of males (%)		
[Add more rows as required]		
Study ID (N=)		
Mean (SD) age		
Proportion of males (%)		
[add more rows as needed]		

Note: add columns and rows as necessary; SD = standard deviation

Report differences in the baseline demographic or clinical characteristics across arms in the trials or across trials and indicate whether differences are clinically important and/or statistically significant. For each identified difference, discuss the likely impact on the magnitude and direction of the treatment effect.

Where there are differences between treatment arms (or trials) in terms of the extent or timing of patients lost to follow-up, patient withdrawals, or missed or refused assessments (as described in 2.3.2), present the baseline demographic and clinical characteristics for the following groups (as an attachment):

- patients who were lost to follow-up compared with those who were not;
- patients who withdrew from the trial compared with those who did not;
- patients who missed an assessment compared with those who were assessed.

2.4.3 Treatment details

State whether the dose or treatment regimen (including the use of concomitant treatments) in each trial is in line with the approved dosage, and/or supported by clinical practice guidelines. Justify where the protocol's specified dose (or the actual dose in the trial) differs from recommended dosing[xi].

[xi] Recommended dosing refers to regimens that are in line with HSA approved dosing, or recommended dosing regimens in clinical practice guidelines that inform treatment decisions in Singapore.

Provide the average dose of each treatment administered in each trial, taking the dosing frequency (and/or proportion of participants taking particular doses) and average duration of treatment into consideration. Indicate if different treatment regimens were administered for subgroups (if applicable). Discuss differences of treatment duration across arms and across trials and explain any differences observed.

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

2.4.4 Outcomes

For each trial, present the primary outcome specified in the trial protocol and any secondary outcomes that are patient-relevant (CONSORT 2010 checklist items 6a, 6b, 12a and 12b) in Table 2.4.4. For each outcome:

- state whether it was the primary outcome;
- describe the instrument used to measure the outcome (e.g. questionnaire, blood test) and the personnel who administered the instrument (e.g. investigator, study nurse);
- describe the threshold for categorisation as an outcome, if applicable;
- describe the timing of the outcome assessment;
- describe the personnel who determined whether the outcome had been achieved;
- describe the methods of statistical analysis;
- describe the population in which the analysis is performed (i.e. intention to treat (ITT), per protocol);
- describe how the sample size was determined;
- state how missing data were dealt with;
- summarise the power calculations for outcomes for which the trial was designed to detect a change.

For each instrument, state whether the instrument is validated in the population and the circumstances in which it is applied in the study, and provide a reference(s) for its validation.

Table 2.4.4: Differences in outcomes or analyses for included studies

Outcome	Study ID	Measurement of outcome and timing of assessment	Method of analysis	Sample size, power calculation
Example: overall survival [primary outcome]	Study 1	[description of outcome, instrument used to measure outcome, units of measurement, personnel who determined if outcome was achieved, timing of assessment]	[name of statistical test and sufficient details about how the analysis was performed and the population [ITT etc.] in which the analysis was performed]	[describe how sample size was determined and summarise power calculations]
	Study 2			
	Study 3			
Example: progression-free survival [secondary outcome]	Study 1			
	Study 2			

Note: add columns and rows as necessary (landscape format is recommended)

Composite outcomes

A composite outcome is one in which two or more distinct clinical endpoints (called component endpoints) are combined. A composite endpoint is usually considered to have been experienced when the first of any of the individual component endpoints occurs, even though subsequent component endpoints may also occur.

If one or more of the reported outcomes is a composite, state whether the composite outcome was prespecified, and discuss and compare the clinical importance of each of the components of the composite. Disaggregate the composite outcome (where possible) and present the results of each component as a secondary outcome. The interpretation of a composite outcome should consider which of the components is driving the composite outcome and whether this is similar across study arms.

Surrogate outcomes

A surrogate outcome is an endpoint (either a biomarker[xii] or intermediate endpoint[xiii]) that is intended to provide an indirect measurement of a clinical effect in situations where direct measurement is not feasible or practical.[13] Submissions that do not rely on proposed surrogate measures (PSM) to inform effectiveness in terms of patient-relevant or clinically relevant outcomes are preferred, given few PSMs to date have been robustly shown to be true measures of tangible clinical benefit.

Final clinical endpoints are preferred for measures of effectiveness. Only present a surrogate outcome (that is not the primary outcome) when it is critical to the therapeutic conclusion or economic evaluation. State the target clinical (patient-relevant) outcome (TCO) which the surrogate outcome intends to measure and present evidence[xiv] to establish the biological plausibility for the link between the PSM and the TCO, including the role of the PSM in the causal pathway to the clinical outcome, and any limitations of the evidence or contradictory findings. Present any statistical associations (including the strength of the association and the precision) and include relevant statistical outputs (e.g. regression coefficients and R-squared) as an attachment.

Establish the PSM-TCO comparative treatment effect relationship using empirical evidence (preferably from RCTs that measure both the PSM and TCO). Present the characteristics (e.g. patient and condition characteristics, treatment settings, measurement of PSM and TCO) and results of each trial in a table. Where multiple trials exist for a class of medicine or CTGTP, present results of a meta-analysis for individual studies. Provide any meta-regression outputs, the R-squared for trials, and the surrogate threshold effect.

Discuss the PSM-TCO comparative treatment effect relationship, including details of the shape of the relationship (e.g. linear, exponential) and whether there is any evidence of a floor or ceiling effect, below or above which the comparative treatment effect on the PSM no longer predicts a comparative treatment effect on the TCO.[xv]

Discuss where the PSM-TCO comparative treatment effect relationship differs across trials, treatments or mechanisms of action.[xvi] Where trials are removed, for example, that have treatments of different mechanisms of action or populations that do not reflect the evaluation framework (Subsection 1.1.2), present the estimate of the PSM-TCO comparative treatment effect relationship with all trials included as the base

[xii] A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention (e.g. cholesterol level, HbA1c). A biomarker must lie on the pathophysiologic causal pathway of the disease; must be correlated with a clinical endpoint to be useful in detecting disease and assessing prognosis, and validated.[12]

[xiii] An intermediate endpoint measures a function or a symptom (e.g. disease-free survival, exercise tolerance, angina frequency) but is not the ultimate endpoint of the disease, such as survival or the rate of irreversible morbidity (stroke, myocardial infarction).

[xiv] Evidence may include in vitro studies, animal studies, case reports, cross-sectional observational studies, ecological association studies, retrospective observational cohort studies, non–population based prospective observational cohort studies, or population-based prospective observational cohort studies.

[xv] Further information on methods to validate the PSM-TCO comparative treatment effectiveness relationship is available in a report by the PBAC Surrogate to Final Outcomes Working Group: www.pbs.gov.au/info/industry/useful-resources/pbac-feedback

[xvi] Possible causes of heterogeneity include, but are not limited to mechanism of action, population and disease characteristics, definition or measurement of the PSM or TCO, quality of the trial and treatment settings.

case and only remove less-relevant trials in a sensitivity analysis. Where more than one estimate of the PSM-TCO comparative treatment effect relationship has been established, justify the selection of one estimate for the base case, and present the remainder as sensitivity analyses.

The PSM-TCO comparative treatment effect relationship is usually only considered valid if it is:

- **Condition-specific**. Validity of the relationship should be demonstrated for different stages of a condition;
- **Population-specific**. Validity of the relationship should be justified for populations with a condition who have different characteristics (age, gender, co-morbidities);
- **Class-specific**. The relationship should be validated for each therapeutic class of medicine or CTGTP separately (e.g. LDL-C as a surrogate of CHD event risk is validated for statins but not for fibrates). An attempt to extrapolate the validity of the PSM-TCO relationship to other therapeutic classes within an indication should be justified and substantiated with supporting evidence.

When applying the PSM-TCO comparative treatment effect relationship to the trial evidence for the proposed medicine or CTGTP, it is critical that both the proposed intervention and the main comparator have the same mechanism(s) of action as treatments for which the PSM-TCO comparative treatment effect has been established, otherwise the transformation of the PSM to the TCO will be uncertain. In such instances, explain how any differences will not result in a different measurement of the PSM-TCO comparative treatment effect relationship.

It is not necessary to describe the transformation of a PSM to TCO in detail if the surrogate outcome has previously been accepted as valid by one of ACE's decision-making committees or an international HTA agency (e.g. PBAC/MSAC, NICE or CDA-AMC) and:

- The proposed treatment effect is within the range of the comparative treatment effect identified in the clinical evidence associated with the transformation that was previously accepted;
- The proposed medicine or CTGTP will be used in the same population as the previously accepted transformation; and
- The treatments in the evidence used to previously validate the surrogate, the main comparator and the proposed medicine or CTGTP are all in the same class or have a similar mechanism of action.

If available, provide a summary of previous decisions about the PSM-TCO comparative treatment effect relationship reported by international HTA agencies (e.g. NICE, PBAC/MSAC, CDA-AMC) as supporting evidence.

Patient-reported outcome measures

Patient-reported outcomes describe any outcomes evaluated directly by a patient (or their carer/family), based on their perception of their current health state. They are reported using generic (e.g. Short Form-36 [SF-36]), condition-specific (e.g. St George's respiratory questionnaire) or population-specific questionnaires (e.g. Child health questionnaire), that measure quality of life, health status, symptoms or function.

Patient-reported outcome measures may also include multi-attribute utility instruments (MAUIs), in which the scoring method for the instrument is anchored on a quality-adjusted life year scale of 0 (death) to 1 (full health). Several commonly used MAUIs which can be used in submissions without a detailed discussion of their validity or reliability, are the Health Utilities Index (HUI2 or HUI3), the EQ5D-3L ('EuroQol'), the SF-6D (a preference-based single index measure derived from a selection of SF-36 items), the Assessment of Quality

of Life (AQoL) instruments, and the Child Health Utility 9D (CHU9D) index for children and adolescents.

Where a less common patient-reported outcome measure or MAUI is used in the submission, provide a reference (as an attachment) that describes:

- domains of quality of life, symptoms or function that are covered by the instrument;
- scoring method of the instrument;
- validity and reliability of the instrument;
- responsiveness of the instrument to differences in health states between individuals and to changes in health states over time experienced by an individual;
- clinical importance (MCID) of any differences detected by the instrument.

For all patient-reported outcome measures, explain how they are used within the study, including

- the timing of assessments (frequency and at what points in the study the instruments were administered);
- who administered the instrument and in what setting; and
- why assessments were missed and how missed assessments were dealt with.

Provide the characteristics of the patients who missed or refused to complete the relevant instruments, and compare them with those patients who completed them. Describe any methods that were used to adjust for response bias, or describe the effect of missed assessments on the comparison of patient-reported outcome measures across the arms of the study.

2.4.5 Minimal clinically important difference (MCID)

An MCID is the smallest difference in a particular outcome that patients perceive as important (beneficial or detrimental). An MCID should be specified for the primary outcome and the main patient-relevant outcome (where this is not the primary outcome).

In Table 2.4.5, describe the proposed MCIDs for the key outcomes in the included studies. Sources of MCIDs are variable and can include:

- the study protocol;
- a MCID previously accepted by the MOH Drug Advisory Committee (DAC), or by another reference HTA agency (e.g. PBAC/MSAC, Pharmac, NICE or CDA-AMC), that is relevant to both the study population and the indication under evaluation;
- a commonly accepted MCID in the literature, relevant to the population/indication under evaluation;
- expert consensus elicited through an internal study.

If alternative MCIDs for the same outcome are available, discuss any differences and justify the choice of MCID for the purpose of this submission.

Table 2.4.5: Details of MCIDs for key outcomes in the included trials

Proposed MCID (value)	[Present this as an absolute change in units]
Source of MCID	[Provide source]
Method of derivation of the MCID	[e.g. anchor-based assessment, expert consensus, statistical methods]
Comparison of the derivation of the MCID and the studies included in the submission	[Describe]

Population	[Describe any differences in the population or indication]
Outcome definition	[Describe any differences in the outcome definition]
Baseline value for measurement	[Describe any differences in the baseline value from which change was measured]

Where the primary outcome is a surrogate for another endpoint (e.g. cholesterol levels for cardiovascular events), the justification of an MCID should be the change in the surrogate required to result in a meaningful change in the target outcome.

For patient-relevant outcomes that are measured on a scale (e.g. a patient-reported outcome measure, a quality-of-life instrument, the Visual Analogue Scale, the 6-Minute Walk Distance test), the MCID should preferably be established using an anchor approach.[14,15] For these types of outcomes, the MCID can be used as a threshold, beyond which a patient would be regarded as a 'responder'.

2.4.6 Non-inferiority margin

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

Establish a non-inferiority margin for the primary outcome and the most important patient-relevant outcome (where this is not the primary outcome) based on statistical reasoning and clinical judgement to assure that the proposed medicine or CTGTP is not inferior to the main comparator by an important difference. Propose a magnitude of difference in each outcome that would be regarded as unimportant (e.g. less than a minimal clinically important difference) and can be used as the non-inferiority margin, indicating whether there is agreement across multiple sources.

Where the included trial has pre-specified a non-inferiority margin, present and justify the choice of the margin (referring to the trial protocol and/or additional supporting evidence).

Often non-inferiority margins are defined post hoc (not pre-specified) when there are:

- failed superiority trials of the proposed medicine or CTGTP versus comparator;
- indirect comparisons of the proposed medicine or CTGTP versus the comparator via a common reference; and
- outcomes that did not have a pre-specified non-inferiority margin.

When selecting post hoc non-inferiority margins, demonstrate that an exhaustive search has been conducted to identify relevant information, which justifies a similar proposed margin that represents an unimportant loss of treatment effect. Justify the selection of one particular estimate as the proposed non-inferiority margin.

2.5 Results: whole trial population

KEY INFORMATION REQUIRED

- ☐ Present the results from each included study for all relevant outcomes for the whole trial population
- ☐ Present adverse event data

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

2.5.1 Clinical effectiveness

Present results for all relevant outcomes defined in Subsection 2.4.4 for the whole trial population in each included study. Cross-reference the results to the relevant pages of the CSRs or trial publications.

Examples of how to present the different types of data are shown in Tables 2.5.1a-2.5.1c (adapt tables as required). Where possible, the following information should be presented for each outcome:

- the timing of the outcome assessment (e.g. FEV_1 at week 12);
- the number of patients at risk or providing data to the results;
- the number of patients experiencing the event (if appropriate);
- the percentage of patients with the event, and means (standard deviation) or medians (interquartile range) within groups as appropriate;
- the size of the treatment effect (both relative and absolute differences between groups, and CIs);
- an interpretation of the results;
- a discussion of any clinically important differences in the results between the arms of the study and between studies, in the context of the nominated MCID.

Dichotomous data

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

Study ID	n/N with event (%) for proposed medicine or CTGTP	n/N with event (%) for main comparator	Relative risk (95% CI) (p value)	Risk difference (95% CI) (p value)
Study 1	[add]	[add]	[add]	[add]
Study 2	[add]	[add]	[add]	[add]
[etc]	[etc]	[etc]	[etc]	[etc]

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

Continuous data

Many studies measure a continuous variable at baseline and again at a pre-specified time point. Analysis of covariance (ANCOVA) is the most commonly used approach to measure treatment effectiveness from such studies. It is usually presented as the difference in mean change scores, adjusted for baseline scores (as per Table 2.5.1b).

In addition to the information reported in Table 2.5.1b, report and justify the covariates used in the ANCOVA (and how they were tested) and discuss the effect of controlling for covariates on the estimated comparative treatment effect.

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

Study ID	Mean (SD) [Proposed medicine or CTGTP]			Mean (SD) [Main comparator]			Mean difference (95% CI)	ANCOVA (95% CI)
	Baseline	End point	Change	Baseline	End point	Change		
Study 1[a]	[add]	[add]	[add]	[add]	[add]	[add]	[add]	[add]
Study 2[a]	[add]	[add]	[add]	[add]	[add]	[add]	[add]	[add]
[etc]	[etc]	[etc]	[etc]	[etc]	[etc]	[etc]	[etc]	[etc]

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

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

If the outcome was measured at more than one time-point, justify why a specific end point was selected and discuss whether the treatment effect differs across other time points (indicate where relevant data supporting the time-point selected are located in the CSR). Where continuous data are translated to dichotomous data in the economic evaluation or to support the clinical claim, justify the use of the threshold to convert the data. If the threshold is not well supported by the literature, present sensitivity analyses using different thresholds, or present a cumulative distribution function of the continuous outcome separated by treatment arm. Clearly show the effect of the choice of threshold to determine the dichotomous outcome on the comparative treatment effect.

Time-to-event data

Present relevant Kaplan–Meier curves for each included study. The numbers at risk at regular time intervals should also be provided below the Kaplan-Meier curve. Provide sufficient justification if curves cannot be provided.

Table 2.5.1c: Results of [outcome] across the studies: time-to-event data

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

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

Describe the method for analysing the time-to-event data, including any assumptions and how they have been tested. Discuss whether the results are consistent with the assumption of constant proportional hazards. Where the assumption of constant proportional hazards is not reasonable, present alternative methods for estimating comparative effectiveness.

Multi-attribute utility instrument (MAUI) data

Report MAUI results (with 95% CI) for each time point and each arm within the study. Report the number of patients eligible for the questionnaire and the number of patients who responded for each time point. Report the difference between the arms (with 95% CI) as the integrals between the mean utility weights obtained over time up to the median (or other relevant time point) follow-up in the trial. If an alternative approach for comparing MAUIs was used, explain how this was done. Discuss the interpretation of these results.

If the proposed medicine or CTGTP has already been appraised by NICE, use the scoring algorithm derived from the UK population which informed the submission, then present a sensitivity analysis using a scoring algorithm derived from the general population in Singapore (if available). If more than one MAUI has been used in the included study, compare the results from the two MAUIs.

Effectiveness in the context of minimal clinically important difference

Discuss the results of the primary outcome and main patient-relevant outcome with reference to the MCID. State whether the intervention group has achieved a difference as large as or larger than the proposed MCID when compared with the comparator group. Comment on the extent to which the confidence interval for the comparison includes differences smaller than the proposed MCID.

Applying a non-inferiority margin

Compare the least favourable tail of a 95% CI with the non-inferiority margin (defined in Subsection 2.4.6) and determine whether the 'worst' result would be regarded as non-inferior. Assess this using both intention-to-treat and per-protocol approaches, when available, and discuss any discrepancies between both approaches.

Discuss other considerations that may support the conclusion of non-inferiority (e.g. whether the medicines or CTGTPs are from the same class, the point estimate favours the proposed medicine or CTGTP, whether there are safety or tolerability advantages of the proposed medicine or CTGTP).

Explain and justify all approaches undertaken to establish non-inferiority and demonstrate that the proposed medicine or CTGTP is superior to placebo and is not inferior to the proposed comparator by an important extent.

2.5.2 Adverse events

Report the following categories of adverse events in Table 2.5.2a for each study:

- any adverse event;
- any adverse event resulting in discontinuation of the randomised treatment;
- any serious adverse event;
- any adverse event resulting in death;
- any other adverse events (e.g. treatment-emergent adverse events) where the frequency or severity differs substantially across treatment groups in the included studies, if applicable.

Table 2.5.2a: Summary of adverse events in included studies

	Study 1				Study 2			
	Intervention (n = x)	**Comparator (n = x)**	**RR (95% CI)**	**RD (95% CI)**	**Intervention (n = x)**	**Comparator (n = x)**	**RR (95% CI)**	**RD (95% CI)**
Total number of adverse events**	n (%)	n (%)			n (%)	n (%)		
Total number of serious adverse events**	n (%)	n (%)			n (%)	n (%)		
Total number of deaths due to adverse events	n (%)	n (%)			n (%)	n (%)		
Total number of adverse events leading to treatment discontinuation	n (%)	n (%)			n (%)	n (%)		

[Add rows as necessary]								

*For non-comparative studies, only complete the column for the intervention.
** If studies report number of patients who experienced an adverse event or serious adverse event or treatment-emergent adverse event, rather than total number of adverse events (or serious adverse events), amend description in first column.

For treatment-specific adverse events, consider presenting a more detailed summary table (e.g. Table 2.5.2b) to compare their frequency and severity across treatment arms. Analyse the relative adverse event rates (events per period at risk). Present the assumptions associated with any statistical analyses and describe how they were tested.

Table 2.5.2b: Frequency and severity of adverse events in included studies

Study ID								
System organ/ class/adverse events	**All grades**				**Serious adverse events**			
	Intervention (n = x)	**Comparator (n = x)**	**RR (95% CI)**	**RD (95% CI)**	**Intervention (n = x)**	**Comparator (n = x)**	**RR (95% CI)**	**RD (95% CI)**
Class 1 (for example, nervous system disorders)								
Adverse event 1	n (%)	n (%)			n (%)	n (%)		
Adverse event 2	n (%)	n (%)			n (%)	n (%)		
Class 2 (for example, vascular disorders)								
Adverse event 3	n (%)	n (%)			n (%)	n (%)		
Adverse event 4	n (%)	n (%)			n (%)	n (%)		
CI, confidence interval; RR, relative risk; RD, risk difference Adapted from European Public Assessment Reports published by the European Medicines Agency								

2.6 Results: additional analyses

KEY INFORMATION REQUIRED

Present the results of any additional relevant analyses including:

- ☐ subgroup analyses
- ☐ meta-analyses
- ☐ indirect comparisons
- ☐ adjustments for treatment switching

2.6.1 Subgroup analyses

Submissions based on the whole population of a randomised trial are preferred. If only some of the participants from the whole trial population are likely to be eligible for treatment according to the evaluation framework, present a subgroup analysis to show the relative effectiveness of the proposed medicine or CTGTP in eligible participants.

Indicate which subgroup analyses were pre-specified in the trial protocol and whether randomisation was preserved through stratification of the subgroup. If any subgroup analyses were performed post hoc, provide justification for consideration of these subgroups.

Clarify why the trial(s) enrolled a broader population than the subgroup, and why the proposed medicine or CTGTP should not be funded for patients in the complement of the subgroup (e.g. is it not effective in the complement, or does it work in the complement but is not cost effective? etc.).

For each outcome relevant to the submission, present the relative and absolute treatment effect measures for the whole trial population, the subgroup and the complement (Table 2.6.1)[xvii]. Discuss whether the treatment effect differences between subgroups are clinically plausible – with reference to the medicine or CTGTP's mechanism of action or a pharmacological, biological or clinical rationale – and whether the magnitude of the differences is practically important.

Test for interaction between the subgroup and its complement to support and quantify the association between the treatment effect and the covariate defining the subgroup. If the subgroup is defined by a continuous variable, present a sensitivity analysis on the threshold value chosen to define the subgroup for different thresholds.

Present adverse event data for each subgroup in a table. Take care when testing for interaction where the average period at risk per participant varies substantially between the relevant subgroup and its complement.

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

Population	Study ID	Proposed medicine or CTGTP [*n* with event/*N* (%)]	Main comparator [*n* with event/*N* (%)]	RR (95% CI)	RD (95% CI)
Whole trial population	Study 1	[add]	[add]	[add]	[add]
	Study 2	[add]	[add]	[add]	[add]
	Meta-analysis of overall trial results	[add]	[add]	RR (95% CI) (*k* =)	RD (95% CI) (*k* =)
	I^2 statistic with 95% uncertainty interval	–	–	[add]	[add]
Identified subgroup	Study 1	[add]	[add]	[add]	[add]
	Study 2	[add]	[add]	[add]	[add]
	Meta-analysis of identified subgroup	[add]	[add]	RR (95% CI) (*k* =)	RD (95% CI) (*k* =)
	I^2 statistic with 95% uncertainty interval	–	–	[add]	[add]
Complement of subgroup	Study 1	[add]	[add]	[add]	[add]
	Study 2	[add]	[add]	[add]	[add]
	Meta-analysis of complement of subgroup	[add]	[add]	RR (95% CI) (*k* =)	RD (95% CI) (*k* =)
	I^2 statistic with 95% uncertainty interval	–	–	[add]	[add]
Test for treatment effect variation	–	–	–	*P* =	*P* =

***Adapt the table to include continuous or time-series data if required**

– = not required; CI = confidence interval; *k* = number of studies contributing to the pooled estimate of effect; *n* = number of participants with event; *N* = total participants in group; *P* = probability; RD = risk difference; RR = relative risk

2.6.2 Meta-analyses

If more than one study reports a relevant outcome, where feasible, present a meta-analysis[xviii] of the aggregated results of each study that reported the outcome, and state the software used for the analysis (e.g.

[xvii] Where the whole trial population for each trial is adequately captured in Table 2.6.1, there is no need to present extensive tables in Section 2.5.

[xviii] Standardised methods to conduct a meta-analysis are described Chapter 10 of the Cochrane handbook.

RevMan,[16] Stata[17]). Justify any decision to not present a pooled result for any relevant outcomes (e.g. because there is significant clinical heterogeneity between studies.

Use a random effects model[18] to pool group-level trial data. Explain and justify any other method used (e.g. fixed effects). Provide adequate detail of the methods used, and all references which informed the meta-analyses, so that the results are verifiable and can be independently reproduced, if required.

Presenting the results

Present the pooled estimates with their 95% CIs in Table 2.6.2. Report results for the extent of statistical heterogeneity observed using a chi-square (Cochran's *Q test)* statistic*,* degrees of freedom, and the I-squared (I^2) statistic with its 95% uncertainty interval.

Comment on the consistency of treatment effects across the trials. Include a forest plot of relative and absolute treatment effects and discuss the results for each outcome.

Table 2.6.2: Example of tables to include relevant information on pooled (dichotomous*) results

Measurement	Outcome	Chi-square (Q) for heterogeneity, df and *P* value	I^2 statistic with 95% uncertainty interval
Pooled result from random effects model (RR, 95% CI, *k*)	[add]	[add]	[add]
Pooled result from random effects model (OR, 95% CI, *k*)	[add]	[add]	[add]
Pooled result from random effects model (RD, 95% CI, *k*)	[add]	[add]	[add]

***Adapt the table as necessary to report results for continuous outcomes or time-series data**

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

Discuss and explain any heterogeneity of treatment effect across trials and the I^2 statistic. There are several factors that can cause heterogeneity in study treatment effects, such as variations in study design, study participants, treatment dosing, frequency or delivery, setting, geographic location and method of outcome measurement. Where there are strong biological or methodological grounds for heterogeneity, consider presenting sensitivity analyses that explore the impact of these factors. Discuss any implications of factors that may cause heterogeneity of treatment effect with regard to the proposed target population.

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

Discuss the estimate of the magnitude of the pooled treatment effect in the context of its clinical relevance.

Adverse event data

Present a meta-analysis of adverse event data in line with the specifications in Table 2.6.2. Report the duration over which adverse events were recorded for each study.

2.6.3 Indirect comparisons

Indirect comparisons refer to the synthesis of data from studies in which the interventions of interest have not been compared directly (head-to-head) with each other but have been compared indirectly using a common comparator. There are several methods that can be used, such as the Bucher single pairwise

method,[19] matching-adjusted indirect comparison,[20] simulated treatment comparison,[21] network meta-analysis (NMA) or mixed treatment comparison (MTC). All methods chosen to conduct an indirect comparison to inform the submission should be described in sufficient detail and justified. An indirect comparison should not be conducted if the transitivity assumption[xix] is not met.

Where there are multiple common reference arms, it is preferable to perform pairwise indirect comparisons using the Bucher method[xx] for each possible evidence loop and discuss any differences.

More complex methods, such as network meta-analyses, may be presented as supplementary analyses. For network meta-analyses, present the results of pairwise comparisons for each link in the network. It is preferable that non-randomised studies are not included in any network meta-analyses. Where non-randomised studies must be included, present the results of the network meta-analysis both with and without the non-randomised studies.

Unadjusted indirect comparisons (such as a naive comparison between single arms), or indirect comparisons (where differences in study characteristics may affect the transitivity of the studies in the comparison) should be avoided if higher level evidence is available. Where patient-level data are available for at least one study in the comparison, use matching-adjusted indirect comparisons or simulated treatment comparisons to correct for study differences to improve the transitivity of the comparison. Conclusions based on an unadjusted indirect comparison are highly uncertain due to the high potential for the comparison to be influenced by factors other than the treatments being compared.

For all analyses, provide sufficient detail of the methods used, to enable them to be independently replicated, if required, and provide all programming code for statistical software (e.g. Stata or WinBUGS) as an attachment. For methods that require individual patient data (matching-adjusted indirect comparison or simulated treatment comparison), attach the individual de-identified patient dataset in a spreadsheet.

Assess the heterogeneity between results of pairwise comparisons and any disagreement or inconsistencies between the direct and indirect evidence. If inconsistency within a network meta-analysis is found, attempts should be made to explain and resolve these inconsistencies.

If an indirect comparison includes confounders, adjustment using a meta-regression, a matching-adjusted indirect comparison or a simulated treatment comparison may be appropriate, in addition to the pairwise comparisons. Describe all methods undertaken in sufficient detail, to enable the approach to be independently verified, if required.

Presenting the results

Report all results from the indirect comparison in tables:

- For dichotomous outcomes, present the results of each individual randomised trial as the odds ratio, relative risk and absolute risk difference with 95% CIs between the common reference, and the proposed intervention and the main comparator (three separate tables may be required).
- For time-to-event outcomes, present the results of each individual randomised trial as the hazard

[xix] Transitivity assumption requires that the treatment comparisons within the indirect comparison do not differ with respect to the distribution of known effect modifiers.

[xx] The Bucher method is commonly used to indirectly compare the odds ratios from randomised trials that share a common reference arm. However, this method has been extended to include other treatment effect measures, such as relative risk, absolute risk and hazard ratio.[22]

ratio with its 95% CI between the common reference, and the proposed intervention and the main comparator. Also report the median event-free survival in each arm of the common reference, proposed intervention and main comparator.

- Where there is more than one randomised trial in a set, separately pool (meta-analyse) the treatment effect results between the common reference and the proposed intervention, and between the common reference and the main comparator. Present the relevant outcome measures with 95% CIs using the random effects model.
- Calculate the indirect estimate of effect, and present the estimate as a relative risk and odds ratio (or the ratio of hazard ratios) with its 95% CI (and example table is shown below, Table 2.6.3).

Table 2.6.3: Example summary table of results of the indirect comparison (for a dichotomous outcome)*

Study type or estimate	**Study ID**	***n* with event/*N* (%)**	**Common reference *n* with event/*N* (%)**	**Treatment effect (OR)**	**Treatment effect (RR)**
Proposed medicine or CTGTP vs common reference studies	Study 1	*n*/*N* (%)	*n*/*N* (%)	OR (95% CI)	RR (95% CI)
	Study 2	*n*/*N* (%)	*n*/*N* (%)	OR (95% CI)	RR (95% CI)
	Pooled	total *n*/total *N* (%)	total *n*/total *N* (%)	Pooled OR (95% CI)	Pooled RR (95% CI)
Comparator vs common reference studies	Study 3	*n*/*N* (%)	*n*/*N* (%)	OR (95% CI)	RR (95% CI)
	Study 4	*n*/*N* (%)	*n*/*N* (%)	OR (95% CI)	RR (95% CI)
	Pooled	total *n*/total *N* (%)	total *n*/total *N* (%)	Pooled OR (95% CI)	Pooled RR (95% CI)
Indirect estimate of effect adjusted for the common reference	–	–	–	OR (95% CI)	RR (95% CI)

***Adapt the table as necessary to include continuous or time-to-event outcomes**

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

2.6.4 Adjustment for treatment switching

Where one or more of the included studies has participants that switched treatments, check whether the pattern of switching is similar to current clinical practice for the comparator arm and/or future clinical practice for the proposed medicine or CTGTP. If so, adjustment is not needed. Otherwise, the observed comparative treatment effect may not reflect the expected treatment effect in the Singapore population, and adjustment may be appropriate.

Preferred approach for adjusting the treatment effect for treatment switching

For each arm of each relevant study, explain:

- the extent of the switching and which medicines or CTGTPs were involved;
- whether the treatment switching from the comparator arm reflects or differs from current clinical practice; and
- whether the treatment switching from the intervention arm is likely to reflect future clinical practice.

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

- Provide the reasons for switching (e.g. progression of condition, or toxicity) and the patient numbers for each category;
- Indicate whether treatment switching and/or specific analyses to adjust for treatment switching were pre-specified in the trial protocol (provide references where applicable);
- Present the baseline characteristics of switchers and non-switchers, as well as the characteristics of participants just before switching and summarise any differences between the different groups. If participants switched primarily as a result of progression of their condition, present the characteristics of the participants who were at risk of switching (progressed) but did not switch and compare them with those who did switch;
- Report the extent and timing of treatment switching in Table 2.6.4, and consider the impact of the blinded or open-label design of the study on the nature and extent of switching and the likelihood of treatment switching in clinical practice.

Table 2.6.4: Extent of treatment switching in the randomised trials

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

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

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

Several methods can be used to adjust survival estimates for treatment switching.[23] Provide details on the approach taken (as an attachment), including the assumptions and how they have been tested. Demonstrate that the results would be similar if different approaches to adjusting for treatment switching were undertaken. Discuss the risk of adjustment on overstating the true comparative treatment effect. Provide any additional evidence available that will reduce the uncertainty associated with the estimate of the treatment effect following adjustment.

Results of adjustment for treatment switching

For each of the methods used to adjust the treatment effect for treatment switching, present the adjusted treatment effect and the 95% CI. Explain any heterogeneity of treatment effects across the different methods for adjustment. Present the treatment effect and the 95% CI in the absence of switching, for comparison.

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

If possible, use a number of different statistical approaches to adjust for switching. A similar result from a number of analyses will reduce uncertainty and increase confidence in the result. Comparison with historical controls where there was an absence of switching will also improve confidence in the statistical approaches.

There is a risk of bias associated with the use of subgroups, indirect comparisons and adjustment methods for treatment switching. These approaches should not be combined, as they will be regarded as poor-quality evidence.

2.7 Applicability of study results to the Singapore setting

KEY INFORMATION REQUIRED

- ☐ Identify characteristics of the included studies that may affect the applicability of the results to the Singapore setting
- ☐ Explore important differences between the trial setting and the Singapore setting, and estimate the likely impact on treatment effects

Applicability, also known as external validity, generalisability or transposability, is the extent to which the effects observed in clinical studies are likely to reflect the expected results when an intervention is applied to the population of interest outside the trial setting. In this section, explore possible differences between the observed comparative benefits and harms in the trial setting, and the benefits and harms that are likely to occur in the Singapore setting. The PICO elements in the evaluation framework (Subsection 1.1.2) are useful to identify factors that may affect the applicability of the included studies to the local context (Table 2.7).

Table 2.7: Characteristics of individual studies that may affect applicability to the local context

Domain	Description of applicability of evidence
Population	[Describe the general characteristics of enrolled participants, how they may differ from the Singapore population]. Factors that may limit applicability include: ▪ Narrow eligibility criteria (that require specific tests) and exclusion of participants with comorbidities or concomitant medicines ▪ Large differences between demographics of study population and Singapore patients ▪ Narrow or unrepresentative severity, stage of illness, or comorbidities ▪ Long run-in period with high exclusion rate for non-adherence or side effects ▪ Event rates much higher or lower than observed in population-based studies
Intervention	[Describe any differences in the general characteristics of the intervention (e.g. how it is administered) between the trial and local clinical practice in Singapore]. Factors that may limit applicability include: ▪ Doses or schedules used in trials not reflected in Singapore clinical practice ▪ Monitoring practices or visit frequency in trials not used in Singapore clinical practice ▪ Older versions of an intervention used in trial no longer in common use in Singapore ▪ Level of training/proficiency with intervention required for the trial setting not widely available in Singapore

Comparator(s)	[Describe whether the comparator(s) reflect best alternative treatment in Singapore clinical practice and how this may influence treatment effect size]. Factors that may limit applicability include: ▪ Inadequate dose of comparator ▪ Use of substandard alternative therapy
Outcomes	[Describe whether the measured outcomes and timing of assessments reflect the most important clinical benefits and harms]. Factors that may limit applicability include: ▪ Short-term or surrogate outcomes ▪ Composite outcomes that mix outcomes of different significance
Setting	[Describe geographic and clinical setting of studies and whether or not they reflect the settings in which the intervention will be typically used in Singapore]. Factors that may limit applicability include: ▪ Standards of care in Singapore differ markedly from trial setting ▪ Intervention is administered in a different care setting in trial compared to how it will be used in Singapore (e.g. inpatient vs outpatient setting)

Adapted from Atkins et al (2011)[24]

2.7.1 Identification of important differences across settings

Tabulate important differences between the trial setting and the Singapore setting in Table 2.7.1 and discuss the likely effect the differences will have on estimates of clinical effectiveness.

Table 2.7.1: Example differences between the trial setting and the Singapore setting

Characteristic	Trial setting	Singapore setting	Conclusion
Disease or condition severity	42% stage I or II, 58% stage III or IV	65% stage I or II, 35% stage III or IV	Requires further investigation [May have an effect on comparative treatment effect]
Comparator chemotherapy regimens	31% participants received 4-6 cycles of platinum-doublet chemotherapy followed by maintenance pemetrexed	~70% patients receive 4-6 cycles of platinum-doublet chemotherapy followed by maintenance pemetrexed	Requires further investigation [May have an effect on comparative treatment effect]
Location of enrolment/treatment	13% East Asian settings	Singapore	Requires further investigation [May have an effect on comparative treatment effect, and resource use]
Age	Median age 64.5 to 66 years	80% diagnosed at 70 years or older	Unknown

Discuss whether any differences between the settings (identified in Table 2.7.1) may affect the comparative safety of the proposed medicine or CTGTP if it is used in the Singapore setting. Possible factors to consider include:

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

Real-world evidence (RWE)[xxi] that is fit-for-purpose and representative of the target local population, can be presented **as supplementary information** in line with *ACE's position statement on the use of real-world data and evidence to support health technology assessment*, to support claims regarding the likely effect of the proposed medicine or CTGTP when used in Singapore clinical practice. This type of information may be useful to:

- provide evidence with higher external validity compared to clinical studies;
- provide more certainty about the safety and effectiveness of the proposed medicine or CTGTP in the local setting and/or in an Asian population (which may be underrepresented in the clinical trials);
- explain patients' treatment expectations and preferences; or
- fill any information gaps in the absence of clinical trials (e.g. when it is not feasible or ethical to conduct an RCT).

Real-world data (RWD) may also be required if there are significant biological differences between Singapore patients and the trial populations that could affect how the medicine or CTGTP should be used or how well it works. For example, differences in body weight, pharmacokinetics and/or pharmacodynamics due to different genetic makeups between Caucasians and Asians which may impact requirements for use (e.g. dosing regimens) and/or the effect of the proposed medicine or CTGTP.

If RWE is included, state the rationale for its use and discuss in the context of all available evidence, state the source of the RWD and the sample size. Describe the methods used to collect and analyse any RWD and provide a summary of the reliability and quality of the data collected. Conduct a risk of bias assessment in line with the methods described in Subsection 2.3.4 for dealing with non-randomised evidence.

Where comparative effectiveness evidence is generated using external control arms constructed from RWD, submissions should also follow *ACE's Guidance on the Design, Conduct and Analysis of External Control Arms in the Generation of Real-World Evidence to Support Health Technology Assessment Evaluations*.

2.8 Interpretation of the clinical evidence

Provide a brief summary of the clinical evidence presented in the submission which considers:

- the level and directness of the evidence;
- the quality of the evidence;
- the clinical importance and patient relevance of the effectiveness and safety outcomes;
- the statistical precision of the findings;
- the size of the effect;
- any uncertainties in the evidence that may affect the overall clinical claim;
- the consistency of the results across the studies presented and their applicability to the Singapore setting; and
- any other relevant factors.

State the therapeutic conclusion for the effectiveness and safety of the proposed medicine or CTGTP in relation to its main comparator(s) (i.e. whether it is therapeutically superior, inferior or non-inferior to the comparator).

[xxi] Real-world data is defined as data collected outside of controlled trials (e.g. from observational studies, electronic medical records, administrative databases for claims and billing activities, product and disease registries, and patient-generated data including surveys, digital health devices). Real-world evidence is defined as evidence that is derived from real-world data.

Example:
[Proposed medicine or CTGTP administered until disease progression for a maximum of 12 cycles] is superior/non-inferior/inferior in terms of effectiveness compared with [comparator administered until disease progression].

[Proposed medicine or CTGTP] is superior/non-inferior/inferior in terms of safety compared with [comparator].

Section 3 Economic Evaluation

Introduction

In Section 3, present an economic evaluation comparing the proposed medicine or CTGTP with the main comparator(s) in line with the evaluation framework (Subsection 1.1.2) and ACE's reference case (Table 3). The economic evaluation may be a cost-utility analysis (CUA) (Section 3A) or a cost-minimisation analysis (CMA) (Section 3B).

A cost-utility analysis requires consideration of both the incremental **direct** health-related costs and health outcomes associated with the proposed medicine or CTGTP, to generate an incremental cost-effectiveness ratio (ICER). This type of analysis is appropriate where the clinical evaluation (Section 2) has concluded that the proposed medicine or CTGTP is:

- therapeutically superior to the main comparator(s), but is likely to result in additional costs to the healthcare system; or
- therapeutically inferior to the main comparator, but likely to result in lower costs to the healthcare system.

A cost-minimisation approach is appropriate where there is a therapeutic claim of non-inferiority and use of the proposed medicine or CTGTP is anticipated to result in equivalent or lower costs to the healthcare system compared to the main comparator(s).

Other economic evaluations (e.g. cost-benefit analyses or cost-consequences analyses) **should not be presented** unless previously agreed by ACE during the pre-submission meeting.

Refer to the following sections for guidance on conducting specific types of economic evaluations:

- Section 3A – guidance for conducting a CUA
- Section 3B – guidance for presenting a CMA

Table 3: Summary of ACE's reference case for economic evaluations submitted for funding consideration

Component of evaluation	Reference Case
Perspective	▪ Singapore healthcare system including payments out of the government's healthcare or insurance (MediShield Life) budgets as well as patients' co-payments including MediSave and out of pocket expenses
Target population	▪ Consistent with the patient population defined in the evaluation framework ▪ Epidemiological data for Singapore presented for the entire target population and relevant subgroups
Comparator(s)	▪ Consistent with the comparator(s) defined in the evaluation framework ▪ Comparator(s) should either reflect the current treatment that is most likely to be replaced by the proposed medicine or CTGTP in routine local clinical practice, or in the case of add-on treatments, the current treatment without the proposed medicine or CTGTP added on
Outcomes	▪ Consistent with the outcomes defined in the evaluation framework ▪ Health outcomes should be patient-relevant and valued from a Singapore healthcare system perspective
Economic evaluation	▪ CMA or CUA may be undertaken ▪ Justification of model structural assumptions and data inputs should be provided. When there are alternative plausible assumptions and inputs, sensitivity analyses of their effects on model outputs should be undertaken. ▪ Results for CUA expressed as incremental cost-effectiveness ratios (ICER)
Calculation of costs	▪ Only direct healthcare costs should be included ▪ Identification, measurement and valuation of costs should be consistent with the perspective of the Singapore healthcare system (government, insurance provider and patient healthcare costs) ▪ Indirect healthcare costs or non-healthcare costs should not be included
Measuring and valuing health effects	▪ Final, clearly defined, clinically meaningful outcomes should be presented ▪ CUA: quality-adjusted life years (QALYs) gained[a] ▪ Life expectancy estimates based on recent Singapore age-specific and gender-specific life tables ▪ EQ-5D-3L UK value set (which ideally have been accepted by NICE) should be used in the scoring algorithm. ▪ EQ-5D-3L Singapore value set can be used in sensitivity analyses
Time horizon	▪ The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the treatments being compared
Discount rate	▪ Costs and health outcomes are discounted at an annual rate of 3%
Handling uncertainty	▪ Explore all relevant structural, parameter source, and parameter precision uncertainty ▪ One-way deterministic sensitivity analysis should be presented for all uncertain parameters ▪ Multivariate probabilistic sensitivity analysis may also be performed to address simultaneous impact of all uncertain parameters

a The QALY is considered to be the most appropriate generic measure of health benefit that reflects both mortality and health-related quality of life effects.

Although the reference case specifies the preferred methods for economic evaluations submitted for funding consideration, it does not preclude decision-making committees from considering non-reference case analyses (presented as supplementary analyses) if appropriate, and well justified.

3.1 Published economic evaluations

Review the literature for relevant published economic evaluations involving the proposed intervention and/or comparator treatments for a similar patient population. This should include published HTA reports and models considered by national HTA agencies (e.g. PBAC, MSAC, NICE, CDA-AMC, Pharmac etc.). Provide a brief overview of each identified study in Table 3.1.

Table 3.1: Summary of published economic evaluations

Study	Year of publication	Type of economic evaluation	Perspective and country	Strategies compared	Time horizon	Patient population	LYG/QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (cost per LYG/QALY gained)
Study 1									
[add rows as needed]									

LYG= life years gained; QALY= quality-adjusted life year; ICER= incremental cost-effectiveness ratio. **Convert table to landscape**.

Section 3A Cost-effectiveness analysis

3A.1 Overview of the economic evaluation

KEY INFORMATION REQUIRED

- ☐ Describe the economic evaluation presented and outcome measures used
- ☐ Use a Singapore healthcare system perspective to inform analyses
- ☐ Apply an annual discount rate of 3% to costs and outcomes in base case analyses
- ☐ Describe the model structure and modelling technique used
- ☐ Justify the time horizon used
- ☐ Describe the sources of the model input parameters
- ☐ Provide an executable electronic copy of the economic model

3A.1.1 Summary of the economic evaluation

Summarise the key components of the economic evaluation in Table 3A.1.1.

Table 3A.1.1: Summary of the key components of the economic evaluation

Component	Description
Type of analysis	[e.g. CUA]
Outcomes presented	[e.g. LYG, QALYs]
Type of model	[e.g. Markov model, microsimulation]
Time horizon	[x] months/years in the base case [x]-[y] months/years modelled in sensitivity analysis
Health states	[If applicable, present a brief description of all health states]
Cycle length	[x] days/weeks/months/years
Software	[e.g. Excel, TreeAge Pro]

CUA = cost utility analysis; LYG = life years gained; QALY = quality-adjusted life year

3A.1.2 Type of economic evaluation

A cost utility analysis (CUA) should be presented. Differences in costs and outcomes that occur when the proposed intervention or its main comparator(s) are used should be expressed as incremental costs and incremental outcomes between these alternatives in the Singapore setting. Identify the incremental patient-relevant health outcomes (i.e. quality-adjusted life years [QALYs]) and incremental health costs.

3A.1.3 Perspective of the economic evaluation

The economic evaluation should be presented from the perspective of the Singapore healthcare system, including payments out of the government's healthcare or insurance (MediShield Life) budgets as well as patients' co-payments including MediSave and out of pocket expenses. Only direct health-related costs and patient-relevant health outcomes valued from the healthcare system perspective should be presented.

Supplementary analyses which include non-health benefits may be appropriate where the proposed medicine or CTGTP has important societal implications extending beyond the health outcomes of the patient receiving treatment, and beyond the health care system (e.g. economic productivity impact).

3A.1.4 Discounting

The values of costs and benefits incurred or received in the future should be discounted to reflect the present value. In the base-case analysis, discount all costs and health outcomes that occur or extend beyond one year at an annual (compounding) rate of 3%.

Present sensitivity analyses using fixed discount rates of 0% and 5% per year (applied to both costs and outcomes) to test the impact of the chosen discount rate on the ICER.

3A.1.5 Structure of the economic model

Present a diagram that provides a conceptual overview of the model structure. Descriptions of the health states in the diagram should also be provided. Ensure that the model structure captures all relevant health states or clinical events along the pathway of the condition, and that it is consistent with the treatment algorithm(s) presented in Subsection 1.2.1. The model structure should also be informed using the results of the literature review of economic evaluations (Section 3.1), and other relevant literature, including clinical trials, clinical guidelines and burden of disease studies. Provide copies of the original sources of all data not already presented in Section 2 which have been used to inform the model, in an attachment.

Disaggregate patient-relevant events if there are important differences in mortality, disease/condition progression, associated costs, or quality-of-life effects, and if the distribution differs between the proposed medicine or CTGTP and comparator(s).

Assess the model structure(s) to establish face validity. Justify the exclusion of any potentially relevant health states or events identified in the literature (or proposed by local clinical experts) and discuss the potential impact of any exclusions on the model outputs. Where the model structure differs from existing models, explain the basis for the selected approach.

If adequate data are not available to inform the model according to the initially defined structure, consider restructuring the model according to the available data and assess the face validity of alternate model structures. If a valid alternative model structure can be constructed, describe the revisions to the initial model

and discuss the potential impact on the model outputs.

3A.1.6 Model types

Models should avoid unnecessary complexity and should be transparent, well described and reproducible. If a trial-based economic evaluation is being undertaken using individual patient data for costs and outcomes from a clinical trial(s), describe the methods used to do this and provide the statistical plan and statistical outputs as an attachment. This type of evaluation should only be considered if the patients in the trial are directly representative of individuals in Singapore who are likely to use the proposed medicine or CTGTP, and all patient-relevant endpoints were directly measured in the trial over an appropriate time horizon.

If the trial(s) do not provide evidence that sufficiently measures the full clinical and economic consequences of the proposed medicine or CTGTP compared with its main comparator(s) in the Singapore setting, a model-based economic evaluation is required.

For model-based economic evaluations, identify the most appropriate (and least complicated) modelling technique which is feasible to implement the specified model structure (described in 3A.1.5). Decision trees, cohort-based state transition models (Markov models) or partitioned survival analysis models are preferred to assess the cost-effectiveness of medicines. For some medicines or CTGTPs, approaches that combine decision trees with other modelling techniques, such as cohort-based state transition models, can be considered. The proposed modelling approach should be discussed with ACE during the pre-submission stage.

Decision trees

Simple decision trees can be used for models with short time horizons, and/or where an event is expected to only occur once during a discrete period. Decision trees should be developed following good practice guidelines.[25]

Cohort-based state transition (or Markov) models

Cohort-based state transition (Markov) models can be used to represent longer time horizons (for models that can be represented using a manageable number of health states under the constraints of the Markovian [“memoryless”] assumption) and/or when events are expected to reoccur during a discrete period. Markov models assume that a person is always in one of a finite number of health states. The model cohort is usually assigned to an initial health state and then individuals can move between health states at defined recurring intervals (Markov cycles) which are determined by transition probabilities. The model is usually run until all of the cohort moves through to the absorbing state (e.g. “dead” state).

Markov models should be developed following good practice guidelines.[26] The cycle length chosen should be justified and should reflect the minimum time period over which the pathology or symptoms are expected to change in line with the nature of the condition. If clinical events are likely to occur frequently, then a short cycle length should be used. In designing a Markov model, assess if transition probabilities are dependent on time spent in a health state or previous occupancy of associated states. In the cases where there are such deviations from the Markovian assumption, tunnel or intermediary states could be used to circumvent this limitation.

A half-cycle correction is the default approach to represent the time of transition between states. An alternative correction factor may be proposed with justification.

Partitioned survival analysis models

Partitioned survival analysis models are conceptually similar to state transition models in that they are characterised by a series of health states, however, the proportion of patients in each health state is determined by the area under the non-mutually exclusive survival curves (e.g. overall survival and progression-free survival curves), rather than matrices of transition probabilities (as for Markov models). They are commonly used to evaluate cancer drugs but can be used for other conditions. Partitioned survival analysis models should be developed in line with published good practice guidelines.[27]

Individual-level (or microsimulation) models

Individual-level modelling approaches (such as individual-based state transition models or discrete event simulation models) should only be used when a defined model structure cannot be feasibly implemented as a cohort-based model. Describe the characteristics[xxii] of the model structure that prevent a cohort-based model from being used and explain how incorporation of these characteristics in an individual-level model are expected to produce a more accurate representation of the condition pathways, costs and patient outcomes. Individual-level models should be developed in line with published good practice guidelines.[26,28]

3A.1.7 Fully executable electronic copy of the economic model

Models should be developed in Microsoft Excel and/or TreeAge Pro. Use of advanced features or plug-ins (e.g. Crystal Ball) in Excel, or alternative software packages should be avoided unless agreed by ACE prior to submission. All models should include clear instructions on their use.

Provide access to the electronic copy of the economic model. It should be fully executable (unlocked and editable) to allow model inputs to be verified and changed independently (e.g. if the ERC or ACE are required to conduct additional sensitivity or scenario analyses).

If an economic evaluation has been previously submitted to an overseas HTA agency (e.g. PBAC or MSAC (Australia) or NICE (England)) to inform national funding decisions, the model may be adapted (i.e. inputs and structure modified to reflect the Singapore setting) and submitted to ACE.

3A.1.8 Time horizon

Define and justify the time horizon over which the costs and outcomes of the proposed intervention and its main comparator(s) are estimated. Ensure that the time horizon captures all important differences in costs and outcomes between the proposed intervention and the comparator(s), as a result of the choice of treatment.

The time horizon should never be determined by the length of time for which evidence is available. Where observed data are not available to inform an appropriate time period, extrapolation of costs and outcomes over the time horizon will be required (described in 3A.3.2).

Where interventions do not affect mortality and have temporary health or quality-of-life effects (e.g. for treating acute conditions), a shorter time horizon may be appropriate.

[xxii] Potential factors include, but are not limited to, baseline heterogeneity, time-varying event rates and the influence of previous events on subsequent event rates.

The validity of a time horizon should be determined by the population in the model and the inputs. Unrealistic inputs will lead to the model predicting an implausible duration of outcomes or survival and therefore, an implausible time horizon. An assessment of the plausibility of the chosen time horizon should be described, including an explanation of how the model extrapolates the clinical data to reach this time horizon.

Economic claims based on a model with a very extended time horizon and predominantly extrapolated benefits are likely to be more uncertain and should be explored through sensitivity analyses (described in Subsection 3A.9).

3A.1.9 Model inputs

Economic evaluations should be informed by results from direct randomised trials, or indirect comparisons where direct comparisons are not available (as described in Section 2), with any adjustments or additions to the trial data to account for differences in the population and setting, timeframe of analysis or outcomes of interest clearly described.

Describe the methods used to identify data to populate the model input parameters. The method of identifying the data should be robust and transparent (e.g. systematic reviews of the literature and well-designed clinician surveys). Where multiple sources of data exist, the choice of the source used in the base case should be justified. The impact on the ICER of using alternative data sources, where relevant, can be tested in sensitivity analyses.

For partitioned survival analysis where survival curves are used, any adjustment made for treatment switching should be justified and conducted in line with Subsection 2.6.4.

If clinical experts have assessed the applicability of model inputs or approximated any of the clinical parameters, provide sufficient detail on the method used to collect their opinions (e.g. self-administered questionnaire, advisory panel etc.), the number of experts who provided input, and their names, specialties and institutions. Include copies of the questions they were asked and their responses as an attachment. If the majority of clinical parameters are approximated by clinical experts, this will potentially reduce the validity of the model and increase the uncertainty surrounding the base-case ICER.

3A.2 Population and setting

KEY INFORMATION REQUIRED

- ☐ Describe the demographic and patient characteristics for the modelled population
- ☐ Describe any quantitative adjustments to model inputs that are necessary due to differences between the trial and target populations

3A.2.1 Patient characteristics and circumstances of use

The modelled population should represent the target Singapore population defined in the evaluation framework (Subsections 1.1.2 and 1.1.3) who are expected to use the proposed medicine or CTGTP in line with the defined clinical treatment algorithm and any proposed clinical criteria (Subsection 1.3).

Describe the demographic and clinical characteristics of the modelled population including age, sex, ethnicity, health condition (and level of condition severity if applicable), comorbidities and prior treatments (if relevant)

using summary statistics (including SD and 95% CI). Indicate which patient characteristics are incorporated into the model. Describe and justify how heterogeneity in patient characteristics (if relevant) is represented in the cost-effectiveness analysis.

Provide details of any additional circumstances relating to the use of the proposed medicine or CTGTP that are relevant to the modelled population, such as restrictions on the position of the proposed medicine or CTGTP in the clinical management algorithm (e.g. first-line or second-line treatment), stopping criteria, continuation rules or specific requirements (facilities, equipment, care setting, concomitant medical services and treatments including diagnostic tests, contraindications, and qualifications or training for providers, etc.) for administration of the proposed medicine or CTGTP. Explain how these circumstances have been accounted for in the model.

Determine whether any quantitative adjustments to model inputs are necessary due to differences (applicability concerns) between the trial population(s) and the target population in Singapore, and, if so, describe the method(s) for translation. Common methods for translation include subgroup analyses, regression analyses, meta-regression or use of other published studies (only if it is not possible to inform translation using direct clinical evidence for the proposed medicine or CTGTP). Justify the selected approach.

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

Where a regression or meta-regression analysis is used, present and interpret the results in the main body of the submission, and provide a clear description of the regression method, the associated assumptions, and how the assumptions were tested in an attachment and include all statistical commands and output.

3A.3 Transition probabilities

KEY INFORMATION REQUIRED

- ☐ Present the transition probabilities and any modelled variables that are incorporated into the economic model, and identify data sources and any associated translation requirements
- ☐ Explain and justify methods used to extrapolate data, where necessary, beyond the trial follow up period(s)

3A.3.1 Transition probabilities and variables

Transition probabilities inform the movement of patients between health states in decision trees or state transition models[xxiii]. They may differ by treatment or by how long a patient has been in a particular health state (time-varying probabilities).

Describe and justify the methods used to identify and analyse relevant data to derive transition probabilities and/or variables. Transition probabilities that differ by treatment should be estimated using the clinical evidence described in Section 2 and adjusted (as justified) for clinical practice in Singapore. Other transition probabilities may be required that describe the progression of a condition following the experience of an

[xxiii] In discrete event simulations, time-to-event parameters are analogous to transition probabilities.

intermediate outcome event, regardless of treatment allocation. If there is evidence that transition probabilities may change over time for the treatment effect or the condition, describe how this has been accounted for in the model. Where external sources of data (other than clinical evidence from Section 2) are used to inform transition probabilities, or other variables in the model, assess the applicability of these sources of data with respect to the Singapore setting. For example, Singapore age-specific life tables[xxiv] should be incorporated to ensure mortality risks do not fall below age- and sex-matched general population rates, with overall survival hazard capped at background mortality.

Note and justify whether the data are applicable, if they require translation (and describe how this was done) and if they are a source of uncertainty within the model. Describe where the model uses other variables instead of, or in addition to, transition probabilities.

For each transition probability or variable, present the point estimate and interval estimates (e.g. 95% confidence intervals) in a table, along with the source of the estimate. Ensure that values taken from all sources of evidence are appropriately adjusted to represent the transitions required by the model structure (e.g. translate reported rates or cumulative probabilities to the probabilities for timeframes associated with a model cycle, if necessary).[29,30] Assess any potential correlation between transition probabilities and/or input variables (e.g. parameters describing a survival function used for survival extrapolation). Correlation between parameters is particularly relevant when conducting analyses to address uncertainty (Subsection 3A.9.2).

3A.3.2 Extrapolation

Extrapolation may be justified when all important differences in costs and outcomes between the proposed intervention and comparator(s) groups are not represented over the time horizon for which observed data are available in the clinical trial. Many sources of advice on extrapolation techniques for economic evaluations are available in the literature.[31-37] Describe the methodology, limitations and any possible biases associated with extrapolating data required for the base-case economic model.

Extrapolating individual patient time-to-event data

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

Describe and justify the selected time point beyond which extrapolated transition probabilities are applied. External data may be used to justify the selected time point (e.g. the point at which one or more of the curves fitted to the clinical trial data deviates from a curve fitted to observational data from a similar patient cohort with a larger sample over a longer follow-up period). Test alternative truncation points in a sensitivity analysis.

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

Describe whether an assumption of proportional hazards for the entire time horizon is appropriate. Graphs such as log(−log(survival)) plot or relevant statistical tests may be useful for testing the proportional hazards assumption within the observed data. Fit a range of alternative survival models to the observed data (e.g. exponential, Weibull, log-normal, log-logistic, gamma, Gompertz). Multiple points of inflexion (e.g. piecewise

[xxiv] https://www.singstat.gov.sg/publications/population/complete-life-table

spline models) may be appropriate to better facilitate extrapolation based on the section of the Kaplan–Meier curve that is most representative of long-term survival.[38]

Assess and discuss goodness of fit using visual inspection (e.g., Quantile–Quantile (Q–Q) plot for accelerated failure time models), Akaike's information criterion and Bayesian information criterion. Present all Kaplan-Meier plots along with the corresponding chosen modelled curves in a graph.

Discuss the plausibility of the predictions in the unobserved period (e.g. the ongoing hazard ratio and/or treatment effect, the point of convergence and/or residual survival in each arm). Justify the most appropriate model for the base case and test a number of the best-fitting models in sensitivity analyses.

The treatment effect resulting from the independent extrapolation of the survival curves should be plotted over the time horizon of the model. If the treatment effect is maintained or increasing beyond a point which is no longer considered clinically plausible, apply a hazard ratio such that the proposed intervention and comparator curves converge at a plausible time point. The assessment of plausibility should be linked to the justification for the chosen time horizon (Subsection 3A.1.8).

Extrapolating published time-to-event data

If individual patient time-to-event data are not available, extrapolate survival probabilities from published Kaplan–Meier curves using graph digitiser software and established statistical methods for recovery of individual patient survival data.[39,40] Fit a range of alternative survival models (e.g. exponential, Weibull, log-normal, log-logistic, gamma, Gompertz) to the extracted survival data beyond the last point of inflexion to the time point at which the observed data become unreliable because of small numbers of patients remaining event-free.

Present tests of the relative and absolute goodness of fit of the alternative curves. Justify the most appropriate model for the base case, taking into consideration goodness of fit as well as clinical plausibility. Test alternative models in sensitivity analyses.

3A.4 Measuring and valuing health outcomes

KEY INFORMATION REQUIRED

- ☐ Describe the clinical health outcomes included in the model
- ☐ Describe how utility weights were identified and applied, if applicable
- ☐ Provide details of the multi-attribute utility instrument, or other patient-reported outcome measures used to inform the model, if applicable
- ☐ Describe any other sources of utility data applied in the model

3A.4.1 Health outcomes

The measure of health outcome should capture positive and negative effects on length of life and/or quality of life. Nominate and justify the patient-relevant health outcome that will be presented as the denominator in the base-case ICER. Explain whether the outcome was reported directly from identified clinical trials (in Section 2), and, if not, summarise the transformations required to derive the outcome for the economic model.

For cost-utility analyses, **quality adjusted life years (QALYs)** should be calculated. A QALY combines both quality of life and life expectancy into a single index. The valuation methods for health-related quality of life should be equal for the proposed intervention and the comparator(s). In calculating QALYs, each of the health states experienced within the time horizon of the model is given a utility reflecting the health-related quality of life associated with that health state. The duration of time spent in each health state is multiplied by the utility. Deriving the utility for a particular health state usually comprises two elements: measuring health-related quality of life in people who are in the relevant health state and valuing it according to preferences for that health state relative to other states (usually perfect health [=1] and death [=0]).

If available, use quality-of-life or utility data reported in clinical studies in Section 2 to estimate QALYs in the model, or justify the use of alternative indirect methods to estimate QALYs when direct data are not available. Data should be presented as the point estimate of the mean elicited utility weight for each health state (including its standard deviation and 95% confidence interval, where available).

If a claim is made for a change in a non-health outcome that is relevant to the patient, or the proposed medicine or CTGTP is expected to have a measurable but indirect impact on the quality of life of caregivers (e.g. family of the patient), do not include these in the base-case evaluation. They can be presented in supplementary analyses and will be considered on a case-by-case basis at the discretion of ACE's committees.

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

Estimates of quality of life or utility from clinical studies (from Section 2) may inform direct estimates of QALY gains in the populations receiving the proposed intervention and the comparator(s), or inform utility values applied to health states in the cost-effectiveness model.

If a MAUI has been used in an included study to estimate utility weights (as described in Subsection 2.4.4), state where and when the scoring algorithm was derived, and consider how applicable it is to the general population in Singapore. Preference weights based on the general population in the UK (which ideally have been previously accepted by NICE) should be used in the scoring algorithm to calculate utility weights, where available. Singapore-based preference weights can be used in sensitivity analyses.

If patient-reported outcome data from a clinical study are incorporated into the economic model, provide a brief description of the following:

- the duration over which the patient-reported outcome measure informing the utilities was administered during the study compared with the duration of the condition under evaluation;
- if the study participants who reported the outcome measure are representative of the target population;
- if the patient-reported outcome measure (or MAUI) captures all important condition-specific factors.

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

Use of other sources of data to estimate utility weights

Where utility weights or QALY changes cannot be directly estimated from data collected in the clinical studies (Section 2), or there are concerns about the reliability and relevance of the available study-based utilities, provide sufficient justification, and consider other published studies to estimate utility weights for health

states in the economic model.

The validity of the derived utility weights depends on the applied elicitation methods and the relevance of the study populations. If utility weights are sourced from the literature, present the search strategies and any inclusion and exclusion criteria used to identify relevant utility studies. Assess the validity of all identified studies, and describe:

- how the health state was captured (e.g. MAUI, scenario-based);
- how the preference was elicited (e.g. standard gamble, time trade-off);
- whether the health state in each study is representative of the health state in the economic evaluation (including the type and severity of symptoms, and the duration of the health state);
- the sample that was chosen to respond to the MAUI questionnaire or scenario (e.g. the general public, patients, carers, health care professionals etc.); and
- how any potential biases were addressed in the studies.

Depending on the clinical context and available data, there may be more than one acceptable source of utility weights. In this instance, reflect the uncertainty in selecting a specific source by using utility weights from other sources in sensitivity analyses.

Mapping of generic and disease-specific scales

Non-preference-based patient-reported outcome measures will require a mapping algorithm to be transformed into preference-based measures to estimate utilities. Where this occurs, the use of the mapping algorithm should be conducted in line with good practice guidelines.[41] Detail the source of the mapping algorithm and describe the estimation sample (population demographic and clinical characteristics, sample size etc.) including its applicability to the target population evaluated in the submission. Provide details of the source and target measures (e.g. index, dimensional), and the statistical properties of the mapping algorithm. Discuss methods used to measure the mapping performance, validity and applicability. Present the resulting predicted utilities with their associated uncertainty.

Scenario-based methods to indirectly elicit utility weights

Scenario-based methods use vignettes to describe the symptoms of a health state to a sample of the general population, to derive utility weights elicited using an accepted preference-based method. The most common methods to elicit preferences include the standard gamble or time trade-off.

Describe the scenario-based methods used, if applicable, and explain efforts to minimise potential bias.[xxv]

Population matching method to indirectly elicit utility weights

Utility weights for the health states in the cost-effectiveness model can be elicited through a population matching study whereby a sample of patients with characteristics similar to those enrolled in the clinical studies (reported in Section 2) are recruited and complete a MAUI reflecting their current health state which can then be used to estimate utility weights. Matched patients should complete all patient-reported outcome measures that were completed by the study participants. Describe the population-matching methods used, if applicable, and efforts to minimise potential bias.[xxvi]

[xxv] There are many sources of analyst bias that are intrinsic to the scenario-based utility approach, including the non-blinded nature of the presentation of the scenarios, the design of the methods to elicit values, and the analysis and interpretation of the results.
[xxvi] Potential sources of bias for population matching studies include systematic differences between the clinical study participants and the matched patients, and the inability to blind the sampled patients from the objectives of the study.

Presentation of outcomes and health utility value information

If presenting a CUA, summarise the health outcomes (including adverse events) included in the economic evaluation, and any associated utilities or disutilities in Table 3A.4.1.

Table 3A.4.1: Identification of health outcomes used in the model

Health state or event	Mean utility (SD and/or 95% CI) or QALY	Nature of estimate and any translations	Source of estimate	Alternative estimates of utility value (and sources)	Average duration of application in the model: proposed medicine or CTGTP	Average application in the model: comparator
[Health state 1]	[Utility estimates for health state 1]	[e.g. EQ5D data (UK value set)]	[e.g. Study ID (see Section 2)]	[e.g. non-pooled data from study]	[e.g. days/months]	[e.g. days/months]

Note: Adapt table as necessary and present in landscape format if more space is required.
CI = confidence interval; QALY = quality-adjusted life year; SD = standard deviation

3A.5 Healthcare resource use and costs

KEY INFORMATION REQUIRED

- ☐ Identify and define the direct healthcare resource items and their associated costs used in the economic model
- ☐ Non-healthcare costs or indirect healthcare costs **should not** be included
- ☐ Cost of proposed medicine or CTGTP used for the base-case analysis should be aligned to the Request for Proposal

All healthcare resources and costs used to inform the model should be clearly presented in a table with details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

3A.5.1 Healthcare resource use

For trial-based economic evaluations, identify the healthcare resource items where a change in use is associated with substituting the proposed medicine or CTGTP for the main comparator in the target population.

For model-based evaluations, identify the resources used within a relevant time period (e.g. a model cycle for a state transition model) for every health state.

Healthcare resource items

Where appropriate, include the following resource items in the economic model:

- medicines or CTGTPs (direct costs of treatment(s), including medicines and blood products used to treat adverse reactions and monitoring costs);
- medical services, including procedures, diagnostic tests and investigative services;
- administration of medicines or CTGTPs (e.g. materials required to deliver an infusion, preparation of medicine in a laboratory etc.);
- medical services, including procedures;

- hospital services (inpatient and outpatient costs);
- services in the primary care setting (such as general practitioner consultations, patient co-payments, aged care services);
- palliative care; and
- any other direct medical costs.

Describe and justify all resources included in the model and specify their source(s). Describe how the usage pattern of healthcare resources has been measured (e.g. reviewing relevant hospital records, administering a questionnaire to each public healthcare institution). Expert opinion from local healthcare professionals should be sought to validate applicability of resource use (provide details of experts consulted in an attachment). Avoid double counting if the services provided have already been billed as a single charge item to the patient.[xxvii]

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

Use of the proposed intervention and comparator treatments should be based on the approved dosing regimens, and/or consistent with the dosing regimens used in local clinical practice (provided there is sufficient evidence of efficacy to substantiate this dosing regimen if it is different from the approved dose). Any dose adjustments over time should be taken into consideration. The amount of a medicine or other resource that is dispensed is the relevant economic measure rather than the amount of resource consumed. It is important to incorporate wastage in the model (e.g. due to inappropriate vial size, non-compliance or if infusions cannot be stored once prepared), because it is an incurred cost. For the avoidance of doubt, vial sharing should not be considered. Resources to monitor patients for adverse events after administration with the proposed medicine or the comparator(s) should also be defined, if relevant. Any treatments or resources required to manage adverse events should be presented and accounted for in the model.

Exclude types of healthcare resources that are unlikely to have a material influence on the conclusion of the economic evaluation, if appropriate. State and justify the exclusion of any resources and explain how their exclusion is likely to affect the incremental cost of the proposed intervention or the comparator(s).

3A.5.2 Allocation of prices (unit costs) to resources

The identification, measurement and valuation of **direct costs** should be consistent with the perspective of the Singapore healthcare system (including all contributions paid for by the government, insurance provider and patient healthcare costs). Non-healthcare costs or indirect healthcare costs **should not** be included.

Present all unit prices and costs in Singapore dollars with a consistent year of analysis (preferably as close as possible to the submission date). International costs should not be used in the economic model due to differences in resource use in Singapore, even after exchange rate adjustments. Obtaining Singapore costs may require approaching a variety of sources including ACE, public healthcare institutions (PHIs), and using commercially available sales data.

[xxvii] For example, if a patient is charged $50 for drug administration on their bill (and nothing else), then the cost of materials for infusion, or chair time should not be separately included in the model as these services are all covered in the single charge item of $50.

Where available, use the costs recommended in the Singapore Healthcare Resource Sheet[xxviii] to ensure that costs associated with medical and other health-related services are measured consistently. If there are valid reasons to use different unit prices, describe their source(s) and present them as a sensitivity analysis, with appropriate justification.

The selling price to patients (including margins, but before subsidy or insurance is applied) should be used for all medicines or CTGTPs. Please specify the cost price of the proposed medicine or CTGTP, and the margin that has been applied to calculate the selling price. The cost price should include any price reduction offered in the Request for Proposal[xxix] or other arrangements (contingent on a positive funding recommendation).

Costs that are the same for the proposed intervention and the comparator(s) can be validly excluded if there are no significant differences in mortality rates or time periods between treatments.

If multiple cost estimates are identified for specific resources, justify the estimate used in the base case and present alternative plausible estimates in sensitivity analyses. Use of historical estimates of costs is discouraged. However, if they are required, detail the information sources and the methods used to estimate them. Justify the use of the historical cost source as the best estimate available. Use the most relevant Singapore price index (e.g. MOH healthcare consumer price indexes[xxx]) to adjust for inflation to estimate current prices. Value future costs at current prices (i.e. do not allow for future inflation in the calculations).

Clearly present all steps taken to calculate costs in the economic evaluation so the calculations can be independently replicated and verified (it may be necessary to include an unlocked spreadsheet with detailed calculations as an attachment).

Present all healthcare resource items and their associated unit costs relevant to the economic evaluation in Table 3A.5.2 (adapt as necessary). Costs associated with the entire episode of care (i.e. all costs directly relating to the diagnosis and resulting treatment or follow-up) should be included.

Table 3A.5.2: Health care resource items, unit costs and usage included in the economic evaluation

Resource item category	Type of resource item	Unit of measurement	Unit cost (SGD)	Source of unit cost	Usage for proposed medicine or CTGTP	Usage for comparator
Medicines	Proposed medicine	Quantity dispensed	[add]	Proposed selling price	[add usage]	[add usage]
	Comparator	Quantity dispensed	[add]	Average selling price in PHIs	[add usage]	[add usage]
Medical services	E.g. clinician consultation	Service rendered	[add]	Average cost from PHIs	[add usage]	[add usage]
Hospitalisation	Hospital admission	Episode	[add]	Average cost from PHIs	[add usage]	[add usage]
[add rows as necessary]						

PHI = public healthcare institutions; SGD = Singapore dollar

[xxviii] https://go.gov.sg/sg-resourcesheet

[xxix] https://go.gov.sg/company-RFP-template

[xxx] www.moh.gov.sg/resources-statistics/singapore-health-facts/consumer-price-indices-(cpi)-household-healthcare-expenditure

3A.6 Summary of base-case model inputs and assumptions

Tabulate all variables included in the base-case analysis, detailing the values used, range (e.g. confidence interval, standard error or distribution) and sources in Table 3A.6a. Provide a list of all assumptions used in the model in Table 3A.6b.

Table 3A.6a: Summary of variables applied in the economic model

Variable	Value	Range	Source
[Age]	[Mean 56 years (SD 6.8)]	[42 to 77 years]	[Patient registry]
[Overall survival]	[Median 4 months]	[95% CI: 0.2 to 21 months]	[Study ID]
[Add more rows as needed]			

Note: inputs are examples only. Adapt the table as required to capture all relevant variables. CI = confidence interval

Table 3A.6b: List of assumptions used in the economic model

Area	Assumption	Justification
[Time horizon]	[10 years]	[The average age of patients with metastatic cancer in the model is 65 years. An average of 10 more years of life expectancy has been assumed.]
[HRQoL]	[The quality of life of patients is appropriately captured by considering time to death utilities]	[Clinical opinion suggests there is a decline in HRQoL in the final months of life of patients which supports the use of a disutility associated to the terminal stage. Given the limitations of the progression-based approach to reflect appropriate utilities post-progression, a time to death approach was considered in the base case. The impact of considering an alternative approach (i.e. progression-based only) was considered in sensitivity analyses.]
[Add more rows as needed]		

Note: inputs are examples only. Adapt the table as required to capture all relevant assumptions.

3A.7 Model validation

KEY INFORMATION REQUIRED

- ☐ Provide model traces and demonstrate the face validity of the economic model
- ☐ Compare modelled outcomes with outcomes from similar published models (if available) and describe any consistencies and differences

Validation of an economic model to confirm that the computed results depict what they are intended to represent will help to reduce some of the uncertainty associated with modelling, and give decision-makers more confidence in the model predictions. The Assessment of the Validation Status of Health-Economic Decision Models (AdViSHE) Study Group describe a range of validation processes which should be considered in the submission.[42]

Compare the base-case outcomes from the model with the corresponding trial outcomes in Table 3A.7 and discuss any differences.

Table 3A.7: Comparison of model and trial outcomes

Outcome	Proposed medicine or CTGTP		Comparator	
	Base Case	[Study ID]	Base Case	[Study ID]
[Median PFS (months)]	2.2	2.1	3.4	3.2
[Median OS (months)]	10.3	10.3	7.1	6.9
[1-year OS]	45.1%	43.9%	29.8%	30.4%

[2-year OS]	30.2%	-	16.4%	-
[5-year OS]	16.7%	-	7.8%	-
[Add rows as needed]				

Note: inputs are examples only. Adapt the table as required to capture all relevant outcomes. The outcomes should be consistent with those defined in the evaluation framework in Subsection 1.1.2.
PFS = progression-free survival; OS = overall survival

Model traces for the proposed intervention and its comparator(s) provide a clear depiction of the implications of the model and can inform the face validity of the model logic. Use traces to track patients through the model and demonstrate that the logic of the model is correct. Present traces representing the proportions of the cohorts in each health state over time, and the cumulative sum of the undiscounted costs and outcomes (e.g. QALYs) over time. If applicable, state the number of events over time where patient-relevant events occur within a health state.

Compare model traces with corresponding empirical data (e.g. clinical trials), where possible, to identify whether outcomes are consistent. Explain any differences indicated by these comparisons.

Additional cross-validation of the modelled outcomes should be undertaken, where possible, by comparing results with outcomes from similar economic models to identify consistencies or differences.

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

KEY INFORMATION REQUIRED

- ☐ Present the base-case estimate of the incremental outcome(s), incremental cost and ICER(s)
- ☐ Calculate the cost per patient per course of treatment (for acute conditions) or per year (for chronic conditions) with the proposed medicine or CTGTP and the comparator(s)
- ☐ Present disaggregated costs and outcomes for the proposed medicine or CTGTP and the comparator(s)

3A.8.1 Base-case results

Present the base-case estimate of the incremental outcome(s), incremental cost and the cost-effectiveness ratio(s) from the economic evaluation in Table 3A.8.1. If a price reduction or PAP, contingent on funding of the proposed medicine or CTGTP, has been included in the Request for Proposal, this should be reflected in the base-case analysis.

Table 3A.8.1: Base-case results (discounted)

Medicine or CTGTP	Total Costs (SGD)	Total LYG	Total QALYs	Incremental costs (SGD)	Incremental LYG	Incremental QALYs	ICER (SGD/QALY)
Comparator	20,000	1.62	1.09	-	-	-	
Proposed medicine or CTGTP	60,000	2.81	1.96	40,000	1.19	0.87	45,977

ICER = incremental cost-effectiveness ratio; LYG = life years gained; SGD = Singapore dollar; QALY = quality-adjusted life years
Note: Comparator should reflect standard of care in line with the evaluation framework in Subsection 1.1.2. Inputs are an example only. Present incremental ICERs and indicate "dominated" or "extendedly dominated" where applicable. If more than one comparator is being considered, present ICERs compared with the next cheapest, non-dominated treatment option. Adapt table as necessary.

Cost of proposed intervention or comparator treatment per patient

For acute conditions, present the expected costs of the proposed intervention and comparator(s) separately per patient per course of treatment. For long-term, chronic conditions, present the cost of each treatment per patient per year.

3A.8.2 Disaggregated and aggregated base-case results

If a decision-tree model is used, present disaggregated costs incurred at each branch by resource type for the proposed intervention and comparator groups. For state transition models, present disaggregated discounted costs by resource type for each health state for the proposed intervention and comparator groups. In all models, report the proportions of patients predicted to experience alternative target clinical outcomes in the proposed intervention and comparator groups.

Identify which health states and resources contribute the greatest incremental differences between the proposed intervention and the comparator(s). Examples of tables to present disaggregated results are shown below (Tables 3A.8.2a – 3A.8.2c).

Table 3A.8.2a: Health care resource items - disaggregated summary of cost impacts in the economic evaluation by category of resource item

Type of resource item	Subtype of resource item	Costs for proposed medicine or CTGTP (SGD)	Costs for comparator (SGD)	Incremental cost (SGD)	% of total incremental cost
Medicines or CTGTPs	Treatment cost for proposed medicine				
	Administration				
	Monitoring				
	[add as needed]				
	Total				
	Treatment cost for comparator				
	Administration				
	Monitoring				
	[add as needed]				
	Total				
Medical services	GP consultation				
	Genetic test				
	[add as needed]				
	Total				
Hospital services	Hospital admission				
	[add as needed]				
	Total				
Palliative care	[add as needed]				
	Total				

SGD = Singapore dollars; Note: Indicate clearly whether cost values are discounted costs (use of discounted costs is appropriate). Inputs in the table are an example only. Adapt the table as required.

Table 3A.8.2b: List of health states and disaggregated summary of cost impacts included in the model

Health state in model	Resource use by health state (modelled)	Proposed medicine or CTGTP costs (SGD)	Comparator costs (SGD)	Incremental cost (SGD)	Total incremental cost (%)
[Health state 1]	Resource type 1				
	Resource type 2				
	[etc]				
	Total for health state 1				

[Health state 2]	Resource type 1				
	Resource type 2				
	Total for health state 2				
[add rows as needed]					
Total					**100%**

SGD = Singapore dollars

Table 3A.8.2c: List of health states and disaggregated summary of health outcomes included in the economic evaluation

Health state in model	Outcome for proposed medicine or CTGTP	Outcome for main comparator	Incremental outcome	Total incremental outcome (%)
[Health state 1]				
[Health state 2]				
[add rows as needed]				
Total				**100%**

Define the outcome in the first row of the table. Adapt the table as required.

3A.9 Sensitivity analysis

KEY INFORMATION REQUIRED

- ☐ Explain the methods used to represent the uncertainty around the model's input parameters, translations and structure
- ☐ Define the uncertain parameters and variables, and their alternatives, that are tested in sensitivity or scenario analyses
- ☐ Present and discuss the one-way sensitivity analysis conducted
- ☐ Present and discuss any relevant scenario analyses conducted
- ☐ Present and discuss any multivariate analyses and/or probabilistic sensitivity analysis conducted

All economic evaluations involve a degree of uncertainty. It is important that all types of uncertainty are appropriately described, including uncertainty about the source of parameters used in the economic evaluation, the precision of the parameters, and whether the model accurately simulates the cost and effects of the proposed intervention and the comparator(s). Companies are encouraged to refer to the report by *ISPOR-SMDM Modeling Good Research Practices Task Force Working Group 6*[29] which provides comprehensive recommendations on characterising and reporting uncertainty in economic models.

3A.9.1 Defining uncertainty in the model

The types of uncertainty which can affect the results from the economic model are typically divided into two broad areas:

- Structural uncertainty – which includes structural and methodological uncertainty relating to the model; and
- Parameter uncertainty – which includes data uncertainty due to variability in data and/or data sources, and the generalisability of the study results to other populations and/or other contexts.

Structural uncertainty

Models are subject to uncertainty around the structural assumptions used in the evaluation (e.g. how different health states are categorised, or how different treatment pathways are represented). Uncertainty relating to the structural assumptions used in the economic evaluation should be clearly documented. The impact of the structural uncertainty on the cost-effectiveness estimates should be explored by separate analyses of a representative range of plausible scenarios.

Include an analysis of the impact of variation in the time horizon chosen.

If multiple plausible model structures are defined, assess the potential impact of the alternative structures on the model outputs through scenario analyses. If a substantial impact is predicted, use a formal approach to characterise the structural uncertainty. Report the results of each set of plausible structural assumptions.

Conduct other scenario analyses to assess the effects of substantial use of the proposed medicine or CTGTP beyond the intended population. This wider population is expected to have demographic and patient characteristics and circumstances that differ from the target population which may impact the cost effectiveness of the proposed medicine or CTGTP.

Parameter uncertainty

Uncertainty can arise from the choice of data sources to provide values for key parameters in the model, such as different costs and utilities, estimates of relative effectiveness, and the duration of treatment effects. Use commonly adopted statistical standards to represent the uncertainty around the true value of each uncertain input parameter (e.g. beta distributions for transition probabilities; log-normal for relative risks or hazard ratios; logistic distributions to calculate odds ratios; and gamma or log-normal for costs and utility parameters). Justify using alternative distributions.

Use interval estimates (e.g. 95% CIs) derived from fitted probability distributions to define the ranges of the parameter values tested in the deterministic sensitivity analyses. Where there is very little information on a parameter, adopt a conservative approach by defining a broad range of possible parameter values.

Consider correlations between input parameters. If applicable, represent the joint uncertainty of two or more input parameters in sensitivity analyses. It is preferable to characterise the joint uncertainty around transition probabilities in the proposed intervention and comparator groups through the application of a relative treatment effect parameter.

The estimation of multiple input parameters when using regression analysis produces relevant correlation parameters. For example, regression involving time to event data, correlation between the parameters describing a particular survival function is captured in the Cholesky matrix, which is used in probabilistic sensitivity analysis.

3A.9.2 Handling uncertainty – one-way sensitivity analyses and scenario analyses

Univariate deterministic sensitivity analysis (also known as one-way sensitivity analysis [OWSA]) and/or scenario analyses should be conducted for all economic evaluations, to help determine the importance of the different assumptions and modelling parameters on the results in line with good practice guidelines.[29] Tabulate all parameter values and assumptions tested in OWSA or scenario analyses in Table 3A.9.2 and 3A.9.3 respectively. Ensure that the values tested are clinically plausible and not extreme (e.g. do not present

analyses assuming no treatment effect for the comparator(s).

Create a tornado diagram to provide a visual interpretation of the relative effect of the variability of each parameter on the incremental cost-effectiveness result. Identify the input parameters and model assumptions which are key drivers of the economic model.

At a minimum, OWSA should be presented for each uncertain parameter in the economic evaluation. Multivariate and probabilistic sensitivity analysis may also be performed to address simultaneous impact of all uncertain parameters (Subsection 3A.9.3).

Discuss the implications of the OWSA (and scenario analyses if applicable) with respect to the certainty of the base-case ICER estimate. Discuss the likely overall effect of deficiencies in the evidence base on the reported cost-effectiveness of the proposed intervention.

Table 3A.9.2: Results of OWSA characterising the uncertainty around the ICER

Variable or assumption	Base-case value (LL, UL)	Incremental outcomes		Incremental costs		ICER		Description of impact on ICER
		LL	UL	LL	UL	LL	UL	
Base case								
Discounting rate (outcomes and cost)	3% (0%, 5%)	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[describe as required]
Plausible range of treatment effect, if modelled as a variable (e.g. hazard ratio or relative risk)	[add] [e.g. upper and lower 95% confidence intervals around estimate]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[describe as required]
Altered patient characteristics, if relevant	[add] [e.g. upper and lower age range]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[describe as required]
Transition or event probabilities	[add] [e.g. upper and lower 95% confidence intervals around estimate]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[describe as required]
Cost-related assumptions or variables	[add] [e.g. upper and lower 95% confidence intervals around estimate]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[describe as required]
Time horizon	[add] [e.g. trial based; 5, 10,	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[describe as required]

	20 years]							
[add rows as necessary]								

ICER = incremental cost-effectiveness ratio; LL = lower limit; UL = upper limit

Table 3A.9.3: Results of scenario analyses characterising the uncertainty around the ICER

Variable or assumption	Base-case value	Plausible alternative	Incremental outcomes	Incremental costs	ICER	Description of impact on ICER
Base case						
Altered patient characteristics, if relevant	[add]	[e.g. different condition severity]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[describe as required]
Outcome-related assumptions or variables (e.g. alternative methods or sources of utility weights)	[add]	[add]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[describe as required]
Alternative extrapolation variables or assumptions (e.g. assumption regarding ongoing treatment effect)	[e.g. maximum follow-up]	[e.g. median follow-up]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[describe as required]
Any other translation assumptions	[add]	[add]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[describe as required]
Alternative assumptions regarding model structure	[add]	[add]	[alternative estimates]	[alternative estimates]	[alternative estimates]	[describe as required]
[add rows as necessary]						

ICER = incremental cost-effectiveness ratio

3A.9.3 Multivariate and probabilistic sensitivity analyses

Where applicable, describe any multivariate sensitivity analyses undertaken to test the combined effects of the uncertainty around the true values of input parameters to which the base-case incremental cost-effectiveness result was shown to be sensitive in the OWSA. Clearly present all results and justify the inclusion and exclusion of parameters in these analyses.

A probabilistic sensitivity analysis (PSA) should be presented in addition to deterministic sensitivity analyses to characterise parameter uncertainty.[xxxi]

The distributions used in the PSA should be justified and should reflect the available evidence on the parameter of interest.

[xxxi] PSA cannot address translational or structural uncertainty. It can only address uncertainty surrounding the parameters.

If undertaking a PSA on a cohort-based state transition model, the number of iterations (sets of randomly sampled input parameter values included in the analysis) should be enough to provide stability in the model outputs across multiple analyses using alternative random number seeds. This should be clearly demonstrated. Provide the random seed associated with the presented results to enable replication and also ensure that the model permits alternative seeds.

If undertaking a PSA on an individual-level model (e.g. a discrete event simulation), the number of iterations may be selected to balance stability of model outputs and a reasonable time required to undertake a PSA. Present the results of the PSA using cost-effectiveness planes and acceptability curves, and tabulate the interval estimates for the ICER or the incremental net benefits of the proposed medicine or CTGTP. Describe and explain any variation between the incremental cost-effectiveness analysis results estimated in the base-case analysis and the PSA, if applicable.

3A.10 Summary of economic evaluation

Provide a brief summary of the results and conclusion of the economic evaluation.

Section 3B Cost minimisation

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

For a cost-minimisation approach to be accepted, the therapeutic claim of non-inferiority should be adequately supported by the available evidence, and use of the proposed medicine or CTGTP should be expected to result in equivalent or lower costs to the healthcare system compared to the main comparator(s).

Complete Table 3B.1 to summarise the key assumptions and components of the cost-minimisation approach presented in the submission.

Table 3B.1: Key assumptions and components of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, effectiveness is assumed to be [non-inferior/superior]
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is assumed to be [non-inferior/superior]
Evidence base	[direct randomised trials/indirect comparison of randomised trials]
Equi-effective doses, if applicable	Proposed medicine or CTGTP [describe dose/administration/day/course] and comparator [describe dose/administration/day/course]
Direct medicine or CTGTP costs	[Cost of proposed medicine or CTGTP] vs [cost of comparator] (costs are per patient per course for an acute or self-limited therapy, or per patient per year for a chronic or continuing therapy)
Other costs or cost offsets	[Yes/No] [if yes; brief description – e.g. adverse effect–related costs, monitoring costs, administration costs]

3B.2 Other costs and cost offsets

KEY INFORMATION REQUIRED

- ☐ Identify any additional costs or cost offsets that are accounted for in the analysis. This could include cost offsets due to differences in the administration profiles and safety management profiles of the proposed medicine or CTGTP and comparator(s)

The nature of additional costs and cost offsets will vary across submissions. Common additional costs include those associated with treatment administration and managing adverse events; however, other cost offsets may also be relevant. Any other additional costs and cost offsets should be justified in terms of their realisability and relevance to patients, and clearly differentiated between the proposed intervention and the comparator(s) in the cost-minimisation analysis.

3B.2.1 Comparison of administration profiles

Identify differences in the costs of prescribing or administering the proposed intervention and the comparator(s).

The availability of different dosage forms (e.g. tablets, injections, infusions) for the proposed intervention and its main comparator may have cost consequences. In this case, identify the types of other health care resources affected, estimate the extent to which the quantity of each type of resource provided would change (in its natural units of measurement) if the proposed medicine or CTGTP is funded, and multiply by

the appropriate unit costs.

3B.2.2 Comparison of safety and toxicity management profiles

Only use the cost-minimisation approach where the proposed medicine or CTGTP has a safety profile that is superior or non-inferior to the main comparator. Identify any differences in the costs of monitoring or managing adverse events associated with the medicine or CTGTP.

If the proposed medicine or CTGTP is demonstrated to be no worse in terms of effectiveness, but has a superior safety profile to the main comparator, a higher price for the proposed medicine or CTGTP over its main comparator could be proposed on the basis of cost offsets because of reduced costs of monitoring and managing adverse reactions. Provide supporting evidence (e.g. from clinical trials or the HSA product insert) to substantiate a claim that monitoring costs are reduced.

Where safety profiles are similar, but the proposed medicine or CTGTP has a lower magnitude of adverse effects (either in terms of severity or incidence), quantify the safety profile differences between the health technologies, and estimate any corresponding resource-use implications.

Where the adverse effect profiles of a proposed medicine or CTGTP and its main comparator are materially different that are expected to result in differences in health outcomes, a cost-effectiveness or cost-utility analysis is preferred (Section 3A).

3B.3 Estimation of equi-effective doses

KEY INFORMATION REQUIRED

☐ Calculate equi-effective doses for the proposed intervention and the comparator(s)

When estimating equi-effective doses, the following sources of evidence should be considered (presented in order of preference):

- direct randomised trials where doses of the proposed medicine and the comparator(s) are titrated against a response, or where doses of both medicines are fixed if the medicines are administered in routine local clinical practice according to the fixed protocol used in the trials; or
- direct randomised trials where doses of either or both the proposed medicine and comparator(s) are fixed in a way that does not reflect routine local clinical practice. In this instance, present dose-response data for the two medicines to indicate whether the fixed doses are derived from a similar point on the respective dose-response curves, and to confirm that the selected doses do not represent suboptimal doses or doses on the plateau of the dose-response curve. Fixing the dose of just one medicine introduces an unbalanced approach; or
- indirect comparisons of two or more sets of randomised trials involving one or more common references; or
- non-randomised studies.

Indicate whether the doses and methods of titration are consistent with those approved by HSA for the proposed intervention and comparator(s). For medicines administered in line with fixed protocols, compare the total doses required over the entire duration of therapy.

For medicines that require dose titration calculate equi-effective doses at steady state (i.e. the average dose after dose titrations are complete and after excluding participants who discontinue the medicine). Assess the impact of extrapolating dose titration if there is evidence that the trial was of inadequate duration for the doses to have reached steady state.

If there is more than one trial or study, calculate the weighted average dose using the number of participants still on the medicine at steady state as the weighting factor. If the study's primary data is unavailable, the average doses might have to be weighted by the number of participants enrolled (as per published report) rather than the number of participants at steady state. Justify the exclusion of any studies not incorporated into the equi-effective dosing calculations.

If overseas HTA agencies (e.g. PBAC or NICE) have previously agreed on equi-effective doses for the proposed medicine and comparator, provide details in the submission.

3B.4 Results

List all identified costs associated with both the proposed intervention and the comparator, then aggregate these with the selling price of each medicine or CTGTP (for medicines, based on the equi-effective doses) to estimate the net cost difference.

The economic claim should be that, at the price requested, the overall cost of therapy with the proposed medicine or CTGTP is the same as, or less than, the overall cost of therapy with the main comparator.

Provide copies of the original sources of all data (beyond those already presented in Section 2), and expert opinion used to inform the cost-minimisation approach. To enable independent verification of each analysis, provide an electronic copy (e.g. in Excel) of any computer-based calculations of the analysis.

Section 4 Utilisation and financial impact

Introduction

In Section 4, present the expected utilisation of the proposed medicine or CTGTP in local clinical practice if it is recommended for funding, and the associated financial impact, in line with the parameters described in Table 4.

Table 4: Parameters considered when estimating utilisation and financial impact of proposed medicine or CTGTP

Parameter	Base-case analysis
Target population	▪ Consistent with the patient population (and any relevant subgroups) defined in the evaluation framework ▪ Potential population size should be specified, and the estimation method described and justified. Attention should be paid to the evolution of the size of the target population over time with and without funding of the medicine or CTGTP. ▪ Singapore resident population (citizens + permanent residents) should be used in the calculations ▪ Diagnosis rates in line with local clinical practice should also be taken into account when calculating the proportion of patients who are likely to receive treatment
Comparator(s)	▪ Consistent with the comparator(s) defined in the evaluation framework
Health outcomes	▪ No health outcomes are presented in the analysis
Costs	▪ Only the cost of the proposed medicine or CTGTP should be included (i.e. excluding margins) ▪ If a price reduction, PAP or risk-sharing agreement has been included in the pricing proposal for the proposed medicine or CTGTP (contingent on a positive funding recommendation), the net cost price after the price reduction, PAP or other arrangements are applied should be used in the base case ▪ Constant costs, that are not subject to inflation, should be used
Time horizon	▪ Analyses should be conducted over a six-year period (to represent year of DAC meeting, then five years post-funding decision)
Discount rate	▪ No discount rate should be applied

Epidemiological and market-share analyses are the two broad approaches for estimating utilisation, although their use is not mutually exclusive. An epidemiological approach is typically preferred for generating estimates if the submission indicates a superior therapeutic conclusion. However, a market-share approach might be preferred if the submission indicates a non-inferior therapeutic conclusion.

Epidemiological approach

An epidemiological approach estimates the number of people with the health condition in Singapore, and then estimates the use of the proposed medicine or CTGTP and the comparator(s) by the eligible resident patient population (and subgroups where relevant) defined in the evaluation framework.

Market-share approach

The market-share approach estimates the extent of the current market represented by the proposed target population (or subgroup) and, consequently, the share likely to be taken by the proposed medicine or CTGTP if it is recommended for funding.

Chosen analysis

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

Ensure that any estimates of the extent of use of the proposed intervention and the comparator(s) are consistent with evidence presented in the submission. Ensure that uptake of the proposed intervention and any change in the use of the comparator(s) are consistent with their expected use in local clinical practice (defined in Subsection 1.2.1) and the circumstances presented in the economic evaluation (Section 3). Explain and justify any discrepancies.

Provide sufficient information in Section 4 of the submission so the analyses can be clearly interpreted and replicated if necessary. Describe the approach, methods, and potential biases. All calculations, assumptions and data sources should be clearly described within the submission and/or the costing template. Where multiple sources of data are available for an individual variable, present sensitivity analyses for the different estimates across the sources.

Describe how the data are relevant to the present Singapore context. Where data from overseas are used in the absence of local estimates, discuss the applicability of these data to the Singapore setting.

A commissioned study may be required to fill a gap in the data (e.g. conducting a medicine or CTGTP utilisation survey, or extracting registry data). When reporting the results of a commissioned study, provide sufficient background and methodological information to facilitate interpretation of the results. Where a survey of healthcare professionals is conducted, provide their details and public healthcare institution for verification, and indicate the number of patients they treat annually with the condition under evaluation.

When analysing administrative data and registries, provide sufficient information about the method used to sample the dataset, the proportion of the target population included in the dataset, and any assumptions made during the analysis.

Costing template

A standardised Excel template (Costing template[xxxii]) which should be completed with each submission (using the epidemiological and/or market share approach) is available from the ACE website.[xxxiii] Additional spreadsheets can be created to present sensitivity or scenario analyses or provide additional data to support assumptions, where required.[xxxiv]

Ensure that the calculations flow through the spreadsheets, so that changes to any variable in the base case flow on to the results. Apply clear labels to spreadsheet values (where required), and provide the data sources. To facilitate independent assessment of the data, attach copies of the data used.

[xxxii] https://go.gov.sg/company-costingtemplate

[xxxiii] www.ace-hta.gov.sg

[xxxiv] Additional spreadsheets should be stand-alone worksheets and should not be linked backed to any existing worksheets that inform the base-case calculations. Results for sensitivity or scenario analyses should be manually computed and all calculations should be reproducible (unlocked).

4.1 Utilisation and financial impact of the proposed medicine or CTGTP

KEY INFORMATION REQUIRED

- ☐ For an **epidemiological approach**, complete the relevant spreadsheets of the Costing template to estimate the number of:
  - patients with the condition under evaluation in Singapore;
  - patients who are likely to be eligible for the proposed medicine or CTGTP; and
  - units of the proposed medicine or CTGTP that would be required for the target population
- ☐ For a **market share** approach, complete the relevant spreadsheets of the Costing template to estimate:
  - the number of units of the comparator(s) currently dispensed for the condition under evaluation, and the number of patients this represents;
  - the proportion of patients who are likely to switch from the comparator(s) to the proposed medicine or CTGTP if it is recommended for funding (where applicable); and
  - the market growth rate if the proposed medicine or CTGTP is recommended for funding
- ☐ Estimate the cost of each form and strength of the proposed medicine or CTGTP over a 6-year period (to represent year of DAC meeting, then five years post-funding decision)
- ☐ Discuss any uncertainties surrounding the utilisation and cost estimates
- ☐ Describe any proposed risk-sharing agreements (RSA) contingent on a positive funding recommendation for the proposed medicine or CTGTP

4.1.1 Epidemiological approach

Incidence or prevalence data

For an epidemiological approach, describe the methods and assumptions for converting incidence or prevalence data to the number of patients likely to be receiving the proposed medicine or CTGTP each year in Singapore.

The choice to use incidence or prevalence data depends on several factors, including the nature of the health condition, its treatment and the available data. Usually, incidence estimates are most suitable for treatments of short duration while prevalence estimates may be more appropriate for long-term treatments (e.g. for chronic conditions). A combination of prevalence and incidence estimates (denoted as "Mixed" in the costing template) may be required (e.g. to capture intermittent treatments for a chronic condition).

Consider the current prevalent patient population in addition to the incident population – for example, if patients are receiving best supportive care before the proposed medicine or CTGTP becomes available (as there are no alternate treatments available), only calculating the incident population would underestimate the likely number of patients treated in the early years once funding is available.

The choice of disease epidemiological data sources should be relevant to Singapore residents, wherever possible. These sources may include the National Registry of Diseases Office[xxxv], National Population Health

[xxxv] https://www.nrdo.gov.sg/

Surveys[xxxvi], and local epidemiological studies. All assumptions and justifications for the use of epidemiological data should be clearly detailed in the submission.

Estimate the total number of patients with the condition in Singapore

Estimate the likely number of patients over a 6-year period, using the incidence or prevalence approach. If using an incidence approach, also estimate the prevalent population (from years before DAC meeting) that may add to the patient pool treated with the proposed medicine or CTGTP in Year 1. Justify when the addition of a prevalent population is not required.

Estimate the number of patients eligible for the proposed medicine or CTGTP

Estimate the proportions of patients with the condition under evaluation each year who are expected to be eligible for the proposed medicine or CTGTP. Treatment eligibility should be considered in line with the local clinical treatment algorithm and any proposed clinical criteria to determine appropriate use, described in Subsection 1.2.1.

Estimate the number of patients in the target population likely to receive the proposed medicine or CTGTP

Using the annual numbers of eligible patients, estimate the proportions likely to receive the proposed medicine or CTGTP each year. Ensure that the estimates reflect the predicted rate of diagnosis of the condition, the predicted uptake of the proposed medicine or CTGTP, and include the impact of the use of other treatments (comparators most likely to be replaced by the proposed medicine or CTGTP). Justify the diagnosis and uptake rates assumed, and assess variations to these estimates, if necessary, in a sensitivity analysis.

The total number of eligible patients should reflect all patients in the target population, irrespective of whether they are treated in the public or private sector. Indicate in the costing template (under "Reference/Sources/Assumptions" column, but do not adjust the calculations) and in the submission the estimated market share split between the public and private sector in Singapore and justify the estimate assumed.[xxxvii]

Present a table(s) in the submission which summarises the assumptions and patients estimated in the costing template using the epidemiological approach.

4.1.2 Market-share approach

To generate estimates of expected utilisation using the market-share approach, use utilisation data or studies for currently available alternate treatments (comparators) that are most likely to be replaced by the proposed medicine or CTGTP (or that are currently used for the target population if the proposed medicine or CTGTP is an add-on therapy to existing standard of care). This is the basis for predicting whether the market will change when the proposed medicine or CTGTP is funded.

Utilisation of comparator(s)

Estimate the utilisation of the comparator(s) during the most recent 12 months. For medicines, ensure that the estimates reflect the quantities of the dispensed medicine, rather than the quantities consumed, which

[xxxvi] https://www.hpb.gov.sg/community/national-population-health-survey/

[xxxvii] This estimate will be verified by ACE and used to inform internal calculations to estimate the financial impact of funding on the Government budget, if applicable.

may be affected by compliance, dose reductions, discontinuations and wastage.

Estimate the proportion of total units that would have been used by the target population in the public sector with the condition under evaluation. Vial sharing should not be included.

Estimate the market growth (for the current market) over six years in the absence of funding for the proposed medicine or CTGTP based on historical trends or other influences.

If patients are expected to switch from more than one comparator to the proposed medicine or CTGTP, present the market share and rate of growth for each comparator. Disaggregating the estimated growth according to each comparator is important if they are likely to have different rates of growth, or are likely to be replaced by the proposed medicine or CTGTP at different rates. Where all comparators are from the same therapeutic class and the proposed medicine or CTGTP is being considered on a cost-minimisation basis, disaggregation of the estimated growth for each comparator is less important.

Estimate the market share for the proposed medicine or CTGTP

Estimate the rate of switching from the comparator(s) to the proposed medicine or CTGTP where applicable. If the proposed medicine or CTGTP is used as an add-on therapy to standard of care, switching rates do not need to be calculated. Justify the rate assumed (e.g. provide market uptake rates from other countries where the proposed medicine or CTGTP is already used and discuss the applicability of these rates to the Singapore setting).

Present a table in the submission which summarises the assumptions and uptake/switching rates used to estimate market share in the costing template.

Estimate the growth of the market if the proposed medicine or CTGTP is funded

Report the expected increase in patient numbers anticipated once the proposed medicine or CTGTP is funded. Growth may be influenced by multiple factors, and assumptions of linear growth may not be appropriate, particularly where the proposed medicine or CTGTP is not the first therapy approved for use for the target population. Justify where no additional growth in the market is predicted. Where the proposed medicine or CTGTP may be used for patients who are intolerant of, contraindicated for, or have not adequately responded to an existing (comparator) therapy, its availability is likely to increase the overall number of patients treated.

Provide references to justify all assumptions relating to the data inputs, and discuss any risks associated with market growth in the submission, to increase the certainty of the financial implications of funding the proposed medicine or CTGTP.

4.1.3 Cost impact of proposed medicine or CTGTP

Only the cost of the proposed medicine or CTGTP (excluding margins/markups) should be included in the costing template. If a price reduction has been proposed in the Request for Proposal for the proposed medicine or CTGTP (contingent on a positive funding recommendation), the net cost price (after the price reduction is applied) should be used. The cost consequences of comparator(s), treatment effect, adverse events and any other short-term or long-term consequences do not need to be included. If warranted, either time-on-treatment, time-to-discontinuation or time-to-progression curves from relevant pivotal RCTs may be used to account for treatment discontinuations to provide a robust estimation of mean treatment duration.

4.1.4 Uncertainty surrounding utilisation and cost estimates

There are a number of factors that may influence the predicted utilisation patterns and financial implications associated with funding the proposed medicine or CTGTP for the target population. These include, but are not limited to:

- The duration of therapy might be longer than expected from the randomised trials, particularly if trials are truncated;
- Patients could be treated more or less often than expected, particularly in the case of health conditions with episodic manifestations;
- Epidemiological incidence or prevalence or market-share trends may have been inaccurately forecast;
- Outcomes of ongoing or related research might have a positive or negative effect on uptake of the proposed medicine or CTGTP over the forecasted period;
- More prescribers and patients might seek treatment if the proposed medicine or CTGTP treats a health condition for which the alternatives are considered substantially inferior to the proposed medicine or CTGTP (e.g. in terms of effectiveness, tolerability, patient acceptability, convenience);
- Prescribers could find it difficult to determine whether patients are eligible for the proposed medicine or CTGTP (e.g. a difficult differential diagnosis, or poor precision or accuracy in a diagnostic test etc.) leading to lower or higher rates of use;
- The target population represents a subset of patient types eligible for the randomised trial(s) for the proposed medicine or CTGTP, or there is evidence in other health conditions, that may lead to use outside of the intended target population; and
- There is limited access to designated types of health care practitioners which might limit uptake and utilisation.

Describe any of these factors that are expected to have an impact on the patient numbers and costs estimated in the costing template. It might not be necessary to address any or all of these factors if their impact is expected to be small. For any factors described, discuss and quantify (if possible) the direction (underestimate or overestimate) and magnitude of the impact on the estimate(s). Indicate any instances where the effects of some uncertainties are difficult to quantify.

Uncertainty can be reduced by using data from multiple sources, if available, or by using epidemiological and market-share approaches to derive estimates.[xxxviii] Where estimates derived from different sources or by using different methodological approaches are concordant, this may give decision-makers more confidence in the resulting estimates. Sensitivity analyses using multiple sources or methods to explore any uncertainties should be described in the submission.

Current or future activities to reduce existing uncertainties should also be described including:

- proposed educational activities for healthcare professionals that are expected to help identify patients eligible for treatment and ensure that the proposed medicine or CTGTP is used appropriately (e.g. to avoid leakage outside target population); or
- any monitoring efforts or patient/treatment registries that are being set up to ensure that the proposed medicine or CTGTP is being used appropriately.

The role of any proposed risk-sharing agreement (RSA) in managing these existing uncertainties should also

[xxxviii] This is sometimes referred to as 'triangulation' (the use of multiple sources of data or multiple approaches to determine the consistency or otherwise of the conclusions from those sources or approaches).

be discussed. When discussing the proposed activities, state when they will be implemented, and whether such activities will be available to all prescribers (or other healthcare professionals, where applicable), public healthcare institutions and patients. If restrictions are proposed (e.g. limited to specific patients or public healthcare institutions), please provide sufficient details.

4.1.5 Risk-Sharing Agreement

Risk-sharing agreements (RSAs) are instruments used to address uncertainties surrounding proposed medicines or CTGTPs that are likely to affect the DAC's decision. Broadly, RSAs may be financial- or performance-based. Financial-based RSAs mainly seek to address uncertainties in the utilisation or expenditure of a medicine or CTGTP, whereas performance-based RSAs are intended to resolve clinical uncertainties by directly linking the level of funding, price, or continued reimbursement of a medicine or CTGTP to its clinical performance or the health outcomes achieved in intended patient populations.

The company should prepare any RSA proposals in consultation with ACE to ensure that they are feasible to implement and in line with the criteria described below, where applicable. Companies should describe the proposed RSA(s) in the Request for Proposal and explain which uncertainties will be addressed through the proposed arrangement(s). The expected financial impact of the proposed RSA should also be captured in relevant analyses in the economic evaluation and/or budget impact analyses.

Price-volume agreements

Price-volume agreements (PVAs) are the main type of financial-based RSAs considered by the DAC. These agreements set out defined annual expenditure caps that manage the budgetary risk arising from uncertainties in the utilisation or expenditure of the medicine or CTGTP .

PVAs are particularly relevant for following types of uncertainties commonly associated with high-cost or high-budget impact treatments, including cancer medicines and CTGTPs:

- number of patients that are expected to be eligible for funding;
- potential use of the medicine or CTGTP in non-cost effective, off-label, or non-subsidised populations;
- potential for dose escalation (of medicines) beyond what is expected or presented in the submission;
- potential for use beyond disease progression, for a longer duration than is cost-effective or in non-responding patients; and
- risk of use in combination with, or in addition to, current therapy rather than replacing existing therapies.

In general, companies are required to include PVA proposals for **all new cancer medicines and CTGTPs**, and provide sufficient justification for the expenditure caps proposed. Any expenditure caps exceeding S$2 million in any year within the first five years of listing will require additional financing approval from MOH which may lengthen the time to funding implementation.

Performance-based risk-sharing agreements

PVAs will remain the main type of RSA administered by MOH, given their ease of implementation and their effectiveness in managing uncertainties in utilisation and expenditure. However, given the increasing proportion of submissions for which important clinical uncertainties remain unresolved at the point of funding recommendation, performance-based RSAs may have a role in enabling patient access for selected technologies where those uncertainties cannot be resolved by other means.

Performance-based RSAs can be structured in various ways, depending on the specific uncertainties to be resolved and the data available to assess them. Outcomes-based agreements are the principal form of performance-based RSA. These may take one or more of the following forms:

- **individual-level outcomes-based agreements:** the cost of treatment for each patient is adjusted based on the outcomes achieved by that patient;
- **population-level outcomes-based agreements**: the total expenditure on all patients receiving the medicine or CTGTP over the period of the agreement is adjusted based on updated clinical trial data or real-world evidence; and
- **conditional continuation agreements:** continued funding of the medicine or CTGTP is conditional on specified outcome requirements being met. The outcome requirements will be specific to the medicine or CTGTP, and may be assessed using real-world evidence at the individual patient or population level, or updated clinical trial data.

These forms are not mutually exclusive, and a proposed agreement may combine elements of more than one. A performance-based RSA may also operate alongside a PVA, where the uncertainties identified include both the utilisation of or expenditure on the medicine or CTGTP and its clinical performance.

While performance-based RSAs may enable access to promising therapies where important clinical or financial uncertainties remain, these agreements are resource-intensive and place significant demands on all parties, including substantial governance and legal requirements, rigorous and sustained data collection obligations, and significant operational costs. Their use must therefore be intentional and selective, so that any agreement entered into not only addresses the key uncertainties associated with the medicine or CTGTP concerned, but is also proportionate to those uncertainties. Performance-based RSAs will accordingly only be considered in certain circumstances, where the uncertainties identified cannot be adequately addressed through price adjustments or financial-based RSAs, and where the agreement can meaningfully align patient access, evidence generation and sustainable financing.

Additionally, proposed performance-based RSAs should be designed and implemented with the following considerations in mind, to ensure that their effectiveness is not undermined by issues commonly associated with these agreements:

- **operational and data infrastructure requirements**: performance-based RSAs depend on sustained, high-quality data collection from treating clinicians and public healthcare institutions. Companies should demonstrate and ensure that the required data can be collected reliably for the full duration of the agreement, and not only at the point at which the agreement is entered into;
- **specification of outcome measures tracked**: the outcome measures selected should directly address the uncertainties the agreement is intended to resolve, and should be defined with sufficient precision that their interpretation is not open to dispute. The time horizon over which outcomes are assessed should also be pre-specified and proportionate to the evidence sought; and
- **proportionality and equitable patient access**: performance-based RSAs should not be proposed where the uncertainties identified could be adequately addressed by a simpler arrangement. In Singapore's multi-payer financing system, the design of any rebate or payment structure should also have regard to its effect on patient affordability and on equitable access.

Given the above, only performance-based RSAs that fulfil **all four criteria** described in Table 4.1.5a below will be considered by MOH. These criteria provide a transparent and predictable basis for companies to engage MOH on performance-based RSAs, and ensure that any agreement is structured to deliver meaningful value

for patients and the healthcare system.

Table 4.1.5a: Criteria for performance-based risk-sharing agreements in Singapore

Criteria for considering suitability of performance-based risk-sharing agreement
1. The medicine or CTGTP offers high added therapeutic value in an area of significant unmet clinical need. • The medicine or CTGTP must be potentially lifesaving, must fulfil an urgent or important clinical need, and must have no effective clinical alternative. • The company must justify why the uncertainties identified cannot instead be addressed through a direct price reduction or a PVA. • The price proposed at the point of listing, and any accompanying PVA, must be reasonable and proportionate to the value demonstrated. A performance-based RSA will not be accepted as the basis for a price that would otherwise be unacceptable. 2. The design of the performance-based RSA is validated through HTA evaluation. • The outcomes collected must be patient-relevant and must address the key uncertainties identified, including the drivers of clinical and cost-effectiveness. Where the uncertainty concerns survival benefit, for example, the agreement should be based on overall survival rather than a surrogate measure. • Where the agreement relies on population-level data, the data collected must be capable of informing an assessment of the comparative effectiveness of the medicine or CTGTP against relevant comparators. • The agreement must specify the rebates and/or price reductions payable where the agreed outcome requirements are not met, and these must be sufficient to offset the effect on the clinical and cost-effectiveness of the medicine or CTGTP. • The DAC may have regard to the terms of comparable agreements in overseas reference jurisdictions. 3. The performance-based RSA is implementable within the Singapore healthcare system. • Companies must secure written commitments from treating clinicians and participating public healthcare institutions to collect any patient-level data required, so that the data requirements are attainable and the impact on patient care is minimised. • Where the agreement relies on population-level data, the data must already be provided for under an existing clinical trial protocol, or be collectable through an established real-world data registry. Where patient numbers in Singapore are insufficient to support meaningful analysis, the agreement must not rely on locally collected data alone. • The payment and rebate structure, and the time horizon proposed, must be practicable within Singapore's multi-payer financing framework and consistent with prevailing financing policies. 4. The company is responsible for implementing the performance-based RSA.

- The company's responsibilities include implementing the agreement, securing patient consent for the collection and use of the required data, and ensuring compliance with all applicable legislation and data security requirements, including prevailing data governance requirements and the Personal Data Protection Act 2012 (PDPA).
- MOH may audit the implementation of the agreement to ensure that it is properly carried out.

General criteria for risk-sharing agreements

In addition to the considerations described above, all proposed RSAs must be consistent with the general criteria and requirements described in Table 4.1.5b below. These do not displace the requirements described above for PVAs, or the criteria in Table 4.1.5a for performance-based RSAs.

Table 4.1.5b: General Criteria for risk-sharing agreement in Singapore

General criteria for medicines or CTGTPs subject to a risk-sharing agreement
Part A — Criteria for determining whether a risk-sharing agreement is appropriate
1. The medicine or CTGTP treats a significant health condition and the MOH Drug Advisory Committee (DAC) considers that it will generate substantial incremental benefit for the intended patient population.
2. The DAC advises that the medicine or CTGTP is recommended for funding for a specific clinical indication(s) or that it has unique characteristics compared to any available alternative therapies and addresses a therapeutic gap.
3. The DAC considers that the RSA will accrue significant financial benefits to the Singapore healthcare system.
4. The company advises or is advised that not entering into a RSA would prevent a positive funding recommendation, and provides the reason(s), including financial implications, why this arrangement is required.
Part B — Requirements applying to all risk-sharing agreements
5. The company has advised MOH that the effective price and/or any proposed arrangements are consistent with or more advantageous than those in other countries.
6. The RSA is operationally feasible within the context in which it is intended to be implemented.
7. Data gathering requirements for the arrangement can be performed to a high degree of fidelity with existing IT infrastructure or the company is able to provide the required infrastructure otherwise
8. The company acknowledges and accepts that: i. acceptance of any proposal is at the discretion of the Singapore Government; ii. the list of medicines or CTGTPs eligible for government subsidies and/or MediShield Life coverage may allude to the "existence of a Deed of Agreement which contains a 'Risk-Sharing Agreement'" for the submitted medicine or CTGTP in the event of a positive recommendation by DAC ; details of the Deed of Agreement however, will be kept confidential; and

iii. to give effect to any RSA, a Deed of Agreement is required between the company and the Singapore Government.

Deed of Agreement for risk-sharing agreements

An RSA is established through a Deed of Agreement between the Government (as represented by MOH Singapore) and the company. A standard Deed of Agreement template is available on ACE's website. Amendments to the standard clauses in the Deed of Agreement are not accepted unless the attributes of a particular arrangement proposed for a medicine or CTGTP are identified by an DAC as requiring different considerations. All Deeds will need to be executed before a medicine or CTGTP is included on SDL, MAF, CDL or the CTGTP List.

Deeds are generally required to cover a period of five years. MOH will review all Deeds towards the end of their term. Deeds can either lapse or be renewed following review. Where a Deed gives effect to a PVA and an agreement cannot be reached between MOH and the company prior to the expiry of a Deed, the terms of the existing Deed will remain in force until such time an agreement can be reached. This is necessary to ensure the risks associated with the listing can continue to be managed. Where a Deed gives effect to a performance-based RSA, the terms on which funding may continue beyond the expiry of the Deed will be specified in the Deed.

DAC may also periodically review and recommend changes to the list of clinical indications eligible for government subsidies and/or claims or benefits under the MediShield Life scheme for medicines or CTGTPs with existing PVAs. When this occurs, the DAC advise ACE whether any increases to the existing caps are warranted from a clinical and/or cost-effectiveness perspective. Companies will be notified of any updates to affected Deeds following the DAC review.

Specific to performance-based RSAs, the Deed of Agreement will specify the consequences where the agreed outcomes are not achieved, which may include price adjustment, rebate of amounts paid, or cessation of funding. As the appropriate terms will depend on the characteristics of the medicine or CTGTP and the uncertainties the agreement is intended to address, these will be determined for each agreement individually. Where a performance-based RSA reaches the end of its term, the DAC will reassess the medicine or CTGTP in the light of the data collected, and may recommend that funding continue on revised terms, or that the medicine or CTGTP be removed from the relevant list.

All Deeds agreed between MOH and any company are strictly confidential and will not be made publicly available. The confidentiality of all Deeds (and the information contained within) will be preserved through the mandatory Confidentiality Agreement signed between MOH and companies. All documents will also be handled in accordance with MOH's standards for confidentiality and transparency (Section **Error! Reference source not found.**).

Amounts payable and invoicing

Where amounts are payable under a financial-based RSA, ACE will issue invoices for amounts due in respect of a given calendar year by the fourth quarter of the following calendar year. Rebate amounts are calculated from the data specified in the Deed, and ACE will validate these data before any invoice is issued to ensure the accuracy of the amounts due. Invoices will be issued together with the relevant supporting documents for the company's reference, and payment terms are as specified in the Deed. Where the required data are

incomplete or delayed, or where further verification is necessary, invoices may be issued later than the timeframe described above.

Where rebates are payable under a performance-based RSA, the timing of invoicing will follow the payment and reassessment terms specified in the Deed.

4.1.6 Patient assistance programmes

Describe any proposed patient assistance programmes (PAP) included in the Request for Proposal for the proposed medicine or CTGTP. Justify why the proposed PAP is required and confirm that the administrative requirements to implement the PAP are acceptable to all public healthcare institutions that will be prescribing the proposed medicine or CTGTP.

4.1.7 Summary of costing template calculations

Briefly summarise the results of any calculations (including sensitivity analyses) from the costing template in the submission. Supporting calculations do not need to be replicated in the submission but should be provided in the costing template in sufficient detail to allow independent verification. Discuss any differences between the results in the base case and the sensitivity analyses, if applicable.

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Appendix 1 Submission Checklist

1.1 For full or expedited evaluations

The documents that should be sent to ACE as part of a company submission for full or expedited evaluations are shown in the table below. Companies should complete this table and include it as part of their submission. ACE will use it as a checklist to ensure that all relevant documents have been received.

Category[a]	Document required	Included? Y/N
General information	Signed cover letter	
	Executive summary	
	Completed Request for Proposal including a proposed price-volume agreement that is aligned with the budget impact analysis in the submission, where applicable	
Regulatory information – If HSA-approved	Most recent version of the HSA product information and HSA summary report of benefit-risk assessment (if available)	
Regulatory information – If not yet HSA-approved	US FDA and/or EMA assessment report	
	HSA approvable letter	[If not available at time of submission, indicate when it will be provided]
Evidence submission	Completed evidence submission that addresses Sections 1-4 in the guidelines (not exceeding 150 pages, excluding appendices) Include name(s) of third-party consultant(s) appointed to prepare the evidence submission in the cover page (if relevant)	
Documents to support evidence submission	Full clinical study report(s) of key evidence, including trial protocols and amendments. The list of appendices for the clinical study report should be provided, but the appendices are not required in the submission.	
	Publications of all references with filenames in the format *reference number_ author_year_*.	
	Statistical appendix for analyses used in the submission, including any relevant code for statistical software used	
	Search strategy and literature yield from Pubmed (MEDLINE). Literature searches should be updated within four months of the date of evidence submission.	
	Full reports of patient or clinician surveys that were used to inform the submission	
	Minutes from Advisory Board meetings or workshops with clinical experts or patients/carers who informed the submission	
	Unlocked and fully executable economic model or cost-minimisation spreadsheet	
	Completed Costing template	
	Reference list of all publications that informed the submission	
Other[b]	[complete if relevant]	

[a] Documents cannot be removed from this list. If a document is not available or not relevant, please explain why.

[b] Additional relevant documents can be included in the list under the "other" category.

1.2 For abridged evaluations

The documents that should be sent to ACE as part of a company submission for abridged evaluations are shown in the table below. Companies should complete this table and include it as part of their submission. ACE will use it as a checklist to ensure that all relevant documents have been received.

Category[a]	Document required	Included? Y/N
General information	Signed cover letter	
	Completed Request for Proposal including a proposed price-volume agreement that is aligned with the budget impact analysis in the submission, where applicable	
Regulatory information – If HSA-approved	Most recent version of the HSA product information and HSA summary report of benefit-risk assessment (if available)	
Regulatory information – If not yet HSA-approved	US FDA and/or EMA assessment report	
	HSA approvable letter	[If not available at time of submission, indicate when it will be provided]
Reimbursement information	Reimbursement status of overseas HTA agencies	
Evidence submission	Completed evidence submission (not exceeding five pages, excluding appendices) Include name(s) of third-party consultant(s) appointed to prepare the evidence submission in the cover page (if relevant)	
Documents to support evidence submission	Full clinical study report(s) of key evidence, including trial protocols and amendments . The list of appendices for the clinical study report should be provided, but the appendices are not required in the submission.	
	Full reports of patient or clinician surveys that were used to inform the submission	
	Minutes from Advisory Board meetings or workshops with clinical experts or patients/carers who informed the submission	
	Completed Costing template	
	Reference list of all publications that informed the submission	
Other[b]	[complete if relevant]	

[a] Documents cannot be removed from this list. If a document is not available or not relevant, please explain why.
[b] Additional relevant documents can be included in the list under the "other" category.

Appendix 2 NHMRC designations of levels of evidence[xxxix]

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening intervention
I	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies
II	A randomised controlled trial	A study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternative collation or some other method)	A study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternative allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised experimental trial ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

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