

DRUG EVALUATION METHODS AND PROCESS GUIDE

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ACE
agency for
care effectiveness

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Foreword

The Agency for Care Effectiveness (ACE) is the national health technology assessment (HTA) agency in Singapore residing within the Ministry of Health. It conducts technical evaluations to inform subsidy decisions for treatments, and produces guidance on the appropriate use of treatments for public hospitals and institutions in Singapore.

The *ACE Drug Evaluation Methods & Process Guide* outlines the core technical methodology and processes underpinning the assessment of clinical and economic evidence for drugs which are being considered for government subsidy. This guide is not intended to be a comprehensive academic document or to describe all technical details relating to health economic analyses. Rather, the intention of this guide is to standardise and document the methods that ACE follows for drug evaluations, and increase transparency of our processes and decision-making frameworks.

While this document forms an important part of the Ministry of Health Drug Advisory Committee's (DAC) decision-making processes for drug subsidy, it is only a guide – ACE and DAC are not bound to adhere to it in every detail, or in every case.

Information in this guide may also be useful for healthcare professionals and pharmaceutical manufacturers who provide evidence and advice to support ACE's evaluations. ACE will continue to review and update this guide to ensure that it remains a useful resource for the Singapore healthcare system.

Find out more about ACE at www.ace-hta.gov.sg/about

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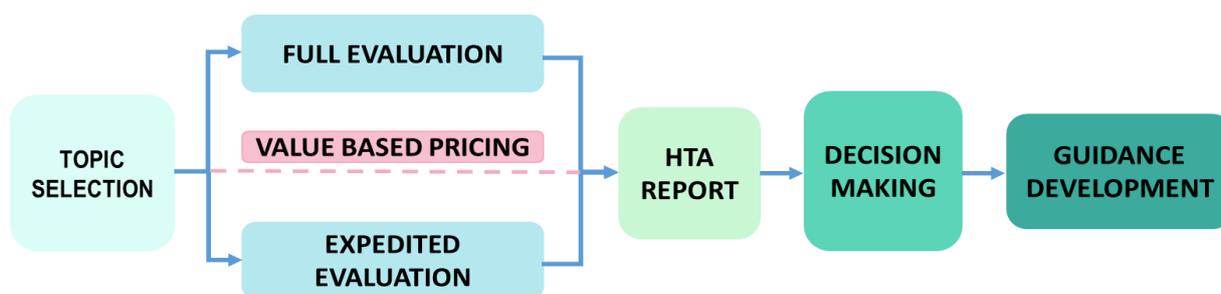
1. Introduction

Health technology assessment (HTA) is an established scientific research methodology to inform policy and clinical decision-making on the relative value of new health technologies, such as drugs, devices and medical services, compared to existing standards of care. It is conducted using analytical frameworks, drawing on clinical, epidemiological and health economic information, to determine how to best allocate limited healthcare resources.

This document provides an overview of ACE's HTA methods and processes for the evaluation of new and existing drugs available in Singapore. It introduces the general methodological concepts underlying each stage of the evaluation process and outlines the key information required from manufacturers who submit evidence to inform ACE's evaluations.

Each core step in the evaluation process is described in sequence, from the selection of the topics for evaluation, through to evidence generation, value-based pricing, decision-making then the development of ACE's guidance (Figure 1).

Figure 1. Overview of drug evaluation process



Specific templates which manufacturers may be asked to complete at various points in the process are also provided in the Annexes for information.

2. Topic Selection

Topic selection is the process for deciding which drugs and indications (drug topics) are appropriate for evaluation by ACE. The process has been designed to ensure that the drugs chosen address priority issues and therapeutic gaps, which will help improve the health of the population, and will support healthcare professionals to provide appropriate care.

2.1 Call for drug topics

Potential drug topics for technology evaluation are identified predominantly through applications by individual public healthcare professionals. New and emerging drugs that might be suitable for evaluation are also identified through literature searches and horizon scanning by the ACE technical team.

Public healthcare institutions are invited to submit applications for the inclusion of drug preparations into the MOH List of Subsidised Drugs on an annual basis (during January to March). The annual invitation for drug applications is sent to the Chairman of the Medical Board (or equivalent body) of each institution at the start of each application cycle by the MOH Drug Advisory Committee (DAC) Secretariat within ACE. All applications should be submitted to the Chairman of the Medical Board (or equivalent body) for endorsement and collation before submission to the MOH DAC Secretariat.

2.2 Filtering of topics

Topic selection decisions are based on the consideration of each potential topic against elimination and prioritisation criteria. The elimination criteria filter out topics which are unsuitable for evaluation. A topic will not be considered for evaluation by ACE if:

- the drug is not registered for use in Singapore by the Health Sciences Authority (HSA) **or**
- the drug topic is identical to a topic that has been evaluated by ACE within the last year and guidance is already in development **or**
- there is insufficient evidence available to conduct an evaluation.

The following topic areas are also currently outside the remit of ACE drug evaluations:

- Vaccinations (including therapeutic vaccines)
- HIV therapy
- Blood products
- Nutritional products (enteral or parenteral)
- Dialysis solutions
- Wound dressings
- Fertility drugs
- Lifestyle drugs
- General Sales List (GSL) medications

Off-label use of HSA-registered drugs will only be considered for evaluation on a case-by-case basis if **all** of the following conditions apply:

- the off-label use of the drug is the current standard of care in local clinical practice and also in line with international best practice; and
- there is a lack of affordable and cost-effective treatment alternatives to the off-label drug; and
- there is sufficient evidence available to assess the safety, efficacy, and cost-effectiveness of the off-label use of the drug.

2.3 Selection of topics

The need to evaluate each remaining topic is then considered against specific selection criteria, which seek to measure the population size and disease severity, clinical need for the new treatment, claimed therapeutic benefit over alternative treatments, and value that ACE could add in conducting a technology evaluation (Table 1).

Scores are assigned for each criterion to generate a total “need score”. Topics are more likely to receive a moderate to high need score and be selected for evaluation if the drug represents a **therapeutic gap** which is expected to be of significant benefit to patients in terms of clinical efficacy or improved side-effect profile, and there is sufficient evidence to support an evaluation.

Table 1. ACE topic selection criteria

No.	Criterion	Definition
1.	Type of gap that drug will fill in clinical practice	Chemical gap: Alternative treatment for the condition of interest is already subsidised but from a different drug class to the new treatment. Therapeutic gap: No treatment for condition of interest is currently subsidised.
2.	Unmet clinical need	Extent to which condition is currently being adequately treated in local clinical practice.
3.	Disease severity	
a	Impact on mortality	Survival or mortality associated with the underlying health condition
b	Impact on morbidity and quality of life	Impact of underlying health condition on morbidity, health related quality of life or both.
4.	Size of affected population in Singapore	The estimated size of the patient population that is affected by the underlying health condition and which may be eligible for the new treatment.
5.	Comparative clinical effectiveness (from published literature)	Added or reduced clinical benefit of the new technology compared to alternatives
6.	Relative safety (from published literature)	Safety of the new technology compared to alternatives.
7.	Cost-effectiveness (from published literature)	Dominance or incremental cost-effectiveness of new technology compared to alternatives.

3. Technology Evaluation

3.1 Type of evaluation

Topics with moderate to high need scores (following the topic selection process) are prioritised for evaluation by the DAC. All evaluations are conducted internally by the ACE technical team with supporting evidence provided by local healthcare professionals from public institutions and pharmaceutical manufacturers, where required.

Evaluations are conducted at two levels - expedited or full – depending on the estimated budget impact and uncertainty around the clinical and cost parameters for each drug:

- High cost drugs (estimated budget impact >\$2 million per year) or drugs which are expected to have high impact on population health due to superior outcomes relative to current standard of care are typically subject to **full evaluation**
- Drugs with a lower budget impact (<\$1 million per year) or which are already available as a generic formulation, are subject to **expedited evaluation**
- Drugs with a moderate budget impact (between \$1 million to \$2 million per year) are considered for expedited or full evaluation on a case by case basis depending on the uncertainty around the clinical and cost estimates. Drugs with uncertain estimates are likely to be subject to full evaluation.

In addition, the extent of information available for evaluation and the availability of ACE technical resources to conduct the evaluation within the required timeframe is taken into account when deciding the type of evaluation required.

A summary of the evidence sourced for each evaluation type, the analyses undertaken by ACE and the average resource required is shown in Table 2.

Table 2. Evidence and analyses included in expedited and full evaluations

Type of evaluation	Types of evidence and analyses included in evaluation	FTE Required
Expedited evaluation	<ul style="list-style-type: none"> • Qualitative written survey of clinical experts to inform local treatment algorithm, define comparator(s), and describe current use of drug(s) in local practice and patients' clinical need for drug subsidy • Literature search of published clinical and economic evidence (local and international studies) and review of retrieved studies • Review of previous assessments by international HTA agencies • Value-based pricing proposal from manufacturer • Budget impact analysis, including estimated annual cost to government for listing drug(s) on SDL or MAF 	2 to 3 months
Full evaluation	<ul style="list-style-type: none"> • Stakeholder workshop with local healthcare professionals to define the scope of the evaluation • Systematic review of published clinical evidence (local and international studies). Indirect comparisons, pairwise meta-analyses and network meta-analyses undertaken if required. • Literature search of published economic evidence (local and international studies) and review of retrieved studies • Development of economic model (cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) as appropriate), using local data inputs where available. Scenario and sensitivity analyses also undertaken to model the uncertainty of key model parameters. Cost minimisation analyses (CMA) may also be undertaken for class reviews if all drugs are considered clinically comparable. • Review of previous assessments by international HTA agencies • Value-based pricing proposal from manufacturer • Budget impact analysis, including estimated annual cost to government for listing drug(s) on SDL or MAF 	6 to 9 months

FTE: full-time equivalent. Timelines are indicative. Actual timelines vary depending on the complexity of the topic and the number of drugs/indications included in each evaluation.

3.2 Evaluation processes

Overviews of the processes for expedited and full evaluations are shown in Figures 2 and 3 respectively.

Figure 2. Overview of expedited evaluation process for drug topics

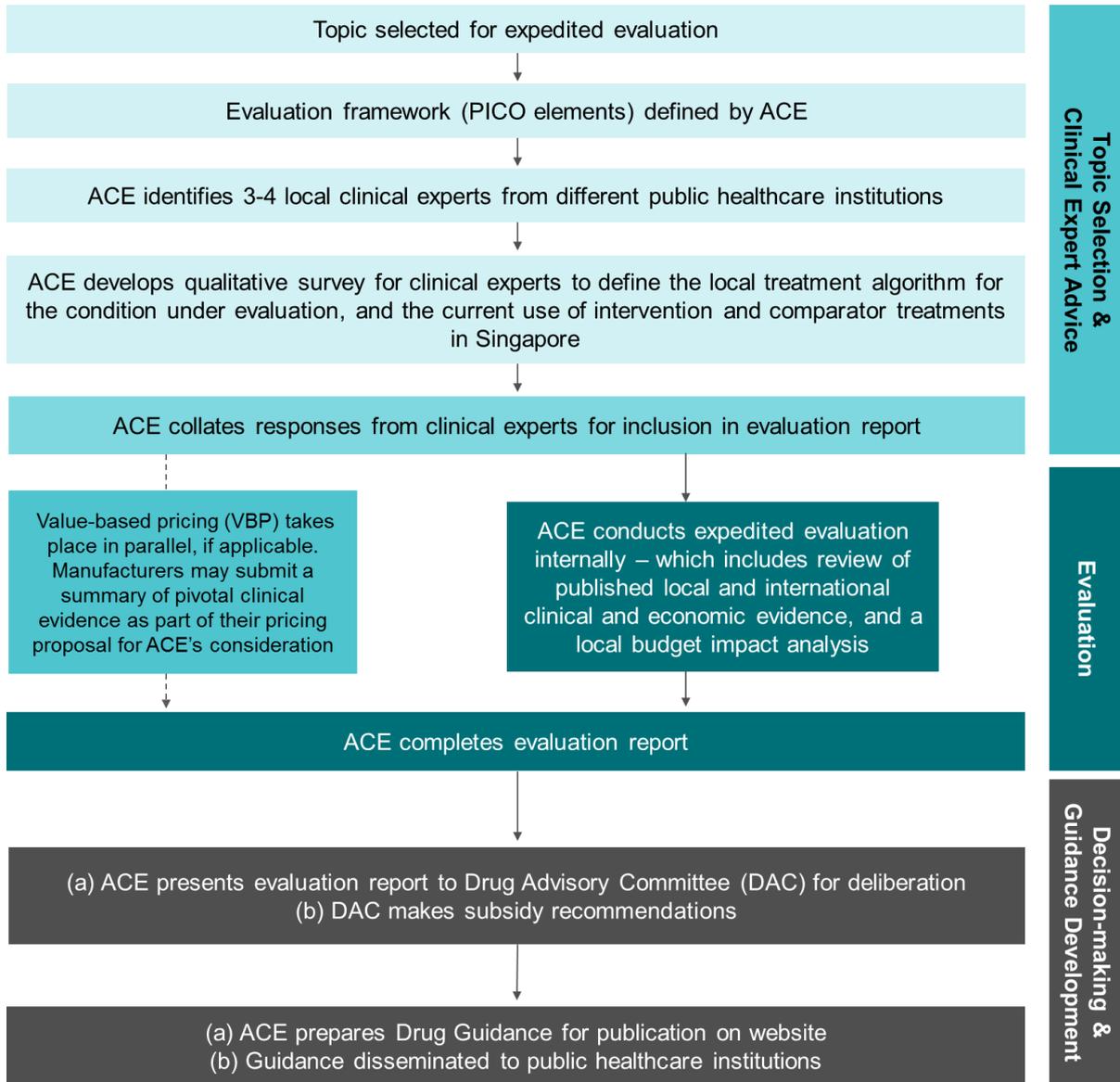
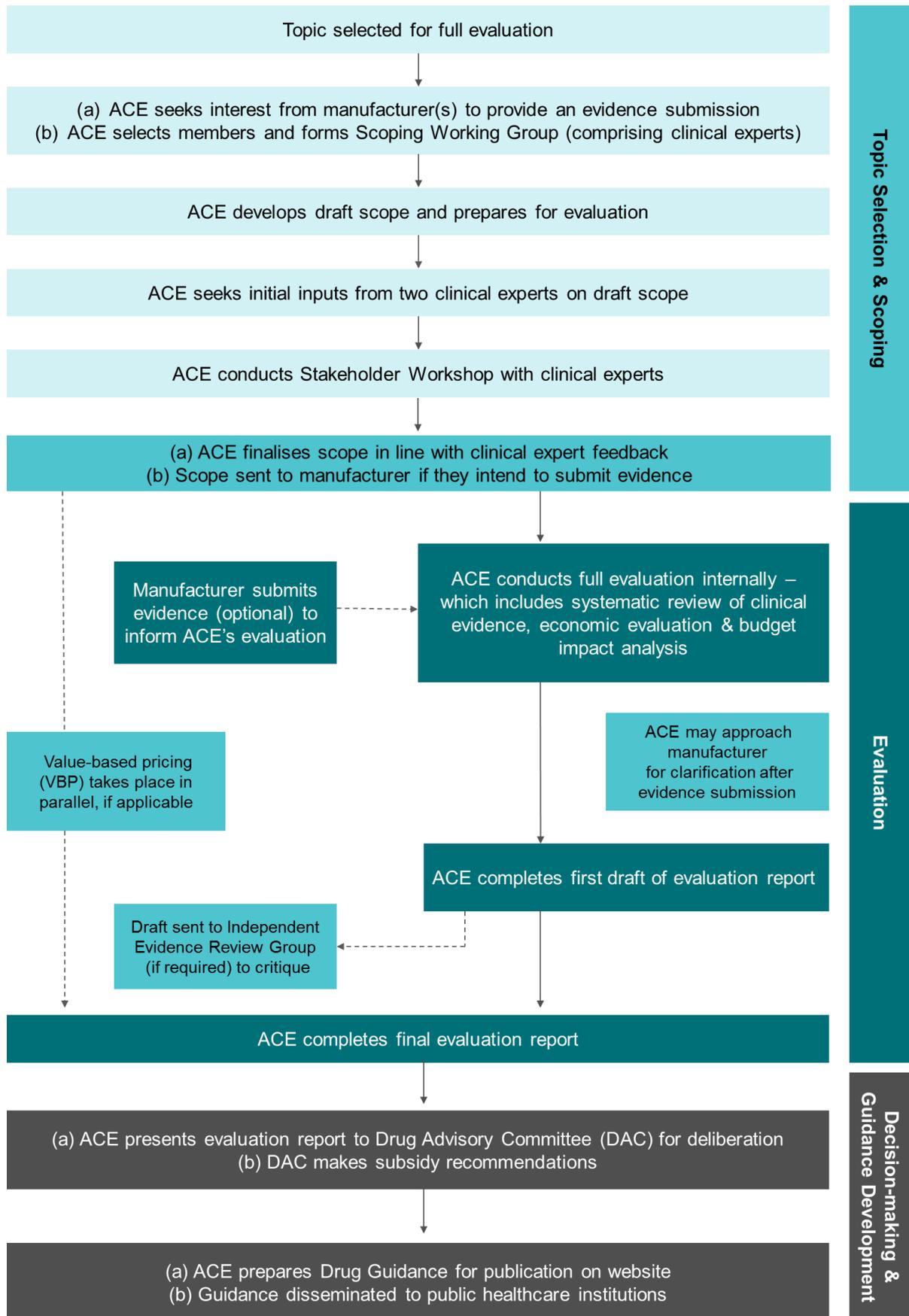


Figure 3. Overview of full evaluation process for drug topics



3.3 Defining the evaluation framework

Before a technology evaluation commences, the ACE technical team use the PICO framework (**p**opulation, **i**ntervention, **c**omparators, and health **o**utcome measures) to define the key elements of interest and the research question that the evaluation is intended to address. This serves to clearly define the purpose and boundaries of the evaluation, and to assist the ACE technical team formulate clear search terms (MESH headings) and yield more precise search results (Table 3).

Table 3. PICO evaluation framework

P	I	C	O
Patient/Population	Intervention/Exposure	Comparator	Outcome
<ul style="list-style-type: none">• Patient or population characteristics• Condition/disease of interest	Drug(s) under evaluation	Alternative treatment option(s) to the intervention used in routine clinical practice	Clinically meaningful health outcomes of interest

For expedited evaluations, the framework is defined by the ACE technical team in line with the indication requested for evaluation by healthcare professionals (see Section 2 for topic selection process).

For full evaluations, the evaluation framework is defined through the scoping process in consultation with local clinical experts through a stakeholder workshop (Section 4.2).

4. Scoping

4.1 Developing the scope

The scope provides a framework for topics which are subject to **full evaluation**. Using the PICO framework, it defines the **p**opulation, **i**ntervention, **c**omparators, and health **o**utcome measures of interest to inform the economic modelling approach, and sets the boundaries for the work undertaken by the ACE technical team. A scope is not drafted for topics undergoing expedited evaluation (because economic modelling is not required), however, PICO elements are still used to ensure that the research question is properly defined and considered within the evaluation report.

The issues for consideration in the evaluation that are described in the scope include:

- the disease or health condition and the population(s) for whom treatment with the drug is being evaluated
- use of the drug in local clinical practice (and the setting for its use; for example, hospital [inpatient and outpatient] or community if relevant)
- the relevant comparator treatments, which reflect the treatments used in current clinical practice in Singapore to manage the disease or condition (this may include off-label alternatives if they constitute routine care)

- the principal health outcome measures appropriate for the analysis, including the length of time over which the benefits and costs will be considered
- consideration of patient subgroups for whom the drug might be particularly clinically and/or cost effective.

A draft scope is developed by the ACE technical team. Two healthcare professionals who have expertise in the disease area under evaluation are invited to review the draft scope and provide their views on the use of the drug in relation to current local clinical practice. The draft scope is then revised by the ACE technical team in line with comments received, and is sent to all stakeholders who have confirmed their attendance at the stakeholder workshop.

4.2 Stakeholder Workshop

To ensure that the evaluation framework for the full evaluation is appropriately defined with relevance to local clinical practice and patient need, ACE holds a roundtable workshop with healthcare professionals with expertise in the disease area or the use of the drug under evaluation.

The aims of the workshop are to:

- ensure that the scope is appropriately defined
- seek further advice from healthcare professionals on:
 - variations between groups of patients, in particular, differential baseline risk of the condition and potential for different subgroups of patients to benefit
 - appropriate outcomes and surrogate outcome measures
 - significance of side effects or adverse reactions and the clinical benefits expected (from clinical trials) or realised in local practice (if drug is already in use in Singapore)
 - relevant potential comparators
 - requirements to implement any guidance on the use of the drug, including need for extra staff or equipment; education and training requirements for hospital staff before using the drug; and ways in which adherence to treatment can be improved.
 - how response to treatment is assessed in clinical practice, and the circumstances in which treatment might be discontinued.

Additional details about the proposed economic modelling approach, input parameters and assumptions, may also be shared by the ACE technical team at the workshop to elicit feedback from the stakeholders.

4.3 Final scope

After the stakeholder workshop, the ACE technical team finalises the scope, taking into account the discussions at the workshop. The final scope is shared with the manufacturer of the drug under evaluation if they intend to provide clinical and/or cost information to support ACE's evaluation.

5. Evidence Generation and Critical Appraisal

5.1 General principles

Consideration of a comprehensive evidence base is fundamental to the evaluation process. While information from multiple sources may inform the evaluation, ACE's preference for different types of evidence to determine comparative treatment effectiveness is influenced by the hierarchy of scientific literature (Table 4).

Table 4. Hierarchy of scientific literature

<ol style="list-style-type: none"> 1. Systematic reviews or meta-analysis 2. Randomised controlled trials (RCTs) 3. Non-randomised controlled trials 4. Cohort studies 5. Case-control studies 6. Descriptive studies, limited series 7. Anecdotal evidence, position papers, non-systematic reviews, expert opinion

When sourcing information, secondary studies, such as systematic reviews and assessments of published information (including HTA reports and clinical guidelines) are typically retrieved first, before primary studies (individual trials). Among primary studies, randomised controlled trials (RCTs) are generally considered to provide the highest standard of evidence on comparative treatment effectiveness. Data from non-randomised studies may also be required to supplement RCT data and inform other evaluation parameters such as costs and utility values.

5.2 Types of evidence

A summary of the different types of evidence used to inform ACE's drug evaluations, and the considerations made by ACE when using each type of evidence are shown in Table 5.

Table 5. Types of evidence considered in ACE evaluations

Evidence type	Considerations
Randomised controlled trials	<ul style="list-style-type: none"> • Randomised controlled trials (RCTs) are considered to be appropriate for measures of relative and absolute treatment effects. If randomisation is conducted properly, observed and unobserved characteristics should be balanced between the randomised groups, so the effect of treatment versus the control on the observed outcomes can be inferred. • The relevance of RCT evidence to the evaluation depends on both the external and internal validity of each trial: <ul style="list-style-type: none"> – Internal validity is assessed according to the design and conduct of a trial and includes blinding (when appropriate), the method of randomisation and concealment of allocation, and the completeness of follow-up. Other important considerations are the size and power of the trial, the selection and measurement of outcomes and analysis by intention to treat.

	<ul style="list-style-type: none"> – External validity is assessed according to the generalisability of the trial evidence; that is, whether the results apply to wider patient groups (and over a longer follow-up), Asian populations, and to routine clinical practice in the local context.
Non-randomised evidence	<ul style="list-style-type: none"> • In non-randomised studies (such as observational or epidemiological studies), the treatment assignment is non-random, and the mechanism of assigning patients to alternative treatments is usually unknown. Hence, the estimated effects of treatment on outcomes are subject to treatment selection bias, and this should be recognised in the interpretation of the results. • Inferences will necessarily be more cautious about relative treatment effects drawn from studies without randomisation or control groups than those from RCTs. The potential biases of non-randomised studies should be identified, and ideally quantified and adjusted for. • Evidence from non-randomised sources is often used to obtain non-clinical model parameters such as costs and utility values. As study quality can vary, critical appraisal and sensitivity analyses are important for review of these data.
Real world data	<ul style="list-style-type: none"> • In its broad definition, real world data encompasses all non-randomised evidence and can include data generated as part of pragmatic controlled trials; however, in HTA, it typically presents as observational data from patient registries, administrative databases, electronic medical records and surveys. • The quality of real world data can vary across different data types and sources. To mitigate potential bias, careful study design is needed and an analysis plan should be created prior to retrieving and analysing real world data.
Qualitative research	<ul style="list-style-type: none"> • Qualitative research, in the form of questionnaire or survey responses from clinical professionals, is often used to explore areas such as patients' experiences of having a disease and/or specific treatment, and clinicians' views on the role of different types of treatment in local clinical practice.
Economic evaluations	<ul style="list-style-type: none"> • Evidence on the cost effectiveness of the drug under evaluation may be obtained from new analyses conducted by the ACE technical team (for full evaluations); however, a comprehensive search of published, relevant evidence on the cost effectiveness of the drug is also conducted to inform the evaluation. • Economic evaluations should quantify how the treatments under comparison affect disease progression and patients' health-related quality of life, and value those effects to reflect the preferences of the general population.
Unpublished evidence	<ul style="list-style-type: none"> • To ensure that the evaluation does not miss important relevant evidence, attempts are made to identify evidence that is not in the public domain. Such evidence includes unpublished clinical trial data such as those in clinical study reports (which is preferred over data in poster or abstract form only). • If unpublished evidence is used to populate an economic model, such information should be critically appraised and, when appropriate, sensitivity analysis conducted to examine the effects of its inclusion or exclusion.

5.3 Evidence submissions from manufacturers

For topics which are subject to **full evaluation**, concise evidence submissions (up to 35 pages) are invited from the manufacturer of the drug under evaluation as supplementary evidence to ACE's assessment. The information in the submission should be in line with the evaluation framework set out in the final scope, and provided within the *company evidence submission template for full evaluations* (Annex 1). A separate Excel workbook to summarise cost information (*Costing template for manufacturers*) should also be included alongside evidence submissions for full evaluations. Manufacturers who express interest in submitting evidence to inform a full evaluation, will be given **8 weeks** to complete the templates.

For topics which are subject to expedited evaluation, a brief summary (up to 5 pages) of key clinical evidence may be submitted by manufacturers with their *Call for Proposal for Subsidy Listing* (see section 8.1). Evidence should be submitted within the *company evidence submission template for expedited evaluations* (Annex 2) within the required timelines (typically 6-8 weeks).

It is not mandatory for manufacturers to complete an evidence submission for full or expedited evaluations. The topic will still be evaluated by the ACE technical team and presented to the DAC to inform subsidy considerations, irrespective of manufacturer involvement.

6. The Reference Case

The DAC has to make subsidy decisions across different drugs and disease areas. It is therefore crucial that analyses of clinical and cost effectiveness undertaken to inform the evaluation adopt a consistent approach. To allow this, ACE has defined a 'reference case' with an aim to promote high-quality analysis and encourage consistency in analytical approaches. Although the reference case specifies the preferred methods followed by ACE, it does not preclude the DAC's consideration of non-reference-case analyses if appropriate. The key elements of analysis using the reference case are summarised in Table 6.

Table 6. ACE's reference case for drug evaluations

Component of drug evaluation	Reference Case
Perspective of the evaluation	<ul style="list-style-type: none"> • Only direct health-care costs from the perspective of the health-care payer should be included in reference case analyses; this includes payments out of the government's health-care or insurance budget as well as patients' co-payments including Medisave and out of pocket expenses • Health outcomes measured in patients and valued from a healthcare payer perspective • If characteristics of treatments have a value to people independent of any direct effect on health, the nature of these characteristics should be clearly explained and if possible the value of the additional benefit should be quantified • Productivity costs may be presented as secondary analyses (not in the reference case)
Target population and subgroups	<ul style="list-style-type: none"> • Consistent with the patient population defined in evaluation framework • Subgroup analyses if appropriate (statistical) justification is provided • Epidemiological data for Singapore presented for the entire target population and relevant subgroups
Comparators	<ul style="list-style-type: none"> • Comparator(s) should be used to allow a robust assessment of relative clinical and cost effectiveness • Comparator(s) should reflect either the treatment that is most likely to be replaced by the new treatment or, in case of add-on treatments, the current treatment without the add-on product

	<ul style="list-style-type: none"> • Comparisons with treatments which are used off-label for the indication under evaluation are allowed only if they reflect common practice in the local setting
Systematic review	<ul style="list-style-type: none"> • Systematic review of the existing clinical studies on the intervention and comprehensive search of published economic studies: best available up-to-date evidence for clinical effectiveness of the technology and its cost-effectiveness relative to its comparator(s); ongoing studies should be mentioned • Reproducible search strategy • Transparent selection criteria and selection procedures • Critical appraisal and quality assessment of the evidence
Economic evaluation	<ul style="list-style-type: none"> • For treatments which are non-inferior (comparable effectiveness and safety) to the comparator(s), a cost-minimisation analysis (CMA) should be undertaken • Cost-effectiveness analysis (CEA) should only be carried out for full evaluations if the technology is clinically superior to, and more costly than the main comparator. CEA is not conducted for expedited evaluations. • CEA should be undertaken for full evaluations to establish whether differences in expected costs between treatment options can be justified in terms of changes in expected health effects • Cost-utility analysis (CUA) should be used in full evaluations if the treatment has an impact on health-related quality of life that is significant to the patient or if there are multiple patient-relevant clinical outcome parameters expressed in different units • Results expressed as incremental cost-effectiveness or cost-utility ratios with their associated upper and lower limits • If an incremental cost-utility ratio is presented as a base case result, corresponding cost per life-year gained should also be presented (if mortality benefits are shown) • Economic models should be based on data from clinical studies comparing the study treatment and the comparator, on data from validated databases and/or data from literature • 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.
Calculation of costs	<ul style="list-style-type: none"> • The identification, measurement and valuation of costs should be consistent with the perspective of the Singapore health-care payer (government, insurance provider and patient health costs) • Non-healthcare costs or unrelated healthcare costs should not be included in the reference case analysis, but are permitted in secondary analyses
Measuring and valuing health effects	<ul style="list-style-type: none"> • Final, clinically meaningful outcomes, preferably clearly defined outcome measures, for which there is little debate about the measurement methods • CEA: life years gained for chronic conditions and acute conditions with long-term sequelae or a relevant short-term outcome for acute conditions with no long term consequences • CUA: QALYs gained • Life expectancy estimates based on Singapore age-specific life tables

	<ul style="list-style-type: none"> • Health-related quality of life weights based on empirical data either from the literature or ideally from a representative sample of the general public in Singapore • Quality of life weights derived with generic instrument (e.g. EQ-5D)
Time horizon	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Costs and benefits are discounted at 3% • Other scenarios can be presented to test sensitivity of results to discount rate applied
Handling uncertainty	<ul style="list-style-type: none"> • 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
Budget impact analysis	<ul style="list-style-type: none"> • Budget impact analyses conducted for full evaluations should follow these principles: • Target population: The analysis should estimate the potential size of the target population and its potential evolution over time (e.g. shifts in incidence, prevalence, disease severity). The methods used to estimate the population size should be described and justified. The degree of penetration of the intervention in the targeted population (e.g. detection rate, compliance, market share etc.) needs to be considered and justified. • Comparator: The analysis should calculate the predicted financial impact of subsidising an intervention compared to the current situation • Costs and outcomes: Tariffs and prices should be kept constant over the years (i.e. not inflated). The cost consequences of the treatment effect, side effects and other short and long-term consequences (e.g. follow-up treatment) should be included in the analysis • Time horizon: The time horizon depends on the time needed to reach a steady state. It is recommended to present the budget impact up to the steady state, with a time horizon of three to five years. • Discount rate: Future costs and savings should not be discounted

6.1 Perspective of the evaluation

The reference case analysis should only include direct healthcare costs from the perspective of the healthcare payer. This includes payments out of the government's and insurance providers' healthcare budget as well as patients' co-payments. Health outcomes should also be valued from a healthcare payer perspective.

Costs and outcomes should be relevant for the patient population involved in the treatment and valued from a healthcare payer perspective. This includes costs paid out of the government's and insurance providers' healthcare budget and patients' co-payments for healthcare, including Medisave and out-of-pocket expenses.

The reference-case perspective on health outcomes aims to maximise health gain from available healthcare resources. If characteristics of a treatment have a value to people independent of any direct effect on health (for example, important reductions in the absence for work or productivity costs), the nature of these characteristics should be clearly explained and if possible the value of the additional benefit should be quantified (for consideration as secondary analyses only).

6.2 Target population and subgroups

The patient population should be consistent with that which is defined in the evaluation framework. If the clinical and/or cost-effectiveness of treatment differs between subgroups, separate subgroup analyses should be performed, provided that appropriate (statistical) justification is given.

The target population should be consistent with the population described in the evaluation framework (and/or scope) and in line with the population in the registered indication for the drug under evaluation unless off-label use is being considered (see section 2.2).

For many drugs, the capacity to benefit from treatment will differ for patients depending on their characteristics. This should be explored as part of the reference-case analysis by providing estimates of clinical and cost effectiveness separately for each relevant subgroup of patients. The characteristics of patients in the subgroup should be clearly defined and should preferably be identified on the basis of an expectation of differential clinical or cost effectiveness because of known, biologically plausible mechanisms, social characteristics or other clearly justified factors. When possible, potentially relevant subgroups will be identified when the evaluation framework is defined with consideration being given to the rationale for expecting a subgroup effect. However, this does not preclude the identification of subgroups later in the process.

6.3 Comparators

The drug should be compared with the most relevant alternative treatment for the condition under evaluation. This is either the treatment that is most likely to be replaced by the new treatment in local clinical practice or, in the case of add-on treatments, the current treatment without the add-on treatment. In some cases, multiple treatments will have to be included as comparators.

Comparisons with treatments which are used off-label for the indication under evaluation are allowed only if they reflect common practice in the local setting. The choice of the comparator(s) should always be justified.

Comparator(s) defined in the evaluation framework (and/or scope) should be used to allow a robust assessment of relative clinical and cost effectiveness.

The comparator can be another medical treatment, best supportive care, watchful waiting or doing nothing (no intervention).

When the comparator is a medical treatment, it should represent a treatment with proven efficacy that is used in established clinical practice in Singapore for the target indication. It may not necessarily be the comparator in the pivotal clinical trials. It is the treatment that most prescribers would replace with the new treatment if it became subsidised. Multiple comparators can be considered if relevant to local clinical practice.

In the case of an add-on treatment, the comparator is the current standard treatment in clinical practice without the add-on treatment.

The choice of the comparator should always be justified. Treatments which are used off-label in routine clinical practice in Singapore for the indication under evaluation can be considered as valid comparators in the economic evaluation.

6.4 Systematic review of clinical evidence

Each evaluation should include a systematic review of the existing clinical studies on the intervention. The search strategy should be reproducible and selection criteria and procedures clearly presented. The review should reveal the best available up-to-date evidence for clinical effectiveness of the drug relative to its comparator(s). The evidence should be critically appraised and its quality assessed.

Estimates of the mean clinical effectiveness of the treatments being compared must be based on data from all relevant studies of the best available quality and should consider the range of typical patients, normal clinical circumstances, clinically relevant outcomes, comparison with relevant comparators, and measures of both relative and absolute effectiveness with appropriate measures of uncertainty.

For a full overview of the clinical effectiveness of a drug, a systematic literature review should be conducted.

A systematic approach to literature searching ensures that:

- the literature is identified in accordance with an explicit search strategy
- the literature is selected on the basis of defined inclusion and exclusion criteria
- the literature is assessed using recognised methodological standards.

The methodology used for the literature search should be clear and reproducible. The search algorithm should be presented, including search terms used for each database and the study selection criteria. The search strategy should be developed in line with the evaluation framework and/or final scope.

Once the search strategy has been developed and literature searching undertaken, a list of possible studies should be compiled. Each study must be assessed to determine whether it

meets the inclusion criteria of the review. A list of ineligible studies should be produced with the justification for why studies were included or excluded. A flow diagram, specifying the yield and exclusions (with the reason for exclusion) should be presented. Each study meeting the criteria for inclusion should be critically appraised and have its quality assessed.

Randomised controlled trials (RCT) directly comparing the drug under evaluation with relevant comparators provide the most valid evidence of relative efficacy and safety. However, such evidence may not always be available and may not be sufficient to quantify the effect of treatment over the course of the disease. Therefore, data from non-randomised studies may be required to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented. The external validity of study results included in the review, and their applicability to local clinical practice in Singapore should be assessed.

Many factors can affect the overall estimate of relative treatment effects obtained from a systematic review. Some differences between studies occur by chance, others from differences in the characteristics of patients (such as age, sex, severity of disease, choice and measurement of outcomes), care setting, additional routine care and the year of the study. Such potential treatment effect modifiers should be identified before data analysis, either by a thorough review of the subject area, extrapolation from relevant studies, or discussion with experts in the clinical discipline.

6.4.1 Pairwise meta-analysis

Synthesis of outcome data through meta-analysis is appropriate provided there are sufficient relevant and valid data using measures of outcome that are comparable.

The characteristics and possible limitations of the data (that is, population, intervention, setting, sample size and validity of the evidence) should be fully reported for each study included in the analysis and a forest plot included.

Statistical pooling of study results should be accompanied by an assessment of heterogeneity (that is, any variability in addition to that accounted for by chance) which can, to some extent, be taken into account using a random (as opposed to fixed) effects model. However, the degree of, and the reasons for clinical and methodological heterogeneity should be explored as fully as possible. Known clinical heterogeneity (for example, because of patient characteristics) may be explored using subgroup analyses and meta-regression. If the risk of an event differs substantially between the control groups of the studies in a meta-analysis, an assessment of whether the measure of relative treatment effect is constant over different baseline risks should be carried out. This is especially important when the measure of relative treatment effect is to be used in an economic model and the baseline rate of events in the comparator arm of the model is very different to the corresponding rates in the studies in the meta-analysis.

6.4.2 Indirect comparisons and network meta-analyses

Data from head-to-head RCTs should be presented in the reference-case analysis. When treatments are being compared that have not been evaluated within a single RCT, data from a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis if appropriate. The DAC will take into account the additional uncertainty associated with the lack of direct evidence when considering estimates of relative effectiveness derived from indirect sources only. Transitivity (consistency between direct and indirect evidence) is also examined. The principles of good practice for standard pairwise meta-analyses should also be followed in adjusted indirect treatment comparisons and network meta-analyses.

Heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies should be reported. If inconsistencies within a network meta-analysis are found, then attempts should be made to explain and resolve them.

In all cases when evidence is combined using adjusted indirect comparisons or network meta-analysis frameworks, trial randomisation must be preserved, that is, it is not acceptable to compare results from single treatment arms from different randomised trials (also known as naïve indirect comparison). If this type of comparison is presented, the data will be treated as observational in nature and associated with increased uncertainty.

When sufficient relevant and valid data are not available to include in pairwise or network meta-analyses, the analysis may have to be restricted to a narrative overview that critically appraises individual studies and presents their results. In these circumstances, the DAC will be particularly cautious when reviewing the results and in drawing conclusions about the relative clinical effectiveness of the treatment options.

6.5 Economic evaluation

For treatments which are non-inferior (comparable effectiveness and safety) to their comparator(s), a cost-minimisation analysis (CMA) should be undertaken.

A cost-effectiveness analysis (CEA) should only be carried out for full evaluations if the technology is clinically superior to the main comparator. It should be undertaken to establish whether differences in expected costs between treatment options can be justified in terms of changes in expected health effects.

Cost-utility analysis (CUA) should be used if the treatment has an impact on health-related quality of life that is significant to the patient or if there are multiple patient-relevant clinical outcome parameters expressed in different units.

Results should be expressed as incremental cost-effectiveness or cost-utility ratios with their associated upper and lower limits. If an incremental cost-utility ratio is presented as a reference case analysis result, the corresponding cost per life-year gained should also be presented, if appropriate.

Economic models should be based as much as possible on data from clinical studies comparing the study treatment and the comparator, on data from validated databases and/or data from literature. Model inputs and outputs should be consistent with existing data and have face validity. 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.

6.5.1 Type of economic evaluation

For topics subject to expedited evaluation, the cost-effectiveness of the intervention relative to its comparator(s) is determined based on a comprehensive review of published literature. Cost minimisation analysis (CMA) is conducted by the ACE technical team for both expedited and full evaluations when relevant:

- **Cost-minimisation analysis (CMA)**

Cost minimisation analyses are used if the effects of two treatments are comparable. It considers that there is no net health change involved in moving from one treatment to another; hence cost-effectiveness decisions can be made on the basis of the difference in the total cost alone, i.e. the treatment with the lowest cost is considered the most cost effective option.

In addition to CMA, other evaluations, including CEA or CUA may be conducted by the ACE technical team for full evaluations.

- **Cost-effectiveness analysis (CEA)**

In cost-effectiveness analyses the outcome should be expressed in terms of life years gained, unless there are compelling arguments to use another physical or clinical outcome variable (e.g. in case of acute diseases without long-term sequelae). The result of a cost-effectiveness analysis is expressed as an incremental cost-

effectiveness ratio (ICER). The ICER reflects the additional (incremental) cost per additional unit of outcome achieved.

- **Cost-utility analysis (CUA)**

Cost-utility analysis is used for economic evaluations that include health-related quality of life in the assessment of treatment outcome. They should be undertaken if the treatment has an impact on health-related quality of life that is significant to patients or the treatment is associated with multiple clinical outcomes that are expressed in different units (e.g. side effects versus survival). Cost-utility is not relevant in all disease areas or treatment situations. For instance, very serious infections associated with a high short-term mortality rate but little quality of life consequences in survivors (e.g. pneumonia), it is more important to look at survival than to health-related quality of life and hence a cost-effectiveness analysis may be more appropriate.

Currently, the quality-adjusted life year (QALY) is considered to be the most appropriate generic measure of health benefit that reflects both mortality and health-related quality of life effects.

ICERs reported must be the ratio of expected additional total cost to the expected additional QALYs compared with alternative treatment(s).

6.5.2 Choice of modelling approach

Modelling provides an important framework for synthesising available evidence and generating estimates of clinical and cost effectiveness in a format relevant to the DAC's decision-making process (see section 9). Situations when modelling is likely to be required include those when:

- all the relevant evidence is not contained in a single trial
- patients participating in trials do not represent the typical patients likely to use the treatment in Singapore
- intermediate outcome measures are used rather than effect on health-related quality of life and survival
- relevant comparators have not been used or trials do not include evidence on relevant populations
- clinical trial design includes crossover (treatment switching) that would not occur in clinical practice
- costs and benefits of the treatment and comparator(s) extend beyond the trial follow-up period.

Different types of models can be used, the major categories being decision trees, Markov models, partitioned survival models and discrete event simulation models. The main principle is that a model should be kept as simple as possible while reflecting sufficient clinical reality, and that its internal structure should be consistent with proven or generally accepted relationships between parameters and health states. The more complex the model, the less likely it is that sufficient data are available to populate it.

Guidelines for good modelling practices have been developed by the modelling task force of ISPOR (<http://www.ispor.org/workpaper/healthscience/tfmodeling.asp>), which are followed by the ACE technical team whenever a model is required. Key considerations relating to the development of models are summarised below (sections 6.5.3 and 6.5.4).

6.5.3 Transformation of evidence

Economic evaluations should ideally be based on studies that report **clinically important outcome measures**. Surrogate measures should only be used where no alternative health outcome data are available. Caution should be used when using surrogate measures, as they may not necessarily translate into clinically relevant and effective outcomes. If there is uncertainty about the clinical significance of endpoints or the correlation between surrogate measure and clinical outcomes, conservative assumptions should be applied in the evaluation regarding their impact (short and/or long term) on survival and/or health-related quality of life. Where possible, clinical trials demonstrating superiority should be analysed using data from the intention-to-treat (ITT) population, rather than per protocol (PP), in order to take account of outcomes from all patients irrespective of whether they received treatment.

All statistically significant clinical events ($p < 0.05$) should typically be included in the economic evaluation. In some cases, clinical events that are considered statistically non-significant (with a p value larger than 0.05), may still be clinically significant and should be incorporated into the economic model because the magnitude of clinical relevance overrides the statistical aspects. Likewise, in some cases, a result considered to be statistically significant should not be used if it has no meaningful clinical effects.

The exclusion of any statistically significant event from the evaluation should be justified and the impact of including or excluding certain parameters should be tested in sensitivity analyses.

Data from clinical trials and other sources need to be translated into an appropriate form for incorporation into a model. Modelling may require:

- extrapolating data beyond the trial period to the longer term
- translating surrogate endpoints to obtain final outcomes affecting disease progression, overall survival and/or quality of life
- generalising results from clinical trials to the Singapore clinical setting
- using indirect comparisons where the relevant head to head trials do not exist.

The methodology, limitations, and any possible biases associated with extrapolating and incorporating data should be clearly described and explored through sensitivity analysis. In the absence of conclusive data, conservative assumptions should be applied in the economic evaluation and tested through sensitivity analyses.

6.5.4 Precision of model structure and hypotheses

The methods of quality assurance used in the development of the model should be described and the methods and results of model validation should be provided. All assumptions made in

the model should be documented and justified, and tested in the sensitivity analysis to show the robustness of the results.

The population for which outcomes are modelled should be specified. This may be a hypothetical population, but should be consistent with the target population for the drug and the sources used for valuing the modelling input parameters. All variables in the model and their sources must be documented.

Clinical trial data generated to estimate treatment effects may not sufficiently quantify the risk of some health outcomes or events for the population of interest or may not provide estimates over a sufficient duration for the economic evaluation. The methods used to identify and critically appraise sources of data for economic models should be stated and the choice of particular data sets should be justified with reference to their suitability to the population of interest in the evaluation. Preference is given to peer-reviewed publications or primary data as the source for the input parameters' values.

Sources used for valuation of costs and assessment of probabilities should also be presented and described in detail.

If no published evidence is available, expert panel consultation is an acceptable source of input; however the need for using expert opinion should be well justified, and the number of experts consulted and their field of expertise should be documented.

Abstracts and oral presentations usually provide insufficient information to assess the quality of their contents. They should be avoided as a source for input values.

For models that extrapolate to longer time periods, such as for chronic conditions or diseases with long-term sequelae, the assumptions used to extrapolate the impact of treatment over the relevant time horizon should have both external and internal validity and be reported transparently. The external validity of the extrapolation should be assessed by considering both clinical and biological plausibility of the inferred outcome as well as its coherence with external data sources such as historical cohort data sets or other relevant clinical trials. Internal validity should be explored and when statistical measures are used to assess the internal validity of alternative models of extrapolation based on their relative fit to the observed trial data, the limitations of these statistical measures should be documented. Alternative scenarios should also be routinely presented to compare the implications of different extrapolation approaches on the results.

The scenarios should all be presented as part of the reference case analysis. By presenting different, sometimes extreme, scenarios, the uncertainty related to the effectiveness of the treatment in the extended period can be assessed. The presentation of scenarios is the most transparent way to show how robust the results are to the extrapolation approach used. Each scenario should be accompanied by appropriate sensitivity analyses on uncertain parameters.

In randomised controlled trials, participants randomised to the control group are sometimes allowed to switch treatment group and receive the active intervention. In these circumstances, when intention-to-treat analysis is considered inappropriate, statistical methods that adjust for treatment switching can also be presented. Simple adjustment methods such as censoring or excluding data from patients who crossover should be avoided because they are very

susceptible to selection bias. The relative merits and limitations of the methods chosen to explore the impact of switching treatments should be explored and justified with respect to the method chosen and in relation to the specific characteristics of the data set in question. These characteristics include the mechanism of crossover used in the trial, the availability of data on baseline and time-dependent characteristics, and expectations around the treatment effect if the patients had remained on the treatment to which they were allocated.

6.6 Measuring and valuing health effects

The measure of health outcome should capture positive and negative effects on length of life and quality of life and should be generalisable across disease states.

For cost-utility analyses, health effects should be expressed in quality adjusted life years (QALYs). The measurement of changes in health-related quality of life should be reported directly from patients and the utility of these changes should be based on public preferences using a generic instrument, such as EQ-5D.

For cost-effectiveness analyses, outcomes should be expressed in terms of life years gained for chronic conditions and acute conditions with long-term sequelae or a relevant short-term outcome for acute conditions with no long-term consequences.

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 all comparators. 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 2 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]). When it is not possible to obtain measurements of health-related quality of life directly from patients, data should be obtained from the person who acts as their carer in preference to healthcare professionals. The valuation of health-related quality of life (which leads to the calculation of utility values) should be based on empirical data, obtained with a descriptive system for health status for which corresponding preference values exist from the general public. The use of Singaporean preference values is preferred if available.

Utility values should be derived with a generic instrument (such as EQ-5D). A summary of valid and reliable instruments which are used widely in economic evaluations is shown in Table 7.

Table 7. Generic instruments as measures of utility

Instrument	Overview
EQ-5D-5L	<p>Description: The EQ-5D classification system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), with each dimension being subdivided into 5 levels (no problems, slight problems, moderate problem, severe problems and extreme problems); the profile system comprises 3125 possible health states. In the EQ-5D questionnaire, the patient describes his or her own current health status in relation to the 5 dimensions and then on a visual analogue scale (VAS) with endpoints of 0 (worst health state) and 100 (best health state); the information can be compared over time for the same patient before and after treatment, with data from other patients or from the general population.</p> <p>Index score: Where EQ-5D is used as a utility measure, patients' responses about their own health over time are collected and then each health state is assigned an index score using population based preference values for the 3125 possible health states. Preference values are based on time trade-off and VAS rating methods.</p> <p>Use: EQ-5D is self-completed by the patient and takes only a few minutes to complete. The instrument is recommended for cost-effectiveness analysis in both the USA (Washington Panel on Cost Effectiveness in Health & Medicine) and the UK (National Institute for Health and Care Excellence, NICE). There is no copyright on EQ-5D, but users are expected to register their study on the EuroQol Group's website, which also provides information on the instrument's use, alternative versions (e.g. telephone/proxy versions, translations, child version) and publications; http://www.euroqol.org.</p>
SF-36	<p>Description: SF-36 was developed as a profile measure and comprises 36 items, which are subdivided into 8 dimensions: physical function, role limitation due to physical problems, bodily pain, general health perception, energy/vitality, social functioning, role limitation due to emotional problems, and mental health. The answers to the questions in the original version vary from dichotomous (yes/no) to 6-point Likert scales. Scores are calculated for each of the 8 dimensions, and they can be transformed on a scale from 0 to 100 by summing the answers under each dimension; a higher score indicates a better health status. Scores on the 8 dimensions can be further summed as a physical (PCS, Physical Component Summary) and a mental (MCS, Mental Component Summary) component.</p> <p>Index score: An index measure (SF-6D) has been developed using standard gamble values to describe health status on the basis of six of the original dimensions.</p> <p>Use: SF-36 is self-completed by the patient and takes about 10 minutes. There is copyright on the use of the SF instruments; see http://www.qualitymetric.com.</p>
HUI Mark 3	<p>Description: The 8 dimensions in HUI3 are vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain; in total, 972,000 health states are described.</p> <p>Index score: HUI3 can be used as a utility measure. The scoring system uses multiplicative multi-attribute utility functions (MAUFs), where preference values based on the standard gamble method have been generated among the general population in Hamilton, Ontario.</p> <p>Use: HUI3 has been included in all major health studies of the Canadian population since 1990. There is copyright on the use of the HUI instruments; see http://www.fhs.mcmaster.ca/hug/.</p>
AQoL	<p>Description: The Assessment of Quality of Life (AQoL) instruments (4D, 6D, 7D, 8D) are multi-attribute tools covering 4, 6, 7 or 8 dimensions from the following: independent living, mental health, relationships, senses, coping, pain, happiness, self-worth, and visual impairment.</p>

	<p>Scores from the dimensions provide a health profile, but the primary purpose of the instrument is to provide a utility index for quality of life.</p> <p>Index score: AQoL preference values are calculated without the “illness” dimension and are based on <i>multi</i>-attribute utility theory. Within each dimension, each level is assigned a preference value, which is obtained from a random sample taken from the general (Australian) population; these values are then combined in dimension scores, which are also combined.</p> <p>Use: As AQoL is relatively new, experience with the instrument is limited. Nevertheless, there have been a number of comparative studies of AQoL and other utility measures. Use of AQoL is free of charge; users are asked to register their study; see http://www.psychiatry.unimelb.edu.au/qol/aqol/use_aqol.html</p>
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Scenarios with validated disease-specific measures for health-related quality of life can be presented as supplementary analyses. A disease-specific measure limits the ability of the DAC to make reasoned trade-offs between competing investments in different disease states, and can undermine comparability and consistency in decision-making, therefore it should not be used in the reference case.

Life expectancy estimates should be based on age-specific life tables for Singapore. These data are available at the Department of Statistics Singapore (<https://www.singstat.gov.sg>).

If not available in the relevant clinical trials, utility data can be sourced from the literature. When obtained from the literature, the methods of identification of the data should be systematic and transparent. The justification for choosing a particular data set should be clearly explained. When more than 1 plausible set of utility data is available, sensitivity analyses should be carried out to show the impact of the alternative utility values.

Mapping valuations from other health-related quality of life instruments (e.g. disease-specific instruments or another generic instrument) to EQ-5D public preference values is only recommended if mapping functions are based on and validated with empirical data. The mapping function chosen should be based on data sets containing both health-related quality of life measures and its statistical properties should be fully described, its choice justified, and it should be adequately demonstrated how well the function fits the data. Sensitivity analyses to explore variation in the use of the mapping algorithms on the outputs should be presented.

6.7 Measurement of costs

The identification, measurement and valuation of costs should be consistent with the perspective of the Singapore healthcare payer (government, insurance provider and patient). Non-healthcare costs or unrelated health care costs should not be included in the reference case analysis.

Validated sources should be used for the unit costs. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.

The perspective for the cost calculation is that of the healthcare payer (government, insurance provider and patient). Valuation of resource use in monetary units must be consistent with the perspective of the analysis and should only include costs from Singapore. The types of direct costs that are included in ACE's economic evaluations are shown in Table 8.

All differences between the intervention and the comparator in expected resource use for the target population(s) should be incorporated in the evaluation. Costs that are the same in both treatment arms can be validly excluded if there is no significant differences in mortality rates or time periods between treatments.

Table 8. Direct costs included in ACE's evaluations

Type of costs	Resource consumption
Drug/Treatment	Community and hospital medicines
Hospital inpatient	Diagnosis, treatment and/or procedures, hospital capital costs, depreciation and overheads (collectively captured through DRGs) ¹
Hospital outpatient	Laboratory services and diagnostics; healthcare professional consultations, hospice visits, treatment administration costs, costs of managing adverse events
Direct patient healthcare (in primary healthcare setting)	General practitioner visits, pharmaceutical co-payments, home or continuing care

The selling price to patient (before any subsidy or insurance coverage is applied) for treatments based on the registered dose should be used in the reference-case analysis. In cases where the registered dose does not reflect current clinical practice in Singapore, the dose should be based on that which is used in routine clinical practice, providing there is evidence of efficacy at the proposed dose.

Importance should be placed on the transparency, reasonableness and reproducibility of cost estimates so that the DAC can assess whether the costs reflect local resource use.

Costs to non-healthcare sectors and indirect healthcare costs should not be included in the evaluations. Indirect patient costs, which relate to lost productivity of the patient due to

¹ Diagnostic Related Groups (DRGs) are a hospital patient classification system that provide data relating to the number and types of patients treated in a hospital to the resources required by the hospital.

treatment, illness or death, of that of family members due to time off work for caring, should not be included in the reference–case analysis, but can be considered as supplementary evidence, if justifiable.

6.8 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.

The time horizon of the economic evaluation should be in concordance with the period over which the main differences in costs and health consequences between the treatment and the comparator are expected. Health consequences include intended as well as unintended consequences (e.g. side effects).

A lifetime time horizon is required when alternative treatments lead to differences in survival or benefits that persist for the remainder of a person's life. For a lifetime time horizon, it is often necessary to extrapolate data beyond the duration of the clinical trials and to consider the associated uncertainty. When the impact of treatment beyond the results of the clinical trials is estimated, analyses that compare several alternative scenarios reflecting different assumptions about future treatment effects using different statistical models are desirable. These should include assuming that the treatment does not provide further benefit beyond the treatment period as well as more optimistic assumptions. In addition, sensitivity analyses should be conducted to evaluate the extent to which changes to the length of the time horizon impact the base case ICER.

Sometimes a shorter time horizon may be justified, for example, when evaluating very acute diseases with no differential mortality or long-term morbidity effect between treatment options and the differences in costs and health-related quality of life relate to a relatively short period. If a shorter time horizon is chosen, this should be substantiated with clear arguments.

The time horizon should never be determined by the length of time for which evidence is available. Where data are not available to inform an appropriate time period, some projection of costs and outcomes into the future will be required.

6.9 Discount rate

Future costs and benefits should be discounted at a rate of 3%. To assess the sensitivity of the results to the discount rate applied, different scenarios can be presented in sensitivity analyses.

Incremental cost-effectiveness ratios (ICERs) should be presented in present values. This means that future costs and benefits should be discounted to reflect the lower value given to future costs and benefits. The choice of the discount rate for costs and benefits is based on the return on risk-free government bonds, which are currently about 3% in Singapore. Rates

of 0% and 5% should be used in sensitivity analyses to test the impact of the chosen discount rate on the ICER.

6.10 Calibration, face-validity and cross-validation of a model

The results of the model should be logically consistent with real-life observations and data (calibration). For example, if age-specific incidences of a disease are used in a model, the total incidence generated by the model should not considerably be higher or lower than the observed incidence in the population, unless the difference can be explained by differences in the population structure. In other words, there must be a logical connection between inputs and outputs of a model.

The results of the model should be intuitively correct, that is, the model should have face-validity. The model description should be transparent enough to allow an explanation of the differences with other models for the same interventions (cross-validation).

The presentation of the results of an economic model as a point estimate together with its appropriate uncertainty range is an absolute prerequisite. An economic model is by definition subject to uncertainty. The results are conditional upon the input data and the assumptions applied in the model. Both the uncertainty about the input data and the assumptions generate uncertainty in the outputs. This uncertainty should be appropriately presented, as the level of uncertainty might be an element in the decision-making process.

6.11 Handling uncertainty and testing robustness of results

All economic evaluations reflect a degree of uncertainty and it is important that all types of uncertainty are appropriately described. These include uncertainty about the source of parameters used in the economic evaluation, the precision of the parameters, and whether models accurately simulate the cost and effects of the intervention and comparators.

Uncertainty surrounding cost-effectiveness estimates should be analysed using appropriate statistical techniques. At a minimum, one-way sensitivity analysis should be presented for each uncertain parameter in the economic evaluation.

Multivariate probabilistic sensitivity analysis may also be performed to address simultaneous impact of all uncertain parameters.

Results and conclusions from economic evaluations are subject to various degrees of uncertainty, which typically is divided into three broad areas:

- Model uncertainty – which includes structural and methodological uncertainty due to the analytical methods chosen to perform the evaluation
- Parameter uncertainty, which includes data uncertainty due to variability in sample data or from uncertainty ranges chosen for non-sample data and uncertainty relating to the variability between patients (heterogeneity) and the generalisability of the study results to other populations and/or other contexts.

- Stochastic uncertainty – which includes the random variability in outcomes between identical patients.

A summary of possible forms of uncertainty in economic evaluations and appropriate methods to address them is presented in the table below (Table 9).

Table 9. Summary of types of uncertainty encountered in economic evaluations

Parameter Uncertainty	Data inputs	Do the point estimates reflect the true values of the parameters? Data uncertainty applies to trial-based economic evaluations as well as to models. In trial-based economic evaluations, statistical analyses can be used to estimate the uncertainty around individual cost and effects data due to choice of data sources and sampling variability. Detailed descriptive statistics, showing the distribution and variability of costs and effects data, should be presented.
	Sample data	Variability of sample data can increase uncertainty. Various samples taken from the same population can result in different data for resource consumption and outcomes.
	Extrapolation	Uncertainty caused by extrapolation from intermediate to final outcomes and uncertainty from extrapolation beyond the study's time horizon.
	Generalisability	Can the results from the study population and the geographical location(s) of the study be applied generally to other populations and locations? Are the results from the study generalisable to daily clinical practice in the local Singapore context?
Model Uncertainty	Analytical methods	Choice of different analytical methods can lead to uncertainty about the results and conclusions. Methodological uncertainty should be tested using scenario analysis.
	Model structure	Uncertainty relating to the structural assumptions used in the analysis should be clearly documented and the evidence and rationale to support them provided. Examples of structural uncertainty may include how different health states are categorised and how different pathways of care are represented in the model. The impact of the structural uncertainty on cost effectiveness estimates should be explored by separate analyses of a representative range of plausible scenarios.

Despite such uncertainties in the evidence base, decisions still have to be made about the use of treatments. Sensitivity analysis is the process by which the robustness of an evaluation is assessed by examining changes in the results when key parameters are varied. If the result does not change when assumptions, parameters, etc. are varied, the result is said to be robust and reliable. The characterisation of uncertainty enables the DAC to make a judgement based not only on a likely estimate of the incremental costs and effects of an intervention, but on the confidence that those costs and effects represent reality.

One-way sensitivity analysis should be conducted for all economic evaluations, to help determine the importance of the different assumptions and modelling parameters (such as price of the drug and the discount rate for costs and outcomes) on the results. Probabilistic sensitivity analyses may be conducted but are not a mandatory requirement to inform DAC's decision-making.

6.12 Budget impact

The following principles apply to budget impact analyses conducted for **full evaluations**:

Target population: The analysis should estimate the potential size of the target population and its potential evolution over time (e.g. shifts in incidence, prevalence, disease severity). The methods used to estimate the population size should be described and justified. The degree of penetration of the intervention in the targeted population (e.g. detection rate, compliance, market share etc.) needs to be considered and justified.

Comparator: The analysis should calculate the predicted financial impact of subsidising an intervention compared to the current situation.

Costs and outcomes: Tariffs and prices should be kept constant over the years (i.e. not inflated). The cost consequences of the treatment effect, side effects and other short and long-term consequences (e.g. follow-up treatment) should be included.

Time horizon: The time horizon depends on the time needed to reach a steady state. It is recommended to present the budget impact up to the steady state, with a minimum time horizon of three years.

Discount rate: Future costs and savings should not be discounted.

Budget impact analyses are conducted from the healthcare payer perspective for full and expedited evaluations to determine the affordability of the drug under evaluation (for government, insurance provider and patients). For topics subject to **expedited evaluation**, the projected cost to government for subsidising the drug on SDL or MAF is estimated based on current and projected drug utilisation volumes from public healthcare institutions, sales data projections from manufacturers, and clinical expert opinion. Where a price discount is offered by the manufacturer through the value-based pricing process (see section 8), multiple budget impact scenarios, using current and discounted prices, may be presented to DAC to inform their subsidy deliberations.

For topics subject to **full evaluation**, budget impact models are developed by the ACE team, using either an epidemiological or market share approach depending on the robustness of the prevalence and/or utilisation data available to inform the analysis. An epidemiological approach is usually preferred for generating utilisation and financial estimates if the evaluation indicates a superior therapeutic conclusion. A market share approach is often used if the evaluation suggests a non-inferior therapeutic conclusion. The aim of the analysis is to provide the most likely uptake of the drug in clinical practice if subsidy is recommended, and the cost impact to the government budget. Typically budget impact analyses are conducted over a 3-5 year period and take the following considerations into account (Table 10).

Table 10. Parameters considered in budget impact analyses for full evaluations

Parameter	Considerations
Target population	<ul style="list-style-type: none"> Population should be consistent with that defined in the evaluation framework and/or scope. Subgroup analyses can be performed if there is appropriate justification. The 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 subsidy of the drug. Diagnosis rates in line with local clinical practice should also be taken into account when defining the proportion of patients who are likely to receive treatment.
Comparators	<ul style="list-style-type: none"> Comparator treatments should be consistent with those defined in the evaluation framework and/or scope. Changes in comparator market share over time following subsidy of the drug under evaluation should be modelled and varied in sensitivity analyses.
Costs	<ul style="list-style-type: none"> Only direct healthcare costs should be considered. Indirect costs should not be included. The cost consequences of the treatment effect, side effects and other short and long term consequences (e.g. follow-up treatment) should be included. Any resource costs related to the use of the drug (including staff training, need for companion diagnostics etc) should be included.
Handling uncertainty	Sensitivity analyses should be performed on key parameters to model their impact on the results.
Discount rate	No discount rate should be applied

In instances where manufacturers choose to submit costing information as part of their evidence submission (for full evaluations) to ACE, relevant information will be incorporated into ACE’s budget impact analyses.

7. Independent Evidence Review Centres (IERC)

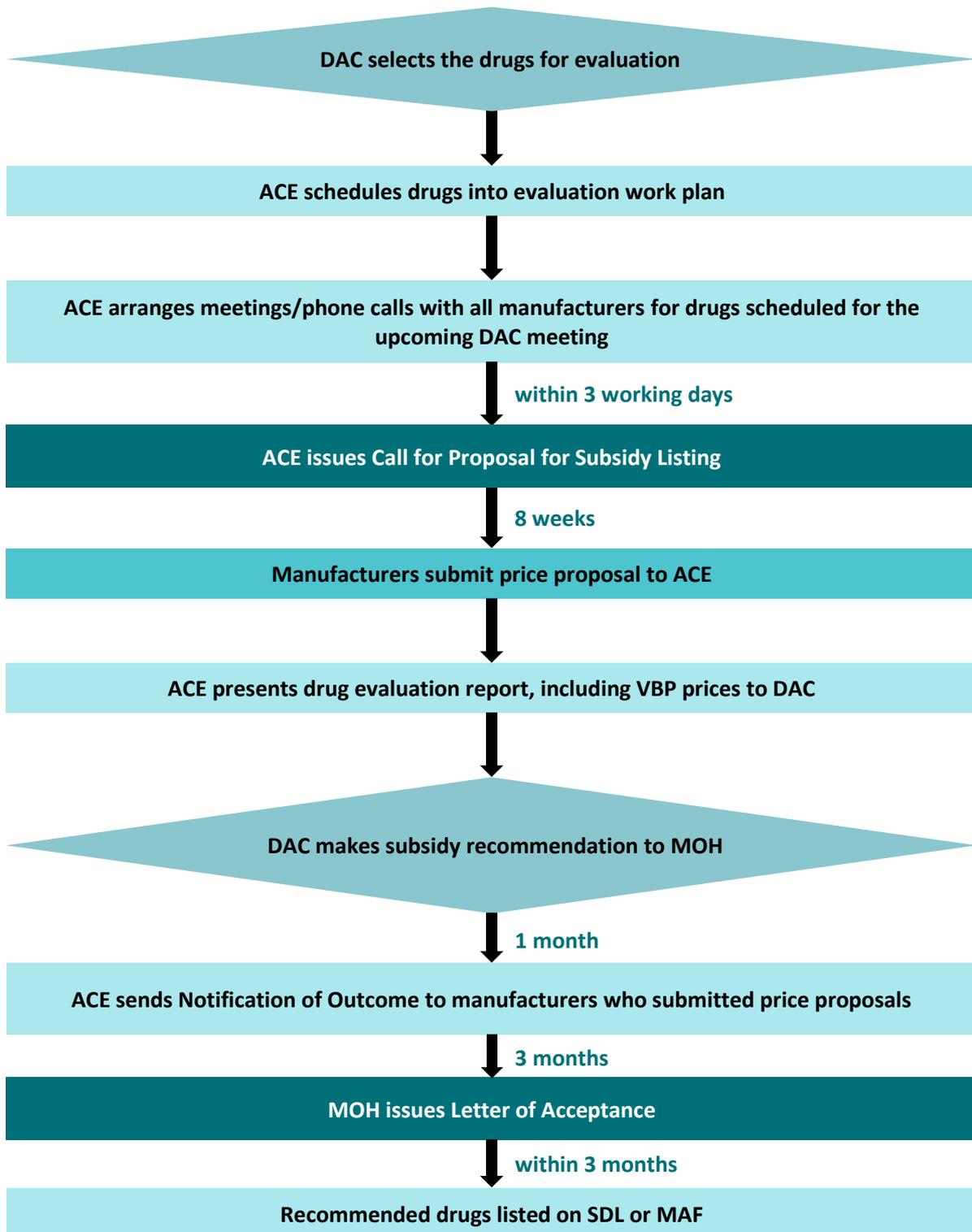
Independent academic centres from overseas institutions which have experience in conducting and appraising HTAs for drug subsidy decision-making are consulted to review and critique ACE’s evaluation report and accompanying economic model for **full evaluations**. Expedited evaluations (which do not require economic modelling), are not subject to external review. Review centres are typically given 4-6 weeks to critique ACE’s evaluations, depending on the complexity of the evaluation, and their comments and suggested amendments are incorporated into the final report for DAC’s consideration.

8. Value-Based Pricing

Value-based pricing (VBP) is conducted in parallel with drug evaluations to ensure that the price of patented drugs recommended for subsidy is commensurate with the drugs’ value in Singapore’s context. The process enables ACE to engage in discussions with manufacturers to determine the price at which the drug best represents a cost-effective use of healthcare resources. VBP is conducted for all drugs, including biosimilars, evaluated by ACE, unless

there are generic formulations registered in Singapore. An overview of the VBP process is shown in Figure 4.

Figure 4. Value-based pricing process



8.1 Request for Proposal (RFP)

The 'Call for Proposal for Subsidy Listing' (Annex 3) invites manufacturers to submit their best cost prices (i.e. the prices at which the manufacturers sell to the hospitals) for their drugs which are being evaluated for subsidy consideration. Manufacturers are also required to provide additional sales information, such as the current cost prices of their drug to each public healthcare institution, the number of units sold in the last 12 months to public patients, and details of any existing patient access programmes operated in Singapore.

The deadline for submission of the RFP is 8 weeks. Any request for an extension, is considered exceptional, and is subject to approval by Head of Evaluation, ACE on a case by case basis. The tenure of the RFP validity is 12 months, on balance of acceptability to manufacturers, as well as the meeting schedule of the Committee.

Proposed prices from the RFP are used to inform ACE's drug evaluation including cost-effectiveness analyses (where applicable) and budget impact assessments. In instances where a manufacturer is required to submit more than one RFP during the course of the evaluation, any new proposal submitted shall supersede previous proposals.

8.2 Notification of Outcome

The Notification of Outcome (NOO) email provides early notice of the DAC's recommendations, within 1 month after each DAC meeting, to allow time for downstream stock supply and inventory management.

It is sent to **all manufacturers** who submitted price proposals. Each manufacturer is only informed of the outcome for their drug. This notification is strictly **confidential** in nature. Manufacturers are not allowed to disseminate the information until the subsidy implementation date.

8.3 Letter of Acceptance

The Letter of Acceptance, that specifies the price and conditions of listing on SDL or MAF, is issued 4 months after the NOO to the **manufacturers of drugs with positive subsidy decisions**.

This is a legally binding agreement, signed by the Permanent Secretary (Health), for and on behalf of the Government of the Republic of Singapore, represented by the Ministry of Health, whereby:

- The manufacturer undertakes to sell the drug at a price not exceeding the VBP negotiated price agreed upon for subsidy listing when supplying the drug to the public healthcare institutions, and
- MOH lists the drug on SDL or MAF.

This agreement sets the cost-effective price for subsidy listing, and provides traction against price increases for a subsidised drug. Any drugs listed on SDL or MAF may be reviewed

periodically, whereupon MOH may revoke or extend the listing, or vary the conditions of listing, at its discretion.

8.4 Resubmission of price proposal in response to negative recommendations

Manufacturers are expected to provide their best and final prices for subsidy consideration of their drug in the RFP. Immediate resubmission of a price proposal for drugs which have not been recommended for subsidy is **not allowed**.

To provide a platform for manufacturers who wish to resubmit prices for DAC's consideration following negative recommendations made **on the basis of uncertain or unacceptable cost-effectiveness or budget impact**, a resubmission form will be sent to all manufacturers that have partaken in the VBP process but have not been successful in securing an SDL or MAF listing for their drugs. The resubmission period is aligned to the annual drug application cycle (January to March each year. See section 2.1). Manufacturers will only be given **one** opportunity to submit a revised pricing proposal for their drugs which received negative recommendations during the previous year. Revised pricing proposals will be scheduled for DAC's consideration depending on the timing of existing procurement agreements between manufacturers and public healthcare institutions for the drug under evaluation and/or its comparators.

8.5 Consideration of "me-too" drugs

Once the first drug in a class is listed on SDL or MAF, **one** additional me-too drug (with same formulation and indication as first drug) may be added, **no earlier than 12 months after** the first drug was listed if its price is considered reasonable by DAC and there is sufficient clinical need for an additional drug to be subsidised. A third drug within the class will only be considered for subsidy on an exceptional basis if it offers substantial benefits over existing subsidised drugs within the class.

If the first drug within a class is currently listed on SDL or MAF but has not been subject to a formal ACE technical evaluation previously, and a me-too drug is scheduled for evaluation, ACE will conduct a class review which includes the requested drug as well as the drug(s) which is already subsidised from the same class. All manufacturers included in the class review will be invited to submit a price proposal (section 8.1) to seek listing or to retain listing of their products. In the event that the existing drug(s) on SDL or MAF is not considered cost-effective on the basis of ACE's evaluation, and offers no additional clinical benefit over other drugs within the class, the DAC may recommend replacing it with other me-too drugs. Drugs which are no longer listed on SDL or MAF for a particular indication will not be considered for re-listing for **at least 3 years**.

8.6 Consideration of biosimilars

Biosimilars will not automatically be subsidised even if their reference products are already on SDL or MAF. All biosimilars are expected to lead to better patient affordability and access and will be subject to a technical evaluation by ACE which will be presented to the DAC to inform their subsidy deliberations. As part of the evaluation, the manufacturers will be invited to submit a price proposal.

On the basis of evidence presented, the DAC may recommend listing no more than one molecule (reference biologic or biosimilar) on a case by case basis. Public healthcare institutions will be informed and given sufficient time to implement the required changes.

9. Decision-making

9.1 MOH Drug Advisory Committee (DAC)

The DAC is an expert committee comprising of 13 senior clinicians from public healthcare institutions, and 1 senior healthcare finance representative from MOH. It is chaired by the MOH Director of Medical Services (DMS). Members are appointed for a 3-year term by the Chairman and may be re-appointed to serve for more than one term.

The DAC is responsible for providing evidence-based advice to MOH so that decisions for public funding of drugs are made in an equitable, efficient and sustainable manner.

The terms of reference of the DAC are:

- To prioritise drug applications, which hold potential for driving significant improvement in health outcomes
- To appraise the effectiveness of drugs based on specific therapeutic, clinical and pharmaco-economic evidence
- To provide drug listing recommendations to the Ministry of Health, including conditions and/or criteria for subsidy

The DAC meets 3 times a year; additional meetings may be called by the Chairman where necessary. A minimum of two-thirds attendance is required for a quorum. ACE drug evaluation reports and pertinent information for the meeting discussion are provided to DAC members at least 2 weeks before the meeting date.

9.2 Factors informing subsidy decisions

The DAC makes subsidy recommendations informed by ACE's drug evaluations. When forming recommendations, four core decision-making criteria are considered for each evaluation:

- Clinical need of patients and nature of the condition
- Clinical effectiveness and safety of the technology

- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives
- Estimated annual drug cost and the number of patients likely to benefit from treatment

Specific factors and judgments which should be deliberated when considering each criterion are described in Table 11.

Table 11. MOH Drug Advisory Committee decision-making framework

Core Criteria	Factors considered	Judgement will also take account of:
Clinical need of patients and nature of the condition	<ul style="list-style-type: none"> • Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on patients' quality of life • Extent and nature of current treatment options 	<ul style="list-style-type: none"> • The nature and quality of the evidence and the views expressed by clinical specialists on the experiences of patients with the condition and those who have used the technology. • Uncertainty generated by the evidence and differences between the evidence submitted for licensing (from clinical trials) and that relating to effectiveness in clinical practice. • The possible differential benefits or adverse outcomes in different groups of patients. • The balance of clinical benefits and risks associated with the technology. • The position of the technology in the overall pathway of care and the alternative treatments that are established in clinical practice
Impact of the new technology	<ul style="list-style-type: none"> • Comparative clinical effectiveness and safety of the technology • Overall magnitude of health benefits to patients • Heterogeneity of health benefits within the population • Relevance of new technology to current clinical practice • Robustness of the current evidence and the contribution the guidance might make to strengthen it 	
Value for money (Cost effectiveness)	<ul style="list-style-type: none"> • Technical efficiency (the incremental benefit of the new technology compared to current treatment) 	<ul style="list-style-type: none"> • Robustness of costing and budget impact information • Out of pocket expenses to patients • Key drivers of cost-effectiveness • Uncertainties around and plausibility of assumptions and inputs in the economic model • Any specific groups of people for whom the technology is particularly cost effective • Any identified potentially significant and substantial health-related benefits that were not included in the economic model • Existing or proposed value-based pricing arrangements
Cost of the technology and the estimated number of patients likely to benefit	<ul style="list-style-type: none"> • Projected cost to healthcare payer (Singapore government, insurance provider and patient) 	

Additional factors, including social and value judgments, may also inform the DAC's subsidy considerations.

The DAC has the discretion to take account of the full range of clinical and economic evidence available, including RCTs, non-randomised studies and qualitative evidence related to the

experiences of healthcare professionals who have used the drug or are familiar with the condition under evaluation.

The impact of the various types of evidence on decision-making depends on the quality of the evidence, its generalisability to Singapore clinical practice, the level of uncertainty surrounding the clinical and cost estimates, and the suitability of the evidence to address the drug topic under evaluation. In general, the DAC places greater importance on evidence derived from high-quality studies with methodologies designed to minimise bias.

The DAC does not use a precise maximum acceptable ICER above which a drug would automatically be defined as not cost effective or below which it would (i.e. an ICER threshold). ICERs are not precise values and are associated with a degree of uncertainty. Therefore, the DAC considers the upper and lower limits of the ICER range, in addition to the base-case point estimate when determining whether a drug represents good value for money.

On the basis of the available evidence, the DAC recommends whether a drug should receive subsidy through listing on the Standard Drug List (SDL) or the Medication Assistance Fund (MAF) (Table 12). It may recommend the use of a drug in line with the full indication under evaluation, or for a subgroup of the population, if:

- there is clear evidence that the drug is likely to be more clinically and/or cost effective in the subgroup, and
- the characteristics defining the subgroup are easily identifiable or routinely measured in clinical practice.

Table 12. Types of recommendations made by DAC

Decision	Type of Recommendation
Drug provides similar or greater benefits at a similar or lower cost than the comparator(s)	Recommended
Drug provides less health benefit at a similar or greater cost than the comparator(s) OR Drug provides similar health benefits at a greater cost than the comparator(s)	Not Recommended

10. Guidance Development and Implementation

10.1 Drafting of guidance

Following the DAC meeting, the ACE technical team draft a guidance document for each topic to outline the subsidy recommendation(s), DAC's rationale for the decision, and a brief summary of the key clinical and economic evidence which informed the DAC's deliberations.

For full evaluations, where an economic model is developed by ACE, actual base case ICERs are not reported in the guidance due to commercial sensitivities regarding pricing information. Instead a range is described as follows:

- Below \$15,000/QALY gained
- \$15,000 to <\$45,000/QALY gained
- \$45,000 to <\$75,000/QALY gained
- \$75,000 to \$105,000/QALY gained
- Above \$105,000/QALY gained

The annual cost to government for subsidising the drug under evaluation is also presented in ranges, as follows:

- <\$1 million
- \$1 million to <\$3million
- \$3 million to <\$5 million
- >\$5 million

The guidances are typically published on ACE's website (www.ace-hta.gov.sg) three times per year, when subsidy is implemented.

10.2 Implementation of guidance

Subsidy implementation for recommended drugs typically occurs within 4 to 6 months after each DAC meeting once financing is approved by the Ministry of Health. To assist with the smooth adoption of the recommendations, ACE communicates subsidy decisions to public healthcare institutions after each DAC meeting to allow sufficient time for them to prepare for implementation, including making changes to their hospital formularies and procurement processes, if necessary.

For subsidy decisions which are contingent on specific drug prices agreed with the manufacturer through the value-based pricing process, public healthcare institutions will be instructed to purchase the drug through the SingHealth Group Procurement Office (GPO), and adhere to a recommended maximum selling price. This ensures that the savings generated from price discounts offered by the manufacturer are passed onto the patients.

To monitor the impact of ACE guidance, MOH will track the utilisation of subsidised drugs, in addition to procurement and selling prices at each institution. Where required, educational

audits will be conducted in the institutions by MOH to improve adherence to the guidance recommendations.

10.3 Review of guidance and subsidy recommendations

Each guidance will be considered for review 3 years after publication. At that time, the ACE technical team will undertake a literature search to determine whether any new clinical evidence or cost information have been published which are likely to have a material effect on the subsidy decision and guidance recommendations.

Where considerable clinical and/or cost information has been published, the topic will be scheduled into the ACE work plan for re-evaluation as a full or expedited topic, depending on the amount of new evidence that has become available. The process for full or expedited evaluations will be followed for all topics subject to re-evaluation. Following DAC's consideration of the new evidence, the existing guidance may remain the same, or be revised, depending on the DAC's recommendations.

For topics where a drug has not been recommended for subsidy due to cost-effectiveness or budget impact considerations, and negative guidance has been published, manufacturers are able to request for the DAC to reconsider their product at a revised price during the annual resubmission period (see section 8.4 for information on price proposal resubmissions). If the DAC recommends a drug for subsidy on the basis of the revised pricing proposal, existing ACE guidance will be updated to include the new recommendations.

Annex 1: Company evidence submission template for full evaluations

Instructions for companies

This is the template for submission of evidence to the Agency for Care Effectiveness (ACE) as part of the **full evaluation process** for drugs. It is not mandatory for companies to complete an evidence submission. The topic will still be evaluated by the ACE technical team and presented to the MOH Drug Advisory Committee (DAC) to inform subsidy considerations, irrespective of company involvement. Any evidence provided by the company will be incorporated into ACE's evaluation. Following appraisal by the MOH Drug Advisory Committee, in most instances for patented drugs, subsidy through the Medication Assistance Fund (MAF) is considered. Less often, a patented drug may be considered for listing on the Standard Drug List (SDL).

Text highlighted in grey is intended to inform companies about the type of information to include in each section and can be removed from final submission. Additional or less information can be included at the company's discretion. The information provided in the evidence submission should be in line with the evaluation framework set out in the final scope.

The submission should be as brief and informative as possible. The main body of the submission **must not exceed 35 pages**, excluding appendices and the pages covered by this template. Font size for text within the body of the submission should not be smaller than Arial size 11. Smaller font sizes may be used in tables. Companies are **not** required to provide an economic model.

The submission should be sent to ACE electronically in Word or PDF format. The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested in the template, but that is considered to be relevant to the submission. A separate Excel workbook to summarise cost information ("Costing template for manufacturers") should also be included alongside the evidence submission.

When making an evidence submission, companies must ensure that all confidential information is **highlighted** and underlined.

AGENCY FOR CARE EFFECTIVENESS

Full Technology Evaluation

[Evaluation title]

Company evidence submission

Contains confidential information	Date of submission
Yes / No	

Section 1: The technology

HSA approved name and brand name	
Registered indication(s) and any restrictions as described in the Package Insert.	
Date of patent expiration	

1.1 Administration and costs of the technology

[Provide details of the treatment regimen, including the method of administration, and costs associated with the technology by completing the table below. Please add additional columns if more than 2 formulations or strengths are being considered in this evaluation. Specify the sources of information and data used to complete the table, for example Package Insert or trial data].

Table X: Administration and costs of the technology being evaluated

Parameter	Pharmaceutical formulation/strength: XXX	Pharmaceutical formulation/strength: XXX	Source
Method of administration			
Dose			
Dosing frequency			
Average length of a course of treatment			
Average cost of a course of treatment			
Anticipated average interval between courses of treatments			

Anticipated number of repeat courses of treatments			
Dose adjustments			
Anticipated care setting			
Number of units sold <u>in the last 12 months</u> to public healthcare institutions			
Current <u>net</u>** cost price (excluding GST) to public healthcare institutions*			
Revised cost price for subsidy consideration***			
<p>* When the registered indication recommends the intervention in combination with other treatments, the cost price of each intervention should be presented.</p> <p>** Cost price to public healthcare institutions after bonusing arrangements or discounts have been applied</p> <p>***Revised cost price should be in line with price discount(s) outlined in value-based pricing request for proposal template (Call for Proposal for Subsidy Listing)</p>			

1.2 Changes in service provision and management

[State whether additional tests or investigations are needed (for example, diagnostic tests to identify the population for whom the technology is licenced, or regular monitoring requirements once a patient begins treatment). Describe whether there are particular administration requirements for the technology and the associated costs or additional infrastructure involved.]

1.3 Overseas regulatory status

[Provide a summary of the regulatory status of the technology in other countries, including Australia, New Zealand, UK and Malaysia (and preferably other Asian countries including Taiwan and South Korea) is also required. If the technology is already reimbursed in other countries, please provide details of the level of subsidy and the indications covered.]

Section 2: Clinical need

2.1 Health condition and position of the drug in the treatment pathway

[Provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.]

Provide information about the life expectancy of people with the disease or condition in Singapore and the source of the data. Please provide information on the number of people in Singapore with the particular therapeutic indication for which the technology is being evaluated.

Describe current clinical practice to manage the condition and list the clinical guidelines (both local and international) which are most commonly used by clinicians in Singapore. If applicable, describe results from any surveys which have been conducted with local clinicians about current clinical practice. Describe any issues relating to current clinical practice, including variations or uncertainty about established practice.

Explain how the technology under evaluation may change the existing treatment pathway if it is subsidised.]

2.2 Proposed criteria for listing technology on the Medication Assistance Fund (MAF)

Based on the proposed position of the drug in the existing clinical treatment pathway for the condition under evaluation (as per section 2.1), suggest specific eligibility criteria to target the use of the drug to patients who are most likely to benefit from treatment and in whom the drug is most likely to be cost-effective, assuming it is listed on the MAF [this population should correspond with the eligible patient population described in the accompanying costing template].

Section 3: Clinical effectiveness

Section 3 provides guidance on the level of information that should be included in the evidence submission template about the clinical effectiveness of the drug under evaluation.

3.1 List of relevant trials

[ACE prefers randomised controlled trials (RCTs) that directly compare the technology with one or more relevant comparators. Provide details of the RCTs that provide evidence on the clinical benefits of the technology at its licensed dosage within the indication being evaluated. There is no need to conduct a systematic review, network meta-analysis, indirect or mixed treatment comparison as part of your evidence submission.

- a. In a table, present the list of relevant RCTs comparing the intervention with other therapies (including placebo) in the relevant patient group. Highlight which studies compare the intervention directly with the appropriate comparator(s) with reference to the final scope. If there are none, state this.
- b. All outcome measures listed in the trial protocol, should be identified and completely defined. When outcomes are assessed at several time points after randomisation, indicate the pre-specified time point of primary interest. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant to the final scope. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQoL), and any arrangements to measure adherence. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within Singapore)

clinical practice). A suggested table format is presented below. The table can be presented in landscape format.].

Table X: List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Outcomes	Primary study reference
Trial 1					
Trial 2					
[Add more rows as needed]					

3.2 Clinical effectiveness results of the relevant trials

[Provide the results for all relevant outcome measures pertinent to the evaluation objective in line with the final scope. For each outcome, provide the following information from each study:

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed both as relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- The number of people in each group included in each analysis and whether the analysis was intention to treat. State the results in absolute numbers when feasible.
- When interim data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of the trial. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may help interpret the results may be included, such as adherence to medication or study protocol.
- Discuss and justify any clinically important differences in the results between the different arms of a trial and between trials.
- Specify whether unadjusted and adjusted analyses were performed, and whether the results were consistent.]

3.3 Non-randomised and non-controlled evidence

[Provide details of the non-randomised and non-controlled studies, including real world data that provide additional evidence to supplement RCT data. Provide a list of the relevant sources and summarise the patient characteristics, methodology and quality assessment for each. Briefly summarise the results.]

3.4 Safety

[Provide details of all adverse reactions experienced with the technology in relation to the indication(s) under evaluation. For each intervention group, give the number with the adverse reaction and the frequency, the total number in the group, and the percentage with the reaction. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse reaction.]

Evidence from comparative RCTs and regulatory summaries is preferred, but findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse reactions commonly associated with the comparator, or that the occurrence of adverse reactions is not statistically significantly different to those associated with other treatments.]

Highlight any safety warnings issued by HSA or international regulatory agencies (e.g. FDA, EMA) related to the use of the technology.]

Describe any ongoing studies specifically relating to safety outcomes and the anticipated date of completion. If any interim results are available from ongoing studies, please summarise them in a table.]

3.5 Interpretation of clinical effectiveness & safety evidence

[Briefly conclude the clinical effectiveness and safety of the technology against the comparators specified in the final scope issued by ACE, including any subgroups. Please indicate whether results show superiority or non-inferiority to comparators for both clinical effectiveness and safety outcomes].

3.6 Ongoing studies

[Provide details of all completed and ongoing studies from which additional clinical effectiveness evidence is likely to be available in the next 12 months for the indication being evaluated.]

Section 4: Cost effectiveness

Companies are **not** required to submit a cost-effectiveness model as part of their evidence submission. All economic models will be produced by the ACE technical team to inform the Committee’s cost-effectiveness considerations.

4.1 Published cost-effectiveness studies

[Describe and compare the methods and results of any published cost-effectiveness analyses available for the technology and/or the comparator technologies (relevant to the technology evaluation). If more than one study is identified, please present the information in a table as suggested below. The table can be presented in landscape format.]

Table X: Summary list of published cost-effectiveness studies

Study	Year	Perspective of analysis	Summary of model	Time horizon	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Study 1								
Study 2								
[Add more rows as needed]								

QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

Section 5: Budget Impact

[Section 5 should present budget impact calculations, over a 5 year period, to provide the most likely extent of use of the technology and financial estimates. This section is important for estimating the likely uptake of the proposed technology in clinical practice if subsidy is recommended, and the cost impact on the Singapore Government budget. Any proposed price discounts should be consistent with prices included in the value-based pricing Request for Proposal. The information provided will be used to inform ACE’s budget impact analyses.]

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

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

Ensure that any estimates of the extent of use of the technology in the Singapore setting are consistent with evidence presented throughout. Ensure that uptake of the technology is consistent with its expected use in clinical practice (at appropriate point in local treatment algorithm).

Please complete the Excel workbook (“Costing template for manufacturers”) and ensure that all calculations, assumptions and data sources are clearly described. The workbook follows an epidemiological approach, however it can be modified by the user to capture any other information that is considered important to include to support the submission.

Briefly summarise the results in a table to show 5-year budget impact to the Singapore government (for **all** clinically eligible patients in line with defined clinical criteria, irrespective of financial eligibility for MAF)].

Section 6: Patient access programs

[Describe any existing patient access programs (PAPs) in Singapore (by institution) that are currently in place for the technology under evaluation, including patient eligibility criteria and the bonusing or discount arrangements offered. If the PAPs differ between public healthcare institutions, please describe these differences and the number of patients who are currently receiving treatment under each program.

Please indicate whether there is a proposed end date for the PAP(s) and/or whether the program will no longer be offered if the treatment is subsidised under SDL/MAF].

References

[Use a recognised referencing style, such as Harvard or Vancouver.]

Appendices

Annex 2: Company evidence submission template for expedited evaluations

Instructions for companies

This is the template for submission of evidence to the Agency for Care Effectiveness (ACE) as part of the **expedited evaluation process** for drugs. It is not mandatory for companies to complete an evidence submission. The topic will still be evaluated by the ACE technical team and presented to the MOH Drug Advisory Committee (DAC) to inform subsidy considerations, irrespective of company involvement. Any evidence provided by the company will be incorporated into ACE's evaluation.

Text highlighted in grey is intended to inform companies about the type of information they may choose to include in each section and can be removed from final submission. Additional or less information can be included at the company's discretion.

The submission should **not exceed 5 pages**. Additional appendices are not permitted. Companies are **not** required to provide an economic model or budget impact analysis. Font size for text within the body of the submission should not be smaller than Arial size 11. Smaller font sizes may be used in tables.

The submission should be sent to ACE electronically in Word or PDF format. When making an evidence submission, companies must ensure that all confidential information is **highlighted** and underlined.

AGENCY FOR CARE EFFECTIVENESS

Expedited Technology Evaluation

[Evaluation title]

Company evidence submission

Contains confidential information	Date of submission
Yes / No	

Technology

HSA approved name and brand name	
Formulations commercially available in Singapore	
Date of patent expiration	

Clinical need

[Describe the expected place of the technology in the local treatment pathway for the indication(s) under evaluation. Explain how the technology may change the existing treatment pathway if it is subsidised (listed on SDL or MAF).]

Summary of clinical effectiveness and safety evidence

[ACE prefers randomised controlled trials (RCTs) that directly compare the technology with one or more relevant comparators. Provide a brief overview of the pivotal clinical trials which demonstrate the clinical effectiveness of the technology at its licenced dosage within the indication being evaluated. Include a summary of any adverse reactions, and safety evidence. There is no need to conduct a systematic review, network meta-analysis, indirect or mixed treatment comparison as part of your evidence submission. Results can be presented as a table or as text.]

[A brief summary of key results from non-randomised evidence sources (including real world data) that provide additional evidence to supplement RCT data can be included].

[Provide details of all ongoing studies from which additional clinical effectiveness evidence is likely to be available in the next 12 months for the indication being evaluated.]

Concluding remarks

[Company can include brief concluding remarks at the end of the evidence submission]

Annex 3: Proposal for Subsidy Listing (RFP template, Form A)

Section 1: Technical Specifications and Costs

We, [name of company in block letters] hereby offer and undertake, on the acceptance of this Proposal, to offer the following drugs with the following specifications for sale to Public Healthcare Institutions and Polyclinics at the following price, in accordance with the Terms and Conditions in Section 2:

Table A1: Price proposals for subsidy listing

Item No.		Indication(s)	Subsidy tier	Cost price per unit, excluding GST (SGD)	Percentage discount on usual cost price (%)
1.	[name of drug, strength and pharmaceutical form]		Select	/ [specify units]	
2.	[name of drug, strength and pharmaceutical form]		Select	/ [specify units]	

(insert more rows as necessary)

2 To assist the Government of the Republic of Singapore, represented by the Agency for Care Effectiveness (“the Authority”) of the Ministry of Health, in assessing this Proposal, we have duly completed and hereby submit the tables in the Appendix for the Authority’s consideration. We confirm and warrant that the information set out in the Appendix is complete, up-to-date and accurate.

3 This Proposal is valid for twelve (12) calendar months from [deadline for submission of the Proposal].

4 We warrant, represent and declare that we are duly authorised to submit and sign this Proposal, receive any instruction, give any information, accept any contract and act for and on behalf of [name of company in block letters].

Dated this [date] day of [month], 20yy

Respondent’s Company or Business Registration No: []	Respondent’s official Stamp:
Authorised Signature: _____ Name: [] Designation: []	

Section 2: Terms and Conditions

1 ACCEPTANCE OF PROPOSAL

- 1.1 The issue by the Authority of a Letter of Acceptance accepting this Proposal shall create a contract (“Contract”) binding the Respondent to offer for sale to all Public Healthcare Institutions and Polyclinics the drugs specified in the Letter of Acceptance (“Drugs”) at a price not exceeding the price set out in this Proposal, for the duration the Drugs are listed for subsidy on the Standard Drug List or Medication Assistance Fund. Where the Respondent has existing agreement(s) of sale of the Drugs with any of the Public Healthcare Institutions and Polyclinics as at the date of the Letter of Acceptance, the Respondent undertakes to take all reasonable steps to vary such agreement(s) so that the cost price of the Drugs to each Public Healthcare Institution and Polyclinic does not exceed the price set out in this Proposal.
- 1.2 For the purpose of this Proposal, and any Contract formed upon the Authority’s acceptance of this Proposal, “Public Healthcare Institutions and Polyclinics” shall refer to the entities listed in Table A2. The Authority may from time to time vary the list in Table A2 at its absolute discretion, and shall notify the Respondent of any such variation in writing.
- 1.3 In consideration of the above, the Authority shall list the Drugs for subsidy on the Standard Drug List or Medication Assistance Fund within 3 months from the issue of the Letter of Acceptance.
- 1.4 Save that the Authority may disclose to all Public Healthcare Institutions and Polyclinics the prices at which the Respondent sells the Drugs to all Public Healthcare Institutions and Polyclinics, the Authority shall not otherwise make publicly available the prices at which the Respondent sells the Drugs to all Public Healthcare Institutions and Polyclinics.

2 SUSPENSION AND TERMINATION OF THE CONTRACT

- 2.1 The Authority shall, after giving seven (7) days prior written notice to the Respondent, have the right to suspend or terminate the Contract if the Authority is affected by any state of war, acts of God or other circumstances seriously disrupting public safety, peace or good order of the Republic of Singapore.
- 2.2 If the Respondent defaults in his performance of this Contract, the Authority may issue a notice of default to the Respondent informing the Respondent of its default. The Respondent shall, within thirty (30) days of the date of the notice of default, remedy the default. If the Respondent fails to remedy the default, the Authority shall have the right to immediately revoke the listing of the drugs for subsidies and terminate the Contract by way of a written notice to the Respondent without the Authority being liable therefor in damages or compensation.

3 OTHERS

- 3.1 The Authority may terminate the Contract and recover from the Respondent the amount of any loss resulting from such termination, if the Respondent shall have offered or given or agreed to give to any person any gift or consideration of any kind as an inducement or reward for doing or forbearing to do or for having done or forborne to do any action in relation to the obtaining or execution of the Contract with the Authority or for showing or forbearing to show favour to any person in relation to any contract with the Authority, or if the like acts shall have been done by any person employed by the Respondent or

acting on his behalf (whether with or without the knowledge of the Respondent) or if in relation to any Contract with the Authority the Respondent or any person employed by him or acting on his behalf shall have committed any offence under Chapter IX of the *Penal Code* (Cap. 224) or the *Prevention of Corruption Act* (Cap. 231) or shall have abetted or attempted to commit such an offence or shall have given any fee or reward the receipt of which is an offence under Chapter IX of the *Penal Code* or the *Prevention of Corruption Act*.

- 3.2 Except with the prior consent in writing of the Authority, the Respondent shall not disclose this Proposal, the Contract or any part thereof.
- 3.3 This Proposal and the Contract shall be subject to, governed by and interpreted in accordance with the laws of the Republic of Singapore for every purpose.
- 3.4 The Respondent and the Authority hereby submit to the exclusive jurisdiction of the Singapore Courts for all purposes relating to this Proposal and the Contract.
- 3.5 A person who is not a party to this Contract shall have no right under the *Contracts (Rights of Third Parties) Act* (Cap. 53B) to enforce any of its terms.
- 3.6 No variation whether oral or otherwise in the terms of this Proposal or the Contract shall apply thereto unless such variation shall have first been expressly accepted in writing by the Respondent and the authorised contract signatory of the Authority.
- 3.7 The right and remedies of the parties under this Contract are cumulative and are in addition and without prejudice to any rights or remedies a party may have at law or in equity. Further, no exercise by a party of any one right or remedy under this Contract shall operate so as to hinder or prevent the exercise by it of any other right or remedy under the Contract, or any other right existing at law or in equity.
- 3.8 In no event shall any delay, failure or omission on the part of either of the Parties in enforcing or exercising any right, power, privilege, claim or remedy, which is conferred by this Agreement, at law or in equity, or which arises from any breach by either Party, be deemed to be or be construed as, (i) a waiver thereof, or of any other such right, power, privilege, claim or remedy, in respect of the particular circumstances in question, or (ii) operate so as to bar the enforcement or exercise thereof, or of any other such right, power, privilege, claim or remedy, in any other instance at any time or times thereafter.
- 3.9 The Contract contains the entire and whole agreement between the parties and supersedes all prior written or oral commitments, representations, arrangements, understandings or agreements between them. Each party warrants to the other that it has not entered into this Contract on the basis of any prior written or oral commitments, representations, arrangements, understandings or agreements between them.

Table A2. List of Public Healthcare Institutions and Polyclinics

1	Alexandra Hospital
2	Ang Mo Kio – Thye Hua Kwan Hospital
3	Bright Vision Hospital
4	Changi General Hospital
5	Institute of Mental Health/Woodbridge Hospital
6	Jurong Community Hospital
7	Khoo Teck Puat Hospital
8	KK Women’s and Children’s Hospital
9	National Cancer Centre Singapore
10	National Dental Centre Singapore
11	National Heart Centre Singapore
12	National Healthcare Group Pharmacy
13	National Healthcare Group Polyclinics
14	National Neuroscience Institute
15	National Skin Centre
16	National University Hospital
17	Ng Teng Fong General Hospital
18	Ren Ci Community Hospital
19	St Andrew’s Community Hospital
20	Singapore General Hospital
21	Sengkang General Hospital
22	Sengkang Community Hospital
23	St Luke’s Hospital
24	Singapore National Eye Centre
25	SingHealth Polyclinics
26	Tan Tock Seng Hospital
27	Woodlands General Hospital

Appendix

1. Volume and current cost price

	Number of units sold in the last 12 months [MM YYYY to MM YYYY] to public healthcare institutions	Usual cost price per [unit], excluding GST (SGD)
[name of drug, strength and pharmaceutical form]	[specify units]	
[name of drug, strength and pharmaceutical form]	[specify units]	

2. Patient Access Programs (PAPs) currently in place (if applicable)

	Please provide details (eligibility criteria, level of subsidy, differences among public healthcare institutions and patient numbers)	
[name of drug, strength and pharmaceutical form]		
[name of drug, strength and pharmaceutical form]		
Will existing PAPs still be valid at the prices offered for subsidy consideration?		Select

3. Existing agreements to sell the Drugs to Public Healthcare Institutions and Polyclinics (if applicable)

	Contracting Party	Date of expiry of agreement
[name of drug, strength and pharmaceutical form]		
[name of drug, strength and pharmaceutical form]		

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