DRUG AND VACCINE EVALUATION METHODS AND PROCESS GUIDE

Version 3.1 September 2023

ACE
agency for
care effectiveness

Record of updates

Date	Version	Summary of changes
February 2018	1.0	Publication of initial drug evaluation methods and process guide.
December 2019	2.0	Updated to include changes to topic selection and value-based pricing processes and DAC decision-making criteria approved since February 2018. A new addendum on methods and processes for the evaluation of treatments under consideration for inclusion in the Rare Disease Fund (RDF) has been added. Minor additions, wording changes and amendments of grammatical errors throughout the document have also been made to improve the clarity of the text.
June 2021	3.0	Title of document has been changed to reflect the inclusion of a new addendum on evaluation processes for vaccines under subsidy consideration. Guide has been updated to include information regarding the evaluation process for exemption items, revisions to the MOH Drug Advisory Committee's terms of reference, and methods for ACE's post-subsidy reviews. The budget impact ranges that are reported in ACE's published guidance have also been updated. Additions and amendments throughout the document (including annexes) have also been made to improve the clarity of the text.
September 2023	3.1	Minor additions, wording changes and amendments of figures throughout the document (including annexes) have been made to improve the clarity of the text and streamline processes. Guide has been updated to include information about how patients provide input to inform ACE's evaluations.

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Foreword

Established by the Ministry of Health (MOH), the Agency for Care Effectiveness (ACE) is Singapore's national health technology assessment (HTA) and clinical guideline agency. It produces evidence-based evaluations of health technologies (e.g. drugs, vaccines and medical technologies) to inform funding decisions by MOH committees, and publishes technology guidance documents for public hospitals and institutions in Singapore to promote the appropriate use of clinically effective and cost effective treatments. Find out more about ACE at https://www.ace-hta.gov.sg/about-us.

The ACE *Drug and Vaccine Evaluation Methods & Process Guide* outlines the core technical methodology and processes underpinning ACE's assessment of clinical and economic evidence for drugs and vaccines which are being considered for funding. 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 staff follow when conducting drug and vaccine evaluations, and clearly outline ACE's processes and decision-making frameworks. Procedures and methods that pharmaceutical companies are expected to follow when preparing an evidence submission to ACE through the company-led submission process, are outlined in a separate document on the ACE website.

While the *Drug and Vaccine Evaluation Methods & Process Guide* forms an important part of the MOH Drug Advisory Committee's (DAC) decision-making processes for drug and vaccine funding, it is only a guide. ACE and the 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, pharmaceutical companies and patient organisations 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.

ACE would like to thank the following experts for their comments during the development of version 1.0 of this guide (appointments listed were current when guide was first published in February 2018):

- Prof Jonathan Craig, Professor of Clinical Epidemiology, School of Public Health, University of Sydney, Australia
- Prof Ron Goeree, Professor Emeritus, Department of Health Research Methods, Evidence and Impact, McMaster University, Canada
- Prof Carole Longson, Director of the Centre for Health Technology Evaluation, National Institute for Health and Care Excellence (NICE), United Kingdom
- Prof Paul Scuffham, Director, Centre for Applied Health Economics (CAHE), Griffith University, Australia
- Prof Mark Sculpher, Centre for Health Economics, University of York, United Kingdom
- Prof Robyn Ward, Deputy Vice-Chancellor (Research), University of Queensland, Australia

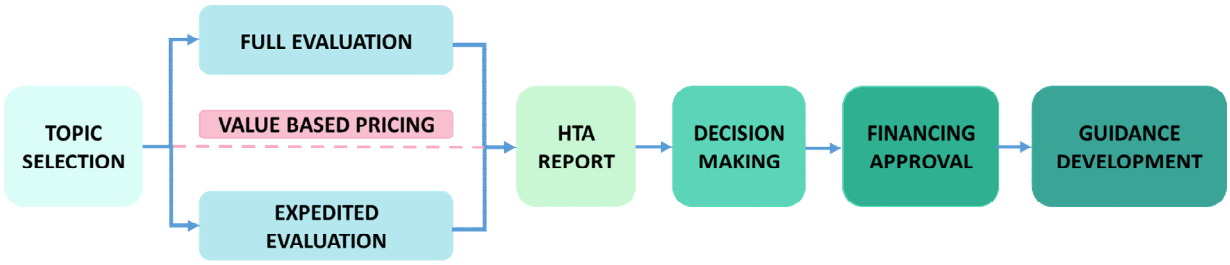
1. Introduction

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, vaccines, 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 the HTA methods and processes that ACE uses when evaluating new and existing drugs and vaccines available in Singapore. It introduces the general methodological concepts underlying each stage of the evaluation process and outlines the key information required from companies 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 evaluation process



Specific templates which companies may be asked to complete to inform ACE's evaluations are also provided in the Annexes for information.

2. Topic Selection for Drugs

Topic selection is the process for deciding which drugs and clinical indications (drug topics) are appropriate for evaluation by ACE. The process has been designed to ensure that the drugs chosen for evaluation address priority issues and therapeutic gaps, which will help improve the health of the population, and will support healthcare professionals to provide appropriate care. Information regarding the selection of vaccines for evaluation is described in **Addendum 2**.

2.1 Call for drug topics

Drugs which are already being used in local clinical practice but are not subsidised are identified as potential topics for evaluation through applications by public healthcare professionals and patient organisations. New and emerging drugs that might be suitable for evaluation are also identified through literature searches and horizon scanning by the ACE

technical team in conjunction with pharmaceutical companies, which are invited to share their regulatory pipeline with ACE in December each year.

Public healthcare institutions and patient organisations are invited to submit applications for the inclusion of drug preparations into the MOH List of Subsidised Drugs on an annual basis (during October to January). The annual invitation for drug applications is sent to the Chairman of the Medical Board (CMB, 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 CMB (or equivalent body) in each institute for endorsement and collation before submission to the MOH DAC Secretariat.

Patient organisations are invited to submit applications by the ACE Consumer Engagement and Education (CEE) team. More information about patient involvement in the topic selection process is described in a separate guide.

2.2 Filtering of drug topics

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

- the drug is not registered for use in Singapore by the Health Sciences Authority (HSA) and the company has confirmed that they do not intend to submit a regulatory dossier for marketing approval **or**
- it 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 health technologies are also currently outside the remit of ACE's drug evaluations:

- Dialysis solutions
- Extemporaneous preparations
- Fertility drugs
- General Sale List (GSL) medications (including homeopathic medicines and traditional Chinese medicines)
- Lifestyle drugs
- Wound dressings

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 in line with international best practice and/or indications approved by reputable overseas regulatory authorities such as the US Food and Drug Administration (FDA) or European Medicines Agency (EMA), and considered standard of care for the proposed population in local clinical practice; and
- there is a lack of affordable and cost-effective treatment alternatives to the off-label drug for the proposed population; and

- there is sufficient evidence available to robustly assess the safety, clinical effectiveness and cost-effectiveness of the off-label use of the drug in the proposed population.

Unregistered products (i.e. exemption items that do not have HSA approval for any clinical indication) will only be evaluated for funding consideration in exceptional circumstances on a case-by-case basis if they are:

1. an additional strength or dosage formulation of an existing subsidised drug preparation that is required for populations in whom the subsidised preparation is unsuitable; or
2. intended to replace an existing subsidised drug preparation which has been permanently discontinued, but was the sole source registered with HSA; or
3. a drug or formulation/strength that is standard of care for a specific subgroup of patients (e.g. paediatric or geriatric patients) who do not have suitable registered treatment alternatives; or
4. a drug or supplement that is standard of care for a rare disease and there are no suitable registered treatment alternatives available.

2.3 Selection of drug topics

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

Table 1. ACE drug topic selection criteria

No.	Criterion	Definition
1.	**Type of gap that drug (intervention) 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 intervention. **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, disability, function, and health-related quality of life.
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 intervention.
5.	**Comparative clinical effectiveness (from published literature)**	Added or reduced clinical benefit of the intervention compared to alternatives.
6.	**Relative safety (from published literature)**	Safety of the intervention compared to alternatives.
7.	**Cost-effectiveness (from published literature)**	Dominance or incremental cost-effectiveness of intervention compared to alternatives.
8.	**Resource impact**	Estimated annual budget impact of the intervention for the condition under evaluation. Cost of additional services, facilities, tests or staff requirements needed if the intervention is funded.

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 addresses a **therapeutic gap** in the MOH List of Subsidised Drugs and is expected to be of significant benefit to patients in terms of clinical efficacy or having an improved side-effect profile compared to existing treatment options, and there is sufficient evidence for ACE to review.

3. Technology Evaluation

3.1 Type of evaluation

Information regarding the evaluation process for vaccines is provided in **Addendum 2**.

Drug topics with moderate to high need scores (following the topic selection process) are prioritised for evaluation by the DAC. Evaluations are usually conducted internally by the ACE technical team with supporting evidence provided by local healthcare professionals from public institutions, patient organisations, and pharmaceutical companies, where required.[1]

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

- High cost drugs (estimated budget impact >SG$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 (<SG$1 million per year) or which are available as a generic formulation or biosimilar, are subject to **expedited evaluation**;
- Drugs with a moderate budget impact (between SG$1 million to SG$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.

A full evaluation is typically required to demonstrate that the drug is:

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

An expedited evaluation is conducted when there is a therapeutic claim of non-inferiority (i.e. the drug under evaluation and the comparator are considered to be clinically equivalent and the use of the drug is anticipated to result in equivalent or lower costs to the healthcare system compared to the comparator).

[1] Since 2021, under the company-led process, pharmaceutical companies are able to provide an evidence submission for certain health technologies to support the DAC's deliberations instead of ACE staff conducting the technical evaluation in-house. The aim of this process is to enable technologies to be evaluated close to the anticipated date of regulatory approval by the Health Sciences Authority (HSA) and expedite funding considerations to improve patient access to clinically necessary treatments. More information about the company-led submission process is available on the ACE website.

In addition, the extent of information available for evaluation and the availability of ACE technical resources to conduct the evaluation within the expected 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 time to complete each evaluation 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	Time Required
Expedited evaluation	• Qualitative written surveys (and/or face-to-face meetings) of clinical and patient experts to inform local treatment algorithm, define comparator(s), and describe current use of the technology in local practice and patients' clinical need for funding • 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 • Cost-minimisation analysis (CMA) may be conducted • Value-based pricing proposal from company • Budget impact analysis, including estimated volume and annual cost to the healthcare system	2 to 3 months
Full evaluation	• Stakeholder workshop, face-to-face meeting and/or written survey of clinical experts to define the scope of the evaluation, inform local treatment algorithm, define comparator(s), and describe current use of the technology in local practice • Patient inputs through qualitative written survey to define the clinical need for the technology under evaluation and patients' preferences for new treatments • 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-utility analysis (CUA)), using local data inputs where available. Scenario analyses 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 company • Budget impact analysis, including estimated volume and annual cost to the healthcare system	6 to 9 months

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

The evaluation processes for expedited and full evaluations are shown in Figures 2 and 3 respectively.

Figure 2. Overview of expedited evaluation process for drug topics

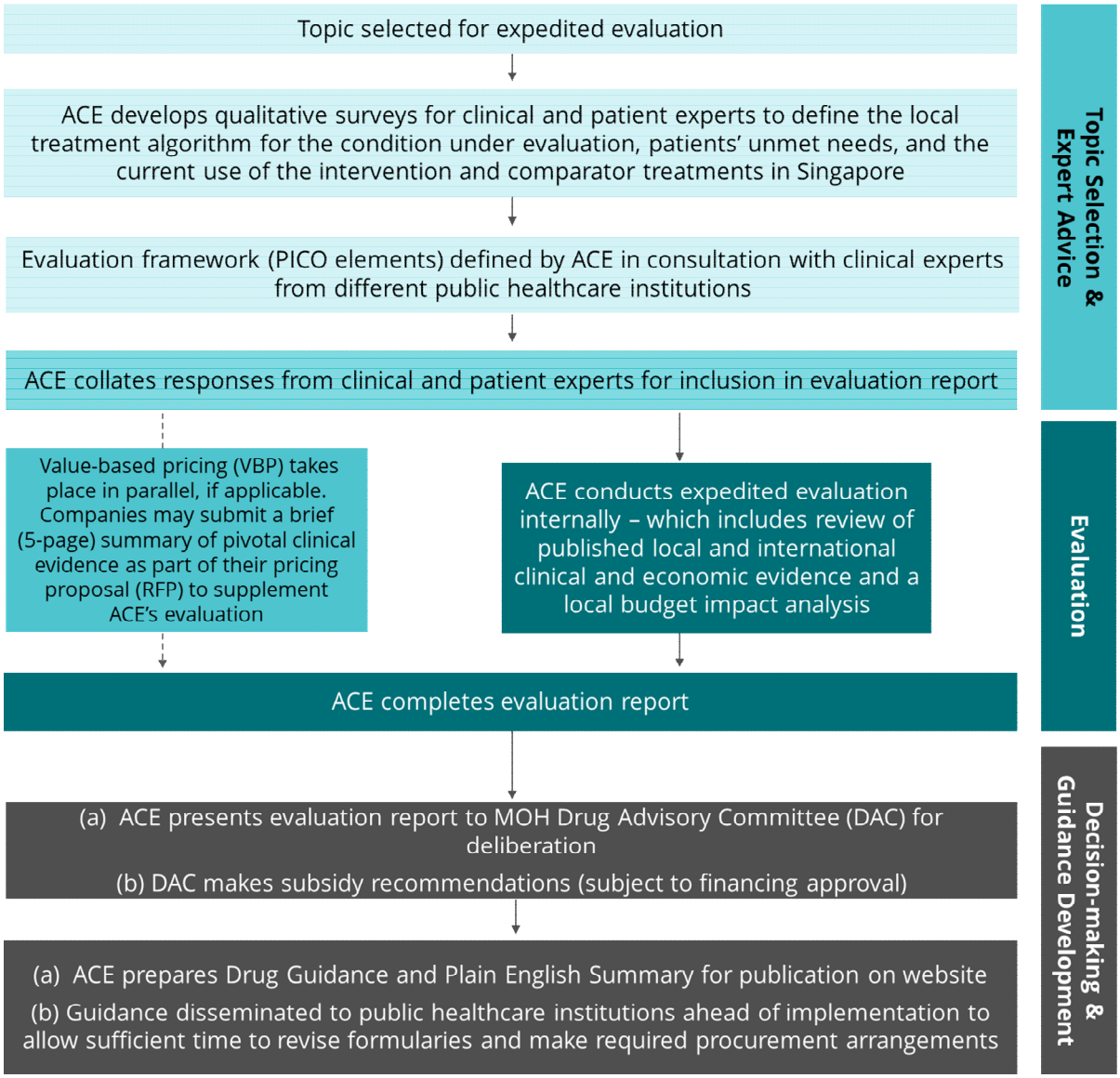


Figure 3. Overview of full evaluation process for drug topics

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, 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**
• Patient or population characteristics • Condition/disease of interest	Technology under evaluation	Alternative treatment option(s) to the intervention used in routine clinical practice	Patient-relevant clinically meaningful health outcomes of interest

For expedited evaluations, the framework is defined by the ACE technical team with inputs from local clinical experts, in line with the indication requested for evaluation by healthcare professionals or patient organisations (for registered products) or the intended registered indication identified through horizon scanning or from company pipelines (for products still pending regulatory approval; 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.

4. Scoping

4.1 Developing the scope

The scope provides a framework for topics which are subject to **full evaluation**. Using the PICO framework, the scope 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 a local cost-utility analysis 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) that is likely to be eligible for the technology being evaluated;
- use of the technology 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 proprietary (branded) and non-proprietary (generic) drugs and biosimilars, or off-label alternatives if they constitute routine care);

- the patient-relevant clinical effectiveness and safety outcome measures appropriate for the analysis, including the length of time over which the benefits and costs will be considered; and
- consideration of patient subgroups for whom the technology might be particularly clinically effective and/or cost effective.

A draft scope is developed by the ACE technical team. Healthcare professionals from public healthcare institutions who have expertise in the disease area under evaluation may be invited to provide their views on the use of the technology in relation to current local clinical practice before the scope is finalised.

4.2 Scoping Workshop

To ensure that the evaluation framework for the full evaluation is appropriately defined with relevance to local clinical practice and patient need, ACE may hold a roundtable workshop with healthcare professionals who have expertise in the disease area or the use of the technology under evaluation. All participants are required to sign a non-disclosure agreement to safeguard any confidential information, and declare any conflicts of interest prior to the workshop.

The aims of the workshop are to:

- ensure that the scope is appropriately defined; and
- 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, patient-relevant 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 technology is already used in Singapore);
  - relevant potential comparators;
  - requirements to implement any guidance on the use of the technology, including need for extra staff or equipment; education and training requirements for hospital staff; and ways in which adherence to treatment can be improved; and
  - 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 experts.

After the scoping workshop, the ACE technical team finalises the scope, taking into account the discussions by the participants.

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 many sources may inform the evaluation, randomised controlled trials (RCTs) directly comparing the technology under evaluation with the relevant comparator(s) are considered to provide the most valid evidence of relative efficacy. When RCTs are not available, data from indirect comparisons of randomised trials are considered. When relevant, good quality non-randomised studies may also be considered as supplementary evidence to inform evaluation parameters such as costs and utility values.

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).

5.2 Types of evidence

A summary of the different types of evidence used to inform ACE's technical evaluations, and the considerations made by ACE when using each type of evidence are shown in Table 4.

Table 4. Types of evidence considered in ACE evaluations

Evidence type	Considerations
Randomised controlled trials	• Randomised controlled trials (RCTs) are 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 the 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: – **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. – **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	• 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. Non-randomised studies may also provide useful supplementary evidence to randomised controlled trials about long-term outcomes, rare events and populations that are typical of real-world practice. As study quality can vary, critical appraisal and sensitivity analyses are important when reviewing these study outcomes.
Real world data	• 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	• Qualitative research, in the form of questionnaire or survey responses from clinical professionals and patient experts, is often used to explore areas such as patients' experiences of having a disease and/or specific treatment(s), and clinicians' views on the role of different types of treatment in local clinical practice.
Economic evaluations	• Evidence on the cost effectiveness of the technology 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 technology 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	• 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 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 on the results.

5.3 Clinical and patient expert advice

During the course of the evaluation, ACE will seek advice from local healthcare professionals experienced in the management of the condition under evaluation; confirm local treatment practices; validate the clinical assumptions included in ACE's evaluation report; and confirm the clinical need for the technology under evaluation compared to alternative options (if available). All local patient organisations with members who are likely to have an interest in the technology or condition under evaluation are also invited to share their views and lived experiences by completing a qualitative survey. All clinical and patient experts are required to declare any conflicts of interest relating to the technology or comparator(s) under evaluation.

For evaluations of cancer therapies, ACE also seeks clinical expert advice from the MOH Cancer Drug Subcommittee (CDS) which comprises senior public and private clinicians experienced in the management of different cancer types in Singapore. The CDS assists ACE to ascertain the clinical value of cancer drugs under evaluation and provides clinical advice on the appropriate and effective use of cancer therapies based on the available clinical evidence. CDS members are not required to comment on the prices or cost effectiveness of cancer drugs.

5.4. Evidence submissions from companies

During the course of the evaluation, ACE will invite the company of the technology under evaluation to submit a summary of key clinical evidence (up to 5 pages) to supplement ACE's assessment. The evidence should be provided within the *Company evidence submission template to support ACE's evaluation* (Annex 1), and submitted with the pricing proposal (see Section 8.1) within the required timelines (typically 4-8 weeks depending on the complexity of the topic).

It is not mandatory for companies to provide an evidence submission to support ACE's evaluations. The topic will still be evaluated by the ACE technical team and presented to the DAC to inform their funding recommendations, irrespective of company involvement.

6. The Reference Case

The DAC has to make funding decisions across different technologies 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' 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 5 for drugs and in **Addendum 2** for vaccines.

Table 5. ACE's reference case for drug evaluations

Component of drug evaluation	Reference Case
Perspective of the evaluation	• Singapore healthcare system including payments out of the government's healthcare or insurance (MediShield Life) budgets as well as patients' co-payments including MediSave and out of pocket expenses
Target population and subgroups	• Consistent with the patient population defined in the evaluation framework • Epidemiological data for Singapore presented for the entire target population and relevant subgroups
Comparators	• Consistent with the comparator(s) defined in the evaluation framework • Comparator(s) should either reflect the current treatment that is most likely to be replaced by the technology under evaluation in routine local clinical practice, or in the case of add-on treatments, the current treatment without the technology under evaluation added on • Comparators may include proprietary (branded) and non-proprietary (generic) drugs and biosimilars • Comparisons with technologies which are used off-label for the indication under evaluation are allowed if they reflect common practice in the local setting
Outcomes	• Consistent with the outcomes defined in the evaluation framework

	• Health outcomes should be patient-relevant and valued from a Singapore healthcare system perspective
Systematic review	• 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	• Cost-effectiveness analysis (CEA) should only be carried out for full evaluations if the technology is clinically superior to, and more costly than the comparator(s). 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 • For treatments which are non-inferior (comparable effectiveness and safety) to the comparator(s), a cost-minimisation analysis (CMA) should be undertaken • Cost-utility analysis (CUA) is the preferred method and should be used in full evaluations if the technology 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 ratios (ICERs) with their associated upper and lower limits • Economic models should be based on data from clinical studies comparing the intervention and the comparator, or using data from validated databases and/or published 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	• Only direct healthcare costs should be included • Identification, measurement and valuation of costs should be consistent with the perspective of the Singapore healthcare system (government, insurance provider and patient healthcare costs) • Indirect healthcare costs or non–healthcare costs should not be included in the reference case analysis, but may be considered in secondary analyses
Measuring and valuing health effects	• Final, clearly defined, patient-relevant, clinically meaningful outcomes should be presented • **CUA:** quality-adjusted life years (QALYs) gained • Life expectancy estimates based on recent Singapore age-specific and gender-specific life tables • EQ-5D-3L utility weights estimated based on the general population in the UK (which ideally have been accepted by NICE) should be used in the scoring algorithm to calculate utility weights, where available • Singapore-based preference weights can be used in sensitivity analyses • Quality of life weights derived from a validated instrument
Time horizon	• The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the treatments being compared

Discount rate	• Costs and health outcomes are discounted at an annual rate of 3% • Other scenarios can be presented to test sensitivity of results to discount rate applied
Handling uncertainty	• Explore all relevant structural, parameter source, and parameter precision uncertainty • One-way deterministic sensitivity analysis should be presented for all uncertain parameters • Multivariate or probabilistic sensitivity analysis may also be performed to address simultaneous impact of all uncertain parameters
Budget impact analysis	Budget impact analyses should follow these principles: • **Target population**: Consistent with the patient population (and any relevant subgroups) defined in the evaluation framework. Should include Singapore resident population (citizens and permanent residents) only. The analysis should estimate the potential size of the target population and its potential evolution over time. The methods used to estimate the population size should be described and justified. The degree of uptake of the technology in the target population needs to be considered and justified. • **Comparator(s)**: Consistent with the comparator(s) defined in the evaluation framework • **Outcomes**: No health outcomes are presented in the analysis • **Costs**: Only the drug acquisition costs should be included (i.e. excluding margins). Where appropriate, other direct healthcare costs may be considered. Prices should be kept constant over the years (i.e. not inflated). If a price reduction or patient assistance programme (PAP) has been proposed by the company (contingent on a positive funding decision), the net cost price after the price reduction or PAP is applied should be used in the base case. • **Time horizon**: The time horizon depends on the time needed to reach a steady state • **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 system. This includes payments out of the government's and insurance providers' healthcare budgets as well as patients' co-payments. Only patient-relevant, clinically meaningful outcomes should be included.

Costs and outcomes should be relevant for the patient population involved in the treatment of the indication under evaluation and valued from a healthcare system perspective. This includes costs paid out of the government's healthcare or insurance (MediShield Life) budgets and patients' co-payments including Medisave and out-of-pocket expenses.

Only direct health-related costs and patient-relevant health outcomes should be presented. The reference case perspective on health outcomes aims to maximise health gains from available healthcare resources. Supplementary analyses which include non-health benefits

may be appropriate when a technology has important societal implications extending beyond the health outcomes of the patient receiving the intervention, and beyond the healthcare system (e.g. economic productivity impact). If characteristics of a technology have a value to people independent of any direct effect on health (for example, important reductions in the absence of 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.

6.2 Target population and subgroups

The patient population should be consistent with the evaluation framework. If the clinical and/or cost-effectiveness of the technology 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 defined by the approved indication for the technology under evaluation unless off-label use is being considered (see Section 2.2).

The capacity to benefit from the technology may differ for patients depending on their characteristics. This should be explored as part of the 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 technology should be compared with the most relevant alternative option for the condition under evaluation. This is either the intervention that is most likely to be replaced by the technology under evaluation in local clinical practice or, in the case of add-on treatments, the current treatment without the technology added on. In some cases, multiple treatment options will have to be included as comparators.

Comparisons with treatments which are used off-label for the condition under evaluation are allowed 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 should represent the current alternative treatment routinely prescribed for the condition in Singapore (i.e. the treatment most likely to be replaced in clinical practice).

The comparator can be another medical intervention, best supportive care, watchful waiting or doing nothing (no intervention). Proprietary (branded) and non-proprietary (generic) drugs and vaccines, as well as biosimilars, can be considered as relevant comparators. The choice of comparator should be determined based on local clinical expert opinion and supported by evidence from other sources such as current local utilisation patterns and evidence-based clinical practice guidelines.

When the comparator is a medical intervention, it should have proven efficacy and be 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 intervention that most prescribers would replace with the technology under evaluation if it was funded. Multiple comparators can be considered if relevant to local clinical practice.

If the technology under evaluation is for a population for which there are no currently available therapies, or it will be used in addition to ("add-on therapy") – rather than replace – a treatment, the comparator would usually be standard clinical management (such as best supportive care, watchful waiting, conservative management, or a surgical procedure).

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

6.4 Systematic review of clinical evidence

Each evaluation should include a systematic review of the existing clinical studies on the technology under evaluation. 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 the clinical effectiveness of the technology relative to its comparator(s). The evidence should be critically appraised and its quality assessed.

Estimates of the mean clinical effectiveness of the interventions 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 technology, 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
- selected on the basis of defined inclusion and exclusion criteria, and
- 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 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 PRISMA flowchart, specifying the yield and exclusions (with the reason(s) for exclusion) should be presented. Each study meeting the criteria for inclusion should be critically appraised and have its quality assessed.

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 will 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 if available. When interventions 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 interventions.

6.5 Economic evaluation

For interventions 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 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) is the preferred method and should be used if the technology 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 ratios (ICERs) with their associated upper and lower limits.

Economic models should be based, as much as possible, on data from clinical studies comparing the intervention and the comparator, on data from validated databases and/or from published 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 also conducted by the ACE technical team for expedited (and full) evaluations when relevant.

- **Cost-minimisation analysis (CMA)**
  Cost minimisation analyses are used if the clinical effects of two interventions are comparable (i.e. there is a therapeutic claim of non-inferiority), the safety profile of one intervention is equivalent or superior (in both nature and magnitude) to the other intervention, and the use of one intervention is anticipated to result in equivalent or lower costs to the healthcare system compared to the other intervention. It considers that there is no net health change involved in moving from one intervention to another; hence cost-effectiveness decisions can be made on the basis of the difference in the total cost alone, i.e. the intervention with the lowest cost is considered the most cost effective option.

In addition to CMA, a CUA may be conducted by the ACE technical team for full evaluations.

- **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 require consideration of both the

incremental direct health-related costs and health outcomes associated with the technology under evaluation to generate an incremental cost-effectiveness ratio (ICER). The ICER reflects the additional (incremental) cost per additional unit of outcome achieved. This type of analysis should be undertaken if the technology is therapeutically superior to the comparator but is likely to result in additional costs to the healthcare system; or therapeutically inferior to the comparator but likely to result in lower costs to the healthcare system.

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 for full evaluations

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 technology 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;
- the clinical trial design includes crossover (treatment switching) that would not occur in clinical practice; and/or
- costs and benefits of the intervention and comparator(s) extend beyond the trial follow-up period.

Different types of models can be used, the major categories being decision trees, cohort-based state transition (or Markov) models, partitioned survival analysis models and individual-level (or microsimulation) models. Models should be kept as simple as possible while reflecting sufficient clinical reality, and their 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. 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, patient-relevant outcome measures**. Surrogate measures should only be used where no alternative health outcome data are available. Surrogate measures should be used with caution, 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 a 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 so they can be incorporated 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; and
- 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 intervention and the sources used for valuing the model 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 consultation is an acceptable source of input; however, the need for using expert opinion should be well justified, and the number of experts consulted, their field of expertise, and any conflicts of interest 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 the intervention 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 the 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 intervention in the extended period can be assessed. Scenario analyses are 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 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 intervention to which they were allocated.

6.6 Measuring and valuing health effects

The measure of health outcome should be patient-relevant, 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 validated instrument.

For cost-utility analyses, quality adjusted life years (QALYs) should be calculated. A QALY combines both quality of life and life expectancy into a single index. The valuation methods for health-related quality of life should be equal for the technology under evaluation and 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 two elements: measuring health-related quality of life in people who are in the relevant health state and valuing it according to preferences for that health state relative to other states (usually perfect health [=1] and death [=0]).

If available, quality of life or utility data reported in clinical studies should be used to estimate QALYs in the model. If a multi-attribute utility instrument (MAUI) such as EQ-5D-3L has been used in a study to estimate utility weights, its applicability to the general population in Singapore should be considered. Preference weights based on the general population in the UK (which have ideally been accepted by NICE) should be used in the scoring algorithm to calculate utility weights, where available. The use of Singapore-based preference weights can be used in sensitivity analyses.

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 recent age-specific and gender-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 one plausible set of utility data is available, sensitivity analyses should be carried out to show the impact of the alternative utility values.

Non-preference-based patient-reported outcome measures will require a mapping algorithm to be transformed into preference-based measures to estimate utilities. This approach 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 direct costs should be consistent with the perspective of the Singapore healthcare system (government, insurance provider and patient). Indirect healthcare costs or non-healthcare 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 Singapore healthcare system (government, insurance provider and patient healthcare costs). 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 for drugs are shown in Table 6.

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 are no significant differences in mortality rates or time periods between treatments.

Table 6. Direct costs included in ACE's drug evaluations

Type of costs	Resource consumption
Drug/Treatment	• Direct cost of community and hospital treatments, including drugs used to treat adverse reactions, and monitoring costs; and • Cost of administration (e.g., materials required to deliver an infusion, preparation of treatment in a laboratory etc.)
Hospital inpatient	Diagnostic and investigational services, treatment and/or procedures, hospital capital costs, depreciation and overheads (collectively captured through DRGs)[2]
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, patient co-payments, home or continuing care, aged care services, palliative care

[2] 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 and their resource consumption.

The selling price to patients (including pharmacy margins but before any subsidy or insurance coverage is applied) for interventions based on the approved dosing regimens should be used in the reference case analysis. In cases where the approved 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 sufficient evidence of efficacy to substantiate this dosing regimen if it is different from the approved 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 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 interventions 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 intervention and the comparator are expected. Health consequences include intended as well as unintended consequences (e.g. side effects). Where there is evidence that a technology affects mortality of long-term outcomes and/or quality of life that persist for the remainder of a person's life, then a time horizon sufficiently long enough to reflect the time span required for nearly all of the cohort in the model to die according to their life expectancy should be used. Life expectancy estimates should be based on recent Singapore age-specific and gender-specific life tables.

It is often necessary to extrapolate data beyond the duration of the clinical trials and to consider the associated uncertainty. When the impact of an intervention 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 intervention 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 an annual rate of 3%. To assess the sensitivity of the results to the discount rate applied, different scenarios can be presented in sensitivity analyses.

The values of costs and benefits incurred or received in the future should be discounted to reflect the present value. In the base case, all costs and benefits that occur or extend beyond one year are discounted at an annual compounding rate of 3%. Fixed discount rates of 0% and 5% per year, applied to both costs and outcomes, 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

Validation of an economic model to confirm that the computed results depict what they are intended to represent will help reduce some of the uncertainty associated with modelling, and give decision-makers more confidence in the model predictions. 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 be considerably 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 may be considered 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 or probabilistic sensitivity analysis may also be performed to address simultaneous impact of all uncertain parameters.

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

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

A summary of appropriate methods to address structural and parameter uncertainty is presented in Table 7.

Table 7. 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 clinical practice in the local Singapore context?
Structural 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 technologies. 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 (univariate) deterministic sensitivity analysis and/or scenario 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 in line with good practice guidelines. Multivariate and probabilistic sensitivity analyses may be conducted to address the simultaneous impact of all uncertain parameters.

6.12 Budget impact

The following principles apply to budget impact analyses:

Target population: Consistent with the patient population (and any relevant subgroups) defined in the evaluation framework. 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 uptake of the intervention in the target population (e.g. diagnosis rate, compliance, market share etc.) needs to be considered and justified.

Comparator: Consistent with the comparator(s) defined in the evaluation framework.

Costs: Only the drug acquisition costs should be included (i.e. excluding margins). Where appropriate, other direct healthcare costs may be considered. Prices should be kept constant over the years (i.e. not inflated). If a price reduction or patient assistance programme (PAP) has been proposed by the company (contingent on a positive funding decision), the net cost price after the price reduction or PAP is applied should be used in the base case.

Outcomes: No health outcomes are presented in the analysis.

Time horizon: The time horizon depends on the time needed to reach a steady state.

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

Budget impact analyses are conducted from the healthcare system perspective for full and expedited evaluations to determine the affordability of the technology under evaluation (for government, insurance provider and patients). The projected cost to the healthcare system to fund the drug is estimated based on current and projected drug utilisation volumes from public healthcare institutions, or budget impact models 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. Table 8 describes the parameters considered in budget impact analyses.

Where a price reduction is offered by the company through the value-based pricing (VBP) process (see Section 8), multiple budget impact scenarios, using the proposed prices, may be presented to the DAC to inform their funding deliberations.

In instances where companies choose to submit costing information as part of their evidence submission to ACE, relevant information may be incorporated into ACE's budget impact analyses.

Table 8. Parameters considered in budget impact analyses

Parameter	Considerations
Target population	• Consistent with the patient population defined in the evaluation framework. Subgroup analyses can be performed if there is appropriate justification. • Singapore resident population (citizens + permanent residents) should be used in the calculations. • Potential population size should be specified and the estimation method described and justified. Attention should be paid to the evolution of the size of the target population over time with and without funding of the technology. • Diagnosis rates in line with local clinical practice should also be taken into account when calculating the proportion of patients who are likely to receive the intervention.
Comparators	Consistent with the comparator(s) defined in the evaluation framework.
Health outcomes	No health outcomes are presented in the analysis.
Costs	• Only the drug acquisition cost should be included (i.e. excluding margins). • Where appropriate, other direct healthcare costs may be considered. Indirect costs should not be included. • If a price reduction or patient assistance programme (PAP) has been proposed by the company in the pricing proposal (contingent on a positive funding recommendation), the net cost price after the price reduction or PAP is applied should be used in the base case. • Constant costs, that are not subject to inflation, should be used.
Handling uncertainty	Sensitivity analyses should be performed on key parameters to model their impact on the results.
Time horizon	The time horizon depends on the time needed to reach a steady state.
Discount rate	No discount rate should be applied.

7. Evidence Review Centres (ERCs)

Academic centres (usually from overseas institutions) which have experience in conducting and appraising HTAs may be consulted to review ACE's evaluation report and accompanying economic model for **full evaluations**. Expedited evaluations (which do not require a cost-utility analysis), are not typically subject to external review. Evidence Review Centres are usually given 4-8 weeks to review ACE's evaluations, depending on the complexity of the evaluation, and their comments and suggested amendments are incorporated into ACE's final evaluation report for the DAC's consideration.

8. Value-based Pricing

Value-based pricing (VBP) is conducted in parallel with technical evaluations to ensure that the price of patented drugs and vaccines recommended for funding is commensurate with their value in Singapore's context. The process enables ACE to engage in discussions with companies to determine the price at which their product best represents a cost-effective use of healthcare resources (Figure 4). VBP is conducted for all drugs, including biosimilars, and vaccines evaluated by ACE, unless there are generic formulations registered in Singapore.

8.1 Request for Proposal (RFP) and Deed of Agreement

Companies are invited to submit their best cost prices (i.e. the prices at which the companies sell their products to public healthcare institutions) and risk-sharing arrangement (RSA) proposal for their technologies under evaluation and detail any proposed patient assistance programmes (PAPs) or other arrangements in a Request for Proposal template. The impact of any proposed arrangements on the effective cost price should be clearly stated.

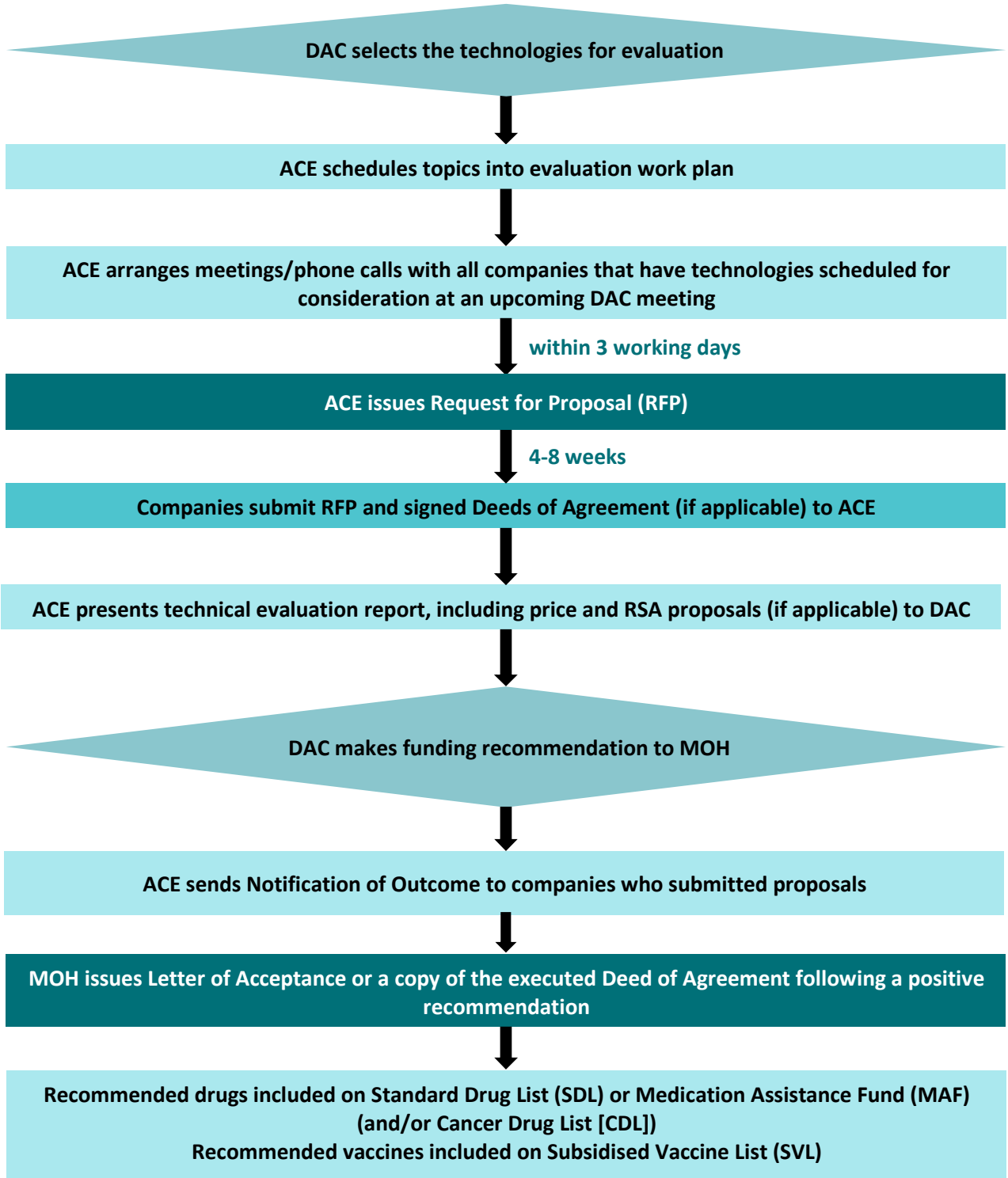
Companies are also required to provide additional sales information, such as the current cost prices of their technology, the number of units sold in the last 12 months to public patients (if applicable), and details of any existing PAPs operated in Singapore.

The deadline for submission of the RFP is typically **4-8 weeks**. Any request for an extension, is considered exceptional, and is subject to approval by ACE on a case by case basis. The tenure of the RFP validity is **18 months**, on balance of acceptability to companies, as well as the meeting schedule of the DAC.

Proposed prices and any RSA outlined in the RFP are used to inform ACE's evaluation, cost-effectiveness analyses (where applicable) and budget impact assessments. In instances where a company is required to submit more than one RFP during the course of the evaluation, any new proposals submitted shall supersede previous proposals, unless otherwise specified.

RSAs are established through a Deed of Agreement between the government (as represented by MOH Singapore) and the company. To confirm commitment to the RSA proposed, the company is required to sign the Deed of Agreement before the DAC meeting where their proposal is being considered. Deeds cannot be executed until the DAC has issued a positive recommendation.

Figure 4. Value-based pricing process



8.2 Notification of Outcome

A Notification of Outcome (NOO) is sent to **all companies** who submitted proposals to advise them of the DAC's recommendations, and provide sufficient time for downstream stock supply and inventory management at the public healthcare institutions. Each company is only

informed of the outcome for their product. Companies that receive a positive recommendation for their technologies should not disseminate the information in the NOO in an indiscriminate manner until the date of funding implementation.

Companies may request to have a post-decision meeting with ACE (via teleconference or in-person) for technologies that are not recommended for funding to discuss the clinical and/or economic evidence that informed the DAC's recommendations, key uncertainties in the evidence deliberated by the DAC and any pricing considerations. Face-to-face meetings are prioritised for companies who wish to address evidence gaps and/or propose a revised price or access arrangement in line with the resubmission process (see Section 8.4).

8.3 Letter of Acceptance or Executed Deed of Agreement

The Letter of Acceptance (LOA) or a copy of the executed Deed of Agreement is issued to **companies of technologies with positive funding decisions**. They specify the cost price and conditions of listing on the Standard Drug List (SDL) or Medication Assistance Fund (MAF) and/or Cancer Drug List (CDL) (for drugs) or on the Subsidised Vaccine List (SVL, for vaccines), and any terms for other pricing or access arrangements.

The LOA and Deed are legally binding agreements 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 company undertakes to sell the drug or vaccine at a cost price not exceeding the negotiated price agreed upon for funding when supplying it to the public healthcare institutions,
- the company undertakes to provide rebates (if applicable) once an agreed amount of expenditure has been exceeded, and
- MOH lists the drug on SDL or MAF (and for cancer medicines, on the CDL), or the vaccine on SVL, in line with specific clinical criteria.

These agreements set the cost-effective price and expenditure caps agreed upon for funding, provide traction against price increases, and ensure budget certainty for a subsidised drug or vaccine. From time to time, prices and details of funding arrangements may be subject to review, including but not limited to, circumstances such as expansion of indications, availability of new evidence that will change the original cost-effectiveness conclusions or regulatory approval of new products that are used in a similar population or used in combination with the original product that was funded.

8.4 Resubmission of price proposal following a negative recommendation

Companies are expected to provide their best and final prices for funding consideration of their product in the RFP. Immediate resubmission of a price proposal, in response to the NOO email, for drugs or vaccines which have not been recommended for funding is not allowed.

During the post-decision meeting, ACE will advise the company about the type of additional information required to address the DAC's concerns that led to the negative recommendation.

Pricing resubmissions are not allowed if the DAC does not recommend a technology for funding on the basis of insufficient clinical evidence. Companies may be invited to resubmit only when sufficient new evidence is available for DAC's reconsideration.

Companies that were unsuccessful in achieving funding for their products on the basis of uncertain or unacceptable cost-effectiveness or budget impact will be allowed to resubmit a revised price proposal once for the DAC to reconsider using a *Resubmission Form* that will be issued by ACE with the NOO email. It is not mandatory for companies to resubmit prices. Revised price proposals can be submitted during the resubmission period from 1 to 30 November in the next calendar year following the DAC meeting in which the technology was evaluated. In some instances, where there is a high unmet clinical need and a lack of treatment alternatives (for example, when none of the drugs within a class review are recommended for funding), companies may be contacted for price resubmissions earlier.

Companies will usually only be given one opportunity to submit a revised pricing proposal, unless the DAC requests further rounds of price resubmissions. Revised pricing proposals will be scheduled for the DAC's consideration at the next available meeting depending on the timing of existing procurement agreements between companies and public healthcare institutions for the technology under evaluation and/or its comparators.

8.5 Consideration of "me-too" products

If multiple drugs within the same class are considered by DAC to be clinically comparable, the lowest priced drug will be recommended for funding on a cost minimisation basis. Once the first drug in a class is listed on SDL or MAF, **one** additional me-too drug (with same formulation and indication as the first drug) may be added, usually **no earlier than 12 to 18 months after** the first drug was listed if its price is considered reasonable by the DAC and there is sufficient clinical need for an additional drug to be funded. A third drug within the class will only be considered for funding on an exceptional basis if it offers substantial benefits over existing funded drugs within the class.

If a drug 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 funded from the same class. All companies included in the class review will be invited to submit a price proposal (Section 8.1) to seek funding or to retain the existing 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 delisted from SDL or MAF for a particular indication will not be considered for re-listing for **at least 3 years**.

The same principles apply to vaccines, taking into consideration additional factors such as national demand and supply stability. More than one brand of vaccine may be listed for funding in the first instance if they are considered to be comparable.

8.6 Consideration of biosimilars

Companies should inform ACE of the availability of any biosimilar before its introduction into the local market to enable timely evaluation for funding consideration. Biosimilars will not automatically be funded even if their reference products or other biosimilars of the same 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 to inform the DAC's funding deliberations. As part of the evaluation, companies of the reference biologic and the biosimilar(s) will be invited to submit price proposals or provide consent for ACE to use the prices submitted for national procurement contracts to inform funding decisions by the DAC.

On the basis of the evidence and pricing proposal(s) presented, the DAC may recommend listing no more than one molecule (reference biologic or biosimilar) on a case-by-case basis. In some instances, the reference biologic may be delisted and replaced by a biosimilar brand. Public healthcare institutions will be informed of the DAC's decision shortly after the meeting and given sufficient time to implement the required changes, including allowing patients time to switch from the reference biologic to a biosimilar (in the event the reference product is recommended for delisting).

Over time, as prices become more competitive, more than one brand may be funded, however, the choice of product listed in the hospital formularies will be at the discretion of the individual public healthcare institutions.

9. Decision-making

9.1 MOH Drug Advisory Committee (DAC)

The DAC is an expert committee comprising senior clinicians (specialists and general practitioners) and pharmacists from public healthcare institutions, and senior regulatory affairs and healthcare finance representatives from MOH. It is chaired by the MOH Director-General of Health (DGH). In view of the members' request to remain anonymous, DAC membership is not published. 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 funding decisions for drugs, vaccines and gene therapies are made in an equitable, efficient and sustainable manner. The terms of reference of the DAC are to:

- prioritise drug applications for subsidy consideration which hold potential for driving significant improvement in health outcomes;
- appraise the clinical and cost-effectiveness of drugs, vaccines and gene therapies based on available therapeutic, clinical and pharmacoeconomic evidence;
- provide listing recommendations to MOH, including conditions and/or criteria for subsidy (SDL and MAF);

- provide recommendations to MOH about MediShield Life coverage for cancer treatments, including conditions and/or criteria for inclusion on the Cancer Drug List (CDL); and
- monitor the impact of ACE guidance on prescribers' behaviours.

The DAC usually meets 3 times a year. Additional meetings may be called by the Chairman where necessary, or decisions may be made via email for simple funding recommendations (e.g. for revisions to strengths of drugs that are already funded). Pre-meetings are also held with the Chairman before each DAC meeting.

A minimum attendance of half the number of members plus one at the DAC meeting is required for a quorum. ACE technical evaluation reports and pertinent information for the meeting discussion are provided to DAC members at least 2 weeks before the meeting date. Individual committee members are appointed as lead discussants for each topic to facilitate discussions during the meeting.

9.2 Factors informing funding decisions

The DAC makes funding recommendations informed by ACE's technical 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; and
- Budget impact.

Specific factors and judgments which are discussed by DAC when considering each criterion are described in Table 9. Additional factors, including social, cultural, and ethical issues, and other value judgments may also inform the DAC's funding considerations.

Table 9. 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	• Disease morbidity, mortality and patient clinical disability with current standard of care • Impact of the condition on patients' quality of life • Extent and nature of current treatment options	• 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 regulatory approval (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
Clinical effectiveness and safety	• Comparative clinical effectiveness and safety of the technology • Overall magnitude of health benefits to patients • Heterogeneity of health benefits within the population • Relevance of the technology under evaluation to current clinical practice	

	• Robustness of the current evidence and the contribution ACE's guidance might make to strengthen it	• The position of the technology in the overall pathway of care and the alternative interventions that are established in clinical practice
Value for money (Cost effectiveness)	• Technical efficiency (the incremental benefit of the technology under evaluation compared to current treatment)	• Robustness of costing information • Out of pocket expenses to patients • Key drivers of cost-effectiveness • Uncertainties around and plausibility of assumptions and inputs in the 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 and risk-sharing arrangements
Budget impact	• Estimated annual cost to healthcare system (Singapore government, insurance provider and patient)	

Additional considerations may also be taken into account for low to moderate cost treatments for rare and ultra-rare[3] diseases that are under consideration for funding, but which are unlikely to be cost effective due to the small number of patients who require them. Such treatments may be considered suitable for funding if they meet **all** of the following criteria:

i. Treatment is for a rare but clinically defined condition that is chronically debilitating, life-threatening or has a significant impact on a patient's quality of life; and
ii. Treatment is considered to be standard of care and clinically essential for the condition under evaluation in line with local and/or international clinical practice guidelines; and
iii. Treatment is registered by the Health Sciences Authority (HSA) or a reputed international regulatory authority (e.g. Food and Drug Administration (FDA, USA) and/or European Medicines Agency (EMA)) for the condition under evaluation (i.e. treatment has proven therapeutic modality); and
iv. There is a lack of affordable treatment alternatives (including non-drug therapy) for patients with the condition; and
v. There is sufficient evidence available to robustly assess the safety and clinical effectiveness of the treatment for patients with the condition.

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 local healthcare professionals and patients 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 topic under evaluation. In general, the DAC places greater importance on evidence derived from high-quality studies with methodologies designed to minimise bias.

[3] Rare is defined as <4 in 10,000 people (i.e. <1600 people with the condition in Singapore). Ultra-rare is defined as <2 in 50,000 people (i.e. <225 people with the condition in Singapore).

The DAC does not use a precise maximum acceptable ICER (i.e. an ICER threshold) to determine if a technology is cost effective. ICERs are not precise values and are associated with a degree of uncertainty. Therefore, the DAC considers sensitivity analyses, in addition to the base-case point estimate when determining if a technology represents good value for money. When assessing the annual cost of the technology to the healthcare system, the DAC is not restricted to only make recommendations below a certain budget impact threshold; however, technologies with a large budget impact will be subject to additional scrutiny and may take longer for MOH to approve for funding.

On the basis of the available evidence, the DAC recommends to MOH (Table 10):

i. whether a drug should receive government subsidy through inclusion on the Standard Drug List (SDL) or the Medication Assistance Fund (MAF);[4]
ii. whether a vaccine should be included on the Subsidised Vaccine List (SVL) and receive government subsidy; and
iii. whether a cancer drug should be included on the Cancer Drug List (CDL) and be eligible for government subsidy and/or claims under MediShield Life and MediSave.

Table 10. Types of recommendations made by DAC

Decision	Type of Recommendation
Technology provides similar or greater health benefits at a lower cost than the comparator(s)	Recommended
Technology provides less health benefit at a similar or greater cost than the comparator(s) **OR** Technology provides similar health benefits at a greater cost than the comparator(s)	Not Recommended
Technology provides greater health benefits at a greater cost than the comparator(s)	Recommended / Not Recommended depending on the magnitude of incremental benefit, clinical need for treatment and other value judgements that informed the DAC's recommendation

The DAC may recommend the use of a technology in line with the full indication under evaluation, or for a subgroup of the population, if:

- there is clear evidence that the technology 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.

The SDL includes low- to moderate-cost therapies essential for the management of common conditions affecting the majority of patients. The MAF typically includes moderate- to high-cost treatments that are not on the SDL but have been assessed to be clinically and cost effective. Drugs listed on the MAF are subsidised for specific indications governed by clinical criteria to ensure appropriate use, whereas drugs on SDL are subsidised for any indications approved by HSA.

[4] Drugs on the SDL are subsidised at 50% for all Singapore citizens who are patients in a public healthcare institution. Patients from lower to middle income households can receive more subsidy up to 75%. For drugs on the MAF, eligible patients can receive 40-75% assistance based on means testing.

The Cancer Drug List (CDL) outlines all cancer drugs and their clinical indications that are claimable under MediShield Life and MediSave. The list also indicates the corresponding claim limits for each drug. Generally, only cancer drugs that have been assessed to be clinically effective and cost effective are included on the CDL.

If the DAC considers a cancer drug for funding, the DAC Chairman and Minister for Health will subsequently determine if it should be included on the Cancer Drug List (CDL) and its corresponding claim limits under MediShield Life and MediSave.

10. Guidance and funding implementation

10.1 Drafting ACE guidance

Following the DAC meeting, the ACE technical team draft a guidance document for each topic to outline the DAC's recommendation(s), the rationale for the recommendation, and a summary of the key clinical and economic evidence which informed the DAC's deliberations. Guidance documents are produced for positive and negative recommendations. A plain English summary (PES) is also produced to explain the DAC's recommendations in non-technical language for patients and the public. Guidance documents and PES are typically published on the ACE website (www.ace-hta.gov.sg) before funding is implemented.

Guidance documents do not contain confidential information. For full evaluations, where an economic model has been developed by ACE, base case ICERs are not reported in the guidance due to commercial sensitivities regarding the price used in the model. Instead, an ICER range is described as follows:

- Dominant (i.e. cost saving and health improving);
- 0 to <SG$15,000/QALY gained; then
- SG$15,000 to <SG$45,000/QALY gained; then
- SG$45,000 to <SG$75,000/QALY gained; then
- SG$75,000 to <SG$105,000/QALY gained; then
- SG$105,000 to <SG$135,000/QALY gained; then
- SG$135,000 to <SG$165,000/QALY gained; then
- SG$40,000 increments to SG$365,000 (i.e. SG$165,000 to <SG$205,000/QALY gained, SG$205,000 to <$245,000/QALY gained etc.); then
- >SG$365,000/QALY gained.

The annual budget impact to the healthcare system for funding the drug under evaluation is also presented in ranges, such as:

- Cost saving
- <SG$1 million
- SG$1 million to <SG$3million
- SG$3 million to <SG$5 million
- SG$5 million to <SG$10 million
- >SG$10 million

10.2 Funding implementation

Funding implementation for recommended drugs and vaccines typically occurs within 4 to 6 months after each DAC meeting once financing is approved by MOH and the LOA and/or Deed of Agreement is signed by MOH and the company (Section 8.3). To assist with the smooth adoption of the recommendations, ACE communicates funding 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, inventories and procurement processes, if necessary. This may be followed by targeted engagements to brief healthcare professionals about the rationale for funding decisions, and to work with them to ensure that funded drugs and vaccines are made available for those who require them.

For funding decisions which are contingent on specific prices agreed with the company through the VBP process, public healthcare institutions will be instructed to purchase the drug or vaccine through ALPS Pte Ltd, and adhere to the maximum selling price (cost price plus stipulated margin) that was recommended by DAC. This ensures that the savings generated from price reductions offered by the company are passed onto the patients and selling prices are consistent across the public healthcare institutions. Companies are required to effect new prices two months before funding implementation dates.

10.3 Evaluation of post-funding drug utilisation

After a drug has been recommended for funding, ACE conducts drug utilisation reviews and monitors procurement and selling prices at each public healthcare institution.

To measure the impact of funding and guidance recommendations, ACE examines the utilisation of drugs before and after funding implementation to understand if the intended consequences have been achieved e.g., whether reducing the affordability barrier through funding has resulted in a positive utilisation trend. Utilisation reviews can be conducted for a specific drug or in conjunction with appropriate alternative treatments (comparators) to assess if guidance recommendations have led to a change in prescribing behaviour. Where required, educational audits will be conducted to improve adherence to the guidance recommendations for identified institutions.

10.4 Review of guidance and funding recommendations

Each guidance will be considered for review 3-5 years after publication to ensure that the recommendations remain relevant to clinical practice. At that time, the ACE technical team will determine whether any new clinical evidence or cost information has become available since the original evaluation, which is likely to have a material effect on the funding decision and guidance recommendations.

Where considerable new clinical and/or cost information becomes available after the original evaluation, the topic will be scheduled into the ACE work plan for re-evaluation. Following DAC's consideration of the new evidence, the existing guidance may remain the same, be revised, or be superseded with new guidance, depending on the DAC's recommendations.

For topics where a technology has not been recommended for funding due to unacceptable cost effectiveness or budget impact, and negative guidance has been published, companies are able to request for the DAC to reconsider their product at a revised price in line with the price resubmission process (see Section 8.4 for information on price proposal resubmissions). If the DAC recommends a technology for funding on the basis of the revised pricing proposal, existing ACE guidance will be updated to acknowledge the new information submitted and the revised funding recommendations, if applicable.

Addendum 1: Evaluation methods and processes for medicines under consideration for inclusion in the Rare Disease Fund (RDF)

Introduction

The Rare Disease Fund (RDF), jointly established by MOH and SingHealth Fund, was launched in July 2019 to provide long-term financial support to patients with rare[5] and ultra-rare[6] genetic diseases who require high-cost treatments. It is a national multi-stakeholder charity fund, overseen by the KK Women's and Children's Hospital (KKH), that combines community donations with 3-for-1 government matching, and is intended to be a last-line of support after government subsidies, insurance and other financial assistance. Specific information about the RDF can be found on the KKH website.

RDF eligibility

Under the RDF, financial support is provided to Singapore citizens who require treatment with medicines that are covered under the fund. Children and adults with rare diseases who are treated at any public healthcare institution in Singapore may apply for RDF financial support.

Explicit criteria to determine whether medicines are eligible for inclusion in the RDF have been developed to guide decision-making. Medicines should also be fairly priced relative to overseas reference jurisdictions to be considered for inclusion in the RDF.

Eligibility criteria for medicines considered for inclusion in the RDF

Medicines supported under the RDF should meet **all** of the following criteria:

1. Medicine is registered by the Health Sciences Authority (HSA) or a reputed international regulatory authority (Food and Drug Administration (US FDA) and/or European Medicines Agency (EMA)) for the condition assessed (i.e. medicine has proven therapeutic modality);
2. Medicine treats a rare, but clinically defined genetic condition that is chronically debilitating or life-threatening;
    - There is acceptable evidence that the condition causes a significant reduction in either absolute or relative age-specific life expectancy or quality of life for patients with the condition;
3. There is acceptable evidence that the medicine is likely to substantially extend a patient's lifespan and improve their quality of life as a direct consequence of its use;
4. There is no cheaper alternative option (including non-drug therapy) for the condition;
5. The medicine is not indicated for the treatment of other conditions, or if it is, the cumulative prevalence across all indications still falls within the definition of rare (<1,600 patients across all indications); and
6. The annual cost of the medicine would constitute an unreasonable financial burden on the patient and/or their family or carer.

[5] Rare is defined as <4 in 10,000 people (i.e. <1,600 people with the condition in Singapore)
[6] Ultra-rare is defined as <2 in 50,000 people (i.e. <225 people with the condition in Singapore)

Topic selection and evaluation

All public healthcare institutions are invited to propose new medicines for inclusion in the RDF each year, alongside the annual call for drug applications for funding consideration (Section 2.1). The annual invitation is sent to the Chairman of the Medical Board (CMB, 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 CMB (or equivalent body) for endorsement and collation before submission to the MOH DAC Secretariat. New medicines which are not requested during the annual call for topics can be submitted to ACE throughout the year by PHIs or individual clinicians responsible for the care of a patient with a rare disease, if there is a high clinical need for the treatment to be included in the RDF.

Each potential topic is prioritised for evaluation by ACE in consultation with the MOH Rare Disease Expert Group (RDEG), which comprises local clinical experts with experience in the treatment of rare diseases.

The role of RDEG is to:

i. provide information regarding the estimated number of patients with specific rare diseases in Singapore and current clinical practice for the management of their conditions;
ii. advise about medicines which meet the eligibility criteria for inclusion in the RDF;
iii. address any clinical questions about specific rare diseases or treatments; and
iv. propose initiation and continuation clinical criteria for each treatment listed on the RDF to ensure treatments are used appropriately and that only patients who have an adequate clinical response to treatment continue to receive funding.

The ACE technical team prepares a clinical briefing document for each topic selected for evaluation in consultation with RDEG, which includes a summary of published clinical evidence, funding decisions from overseas reference agencies, local costing information and published prices in five overseas reference jurisdictions (Australia, New Zealand, UK, South Korea, and Taiwan) where available.

Request for information from local suppliers

All known local suppliers of medicines under consideration for inclusion in the RDF are sent a *Request for Information* (RFI, see Annex 2) by ACE to provide local pricing information, and published overseas prices and ex-manufacturer prices in reference jurisdictions in their local currencies. This information is used for external price referencing and is included in ACE's clinical briefing document to inform funding deliberations.

Decision-making

The RDF is overseen by a voluntary RDF Committee comprising community representatives who approve the medicines covered under the RDF, subject to sufficient funds, and determine the amount of financial support for each eligible patient according to their needs. They are also responsible for supporting fundraising efforts for the RDF. KKH has been appointed as the Secretariat of the RDF Committee.

Recommendations from RDEG and ACE's clinical briefing document are shared with the RDF Committee to inform their deliberations about which medicines should be included in the RDF. Notwithstanding, the assessment and recommendations made by ACE and RDEG are non-binding, and the RDF Committee can choose to deviate from them. The RDF Committee will only allow new medicines to be included in the RDF if there are sufficient funds to cover the estimated life-time treatment cost for patients with the condition, taking into consideration the number of existing patients, and the projected annual incident population over a five-year period.

Furthermore, funding support through the RDF will generally only be extended to a medicine if its price in Singapore is comparable, and not higher than, published prices in overseas reference jurisdictions. This ensures prudent use of charity funds and helps ensure the sustainability of the RDF.

Medicines which are recommended for inclusion in the RDF are published on the KKH website. All suppliers who submit RFIs are informed of the RDF Committee's recommendations through a *Notification of Outcome* (NOO) email sent by ACE.

Procurement of medicines recommended for inclusion in the RDF

Following a positive recommendation from the RDF Committee to include a medicine in the RDF, ALPS Pte Ltd. is responsible for establishing procurement arrangements, and securing supply of the medicine with the supplier for all public healthcare institutions who require it.

ACE provides pricing information gathered during the development of the clinical briefing document to ALPS to assist with their supply negotiations. Any changes to the price of a medicine after it has been recommended for inclusion in the RDF will be communicated to the RDF Committee, who may reconsider the original funding decision and amend funding recommendations at their discretion, if required.

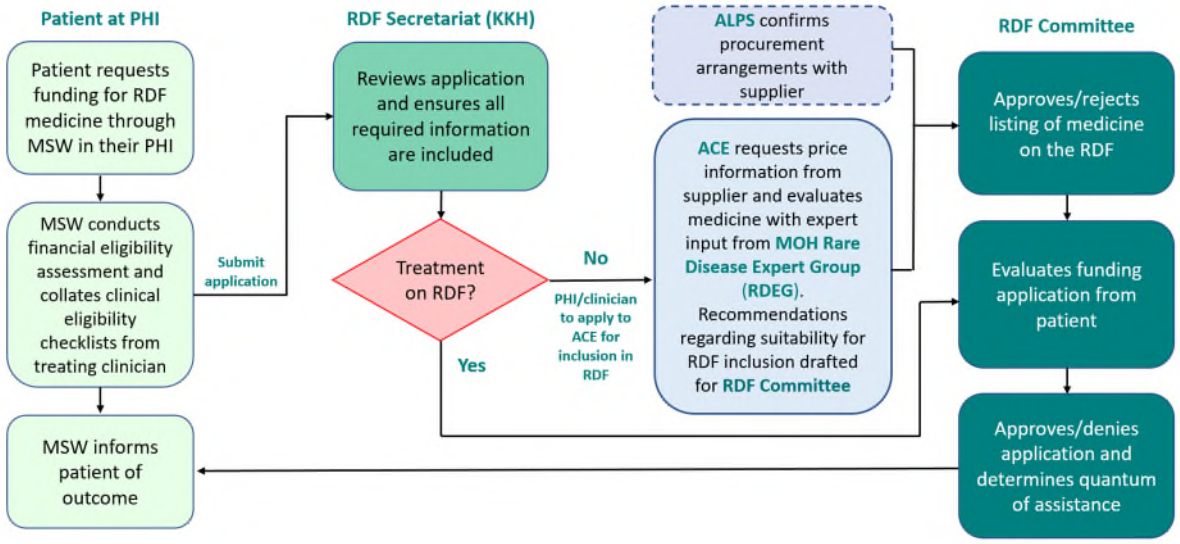
Price resubmissions

Suppliers of medicines that receive a negative recommendation for inclusion in the RDF due to pricing considerations may be contacted by ACE to resubmit a pricing proposal at the RDF Committee's request. For medicines that receive a positive recommendation for inclusion in the RDF, the ACE technical team will review overseas prices periodically and may request suppliers to revise their local prices to ensure they continue to be comparable to reference jurisdictions.

Patient application process

The RDF Secretariat (KKH) has developed workflows to ensure that all applications from patients requesting financial assistance for medicines included in the RDF are handled in a systematic manner. Medical social workers (MSW) in each public healthcare institution (PHI) oversee the application process and assist patients and their clinician(s) prepare the required documentation (Figure A1). Each patient is assessed to determine whether they meet specific clinical and financial eligibility criteria for the treatment, and the amount of financial assistance that they require.

Figure A1: High level process for patient applications for RDF financial support



Key: MSW, medical social worker; PHI, public healthcare institution; RDF, Rare Disease Fund; ALPS, agency responsible for national supply chain and procurement in the public healthcare sector; MOH RDEG, Ministry of Health Rare Disease Expert Group

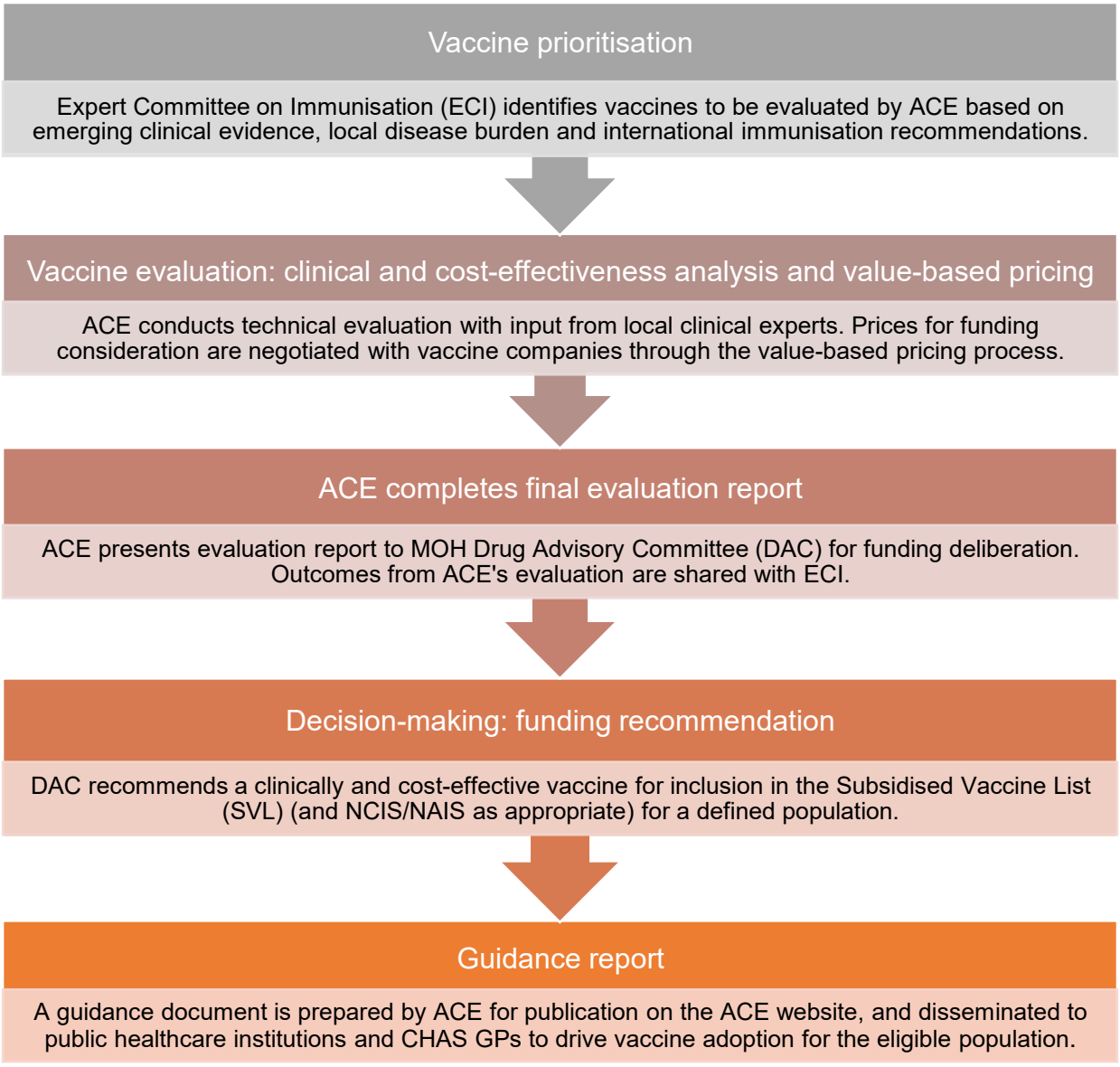
Patient applications are considered by the RDF Committee on a case-by-case basis. The amount of financial assistance provided to a patient each year is determined by the RDF Committee in line with the patient's clinical and financial eligibility assessment. Patients are required to reapply annually for financial assistance through the RDF and will be subject to a review of their clinical and financial eligibility each time.

Addendum 2: Evaluation processes for vaccines under funding consideration

Introduction

Specific brands of vaccines in the Subsidised Vaccine List (SVL) that are administered in public hospitals, specialist outpatient clinics, polyclinics and CHAS GP clinics are eligible for government subsidy when they are used in line with criteria described in the National Childhood Immunisation Schedule (NCIS) and National Adult Immunisation Schedule (NAIS). This addendum describes the evaluation and decision-making processes for vaccines under consideration for inclusion in the SVL. Key steps in the process are shown in Figure A2.

Figure A2: High level process for vaccines undergoing evaluation for funding



Topic selection

The Expert Committee on Immunisation (ECI) advises MOH about vaccines that should be considered for the Singapore population to reduce vaccine-preventable diseases, taking into consideration the local disease burden and vaccine safety and efficacy. They are also responsible for:

1. Prioritising vaccines for evaluation by ACE for funding consideration, according to local disease burden and clinical need, international best practice recommendations, and whether there is sufficient evidence on the safety and clinical efficacy of the vaccine to inform an evaluation; and
2. Providing technical advice to the MOH DAC on matters relating to the evaluation of new vaccines for funding consideration.

Vaccine topics prioritised by the ECI for evaluation are scheduled into ACE's workplan depending on the resources available and the estimated time needed to complete the evaluation.

Evaluation

Vaccines are typically subject to full evaluation, in line with the evidence requirements and processes described for drugs in Sections 5 and 6 of these guidelines. Companies are invited to submit a price proposal for funding consideration through the value-based pricing (VBP) process (see Section 8). Each evaluation can take 6-12 months to complete depending on the complexity of the topic and the type of economic modelling required.

Evaluations may be completed in-house by the ACE technical team and then sent to an ERC to review (see Section 7), or in situations where complex economic modelling is required (e.g. transmission dynamic models), ACE may engage academic centres with specific expertise in vaccine modelling to assist with the evaluation. All evidence is compiled into a full evaluation report by the ACE technical team to inform the funding deliberations.

While the general evidence requirements and processes for evaluating drugs and vaccines for funding consideration are similar, additional information (non-exhaustive) that is taken into consideration for vaccines is summarised in Table B1.

Table B1. Key additional evidence requirements for vaccines

Component of vaccine evaluation	Requirements
Evaluation framework	• **Population** refers to the individuals who will be vaccinated to prevent the target health condition (primary and catch up cohorts should be defined where relevant) • **Intervention** refers to the vaccine under evaluation. This can be a new vaccine for a new condition or an alternative for a vaccine already listed on NCIS/NAIS/SVL. • **Comparator** refers to an alternative vaccine on NCIS/NAIS/SVL which is also used to prevent the target health condition. If there is currently no vaccine available, the comparator is usually standard medical management. Different comparators that may be relevant for different age and/or population groups should also be considered.

	• **Outcomes** refer to measures of vaccine effectiveness including efficacy, immunogenicity outcomes, waning effectiveness, herd immunity and adverse events
Vaccine properties	• Nature of the immunising agent(s) (e.g. live, attenuated or killed; absorbed or non-absorbed; viral or bacterial) • Amounts of antigens (components) • Requirements for cold chain management • Vaccine presentation (e.g. single vial, prefilled syringe, multidose vial) • Proposed dosing schedule including number of doses for each age group to be vaccinated in the context of the NCIS/NAIS and whether primary immunisation and/or booster vaccinations are required • Programme requirements for administration • Consider whether a vaccination course that begins with the vaccine under evaluation can be completed with an alternative vaccine (or vice versa) • Any restrictions on the use of the vaccine in certain populations, seasons or in people with specific risk factors (e.g. underlying medical conditions). Consider if there is any age limit or circumstances after which there would be no benefit in administering the vaccine. • Similarities/differences between the vaccine under evaluation and vaccines currently available on NCIS/NAIS in terms of their antigen content and dosage schedules • Additional medicines that are recommended as part of the vaccine administration (e.g. paracetamol to manage adverse events) • Any expectation from the company of a limited initial supply, where relevant
Clinical assessment	• Consider all available clinical evidence on the effectiveness of the vaccine for the primary cohort and any catch up cohorts, where relevant • Where the clinical assessment of a vaccine is based on short-term surrogates, discuss long-term outcomes such as waning of effect and resulting disease, and long-term sequelae • Components of a vaccine combination product should have an additive (not necessarily synergistic) beneficial effectiveness. For a proposed combination vaccine, assess whether there is any clinically important loss of effectiveness when antigens are combined compared with when they are given individually (i.e. assessing non-inferiority) • Claims of superiority based on immunogenicity surrogates/correlates rather than clinically important outcomes should be scrutinised and only accepted if the standards of measurement are appropriately validated and/or in line with internationally accepted standards • Ensure that the assessment of comparative harms extends beyond those temporarily associated with the administration of the vaccine to those that might emerge sometime after the vaccine course is completed. Consider how adverse events were ascertained in the trials.
Economic evaluation	• Use a static model when the force of infection (probability per unit of time that a susceptible person acquires infection) is constant over time. Static models are usually structured as decision analysis models of Markov models and ignore herd

	immunity effects. A static model is appropriate where a small proportion of the population is going to be vaccinated either through low coverage or targeted vaccination, or the proposed vaccine does not prevent circulation of the pathogen, and herd immunity effects are expected to be negligible. • Use a dynamic model when the force of infection is likely to change after vaccination (i.e. if the proposed vaccine blocks transmission of infection and coverage is extensive), and when the risk or severity of the disease depends on age. Dynamic models allow herd immunity and age shift to be assessed.
Calculation of costs	• Only direct healthcare costs should be included • Identification, measurement and valuation of costs should be consistent with the perspective of the Singapore healthcare system (government, insurance provider and patient healthcare costs) • Indirect healthcare costs or non–healthcare costs should not be included in the reference case analysis, but may be considered in secondary analyses • Consider the costs associated with administration of the vaccine and for additional medicines/monitoring required to manage potential adverse reactions to vaccination
Catch up program	• A catch up program provides coverage of individuals who are older than the age range specified for delivery of the primary vaccination program. A catch up program might provide a faster onset of any herd immunity generated by the vaccine. • Describe the arrangements for any catch up program(s) requested by ECI including the age range(s) of eligible individuals (and any other characteristics of the eligible individuals) and the requested duration(s) of the catch up program. Consider the anticipated vaccine uptake in the proposed catch up cohort(s).
Herd immunity	Evidence supporting likely herd immunity benefits may include any or all of the following factors: • The proposed vaccine protects against a new infection/disease and/or reactivation of an existing infectious pathogen to cause disease • The efficacy of the proposed vaccine is sufficient to reduce the proportion of susceptible individuals, carriage of the relevant pathogen and/or transmission of the pathogen to susceptible non-immunised individuals • The disease is sufficiently severe or prevalent in an unimmunised population to justify maximising the use of the proposed vaccine to achieve a broader community health benefit

Decision-making and guidance production

Vaccine funding decisions are made by the MOH Drug Advisory Committee (DAC) in line with the processes described in Section 9. When required, members from the ECI are invited to attend the DAC meeting and provide expert advice when a vaccine topic is under consideration.

All companies who submit RFPs for vaccines under consideration (Section 8) are informed of the DAC's recommendations through a *Notification of Outcome* (NOO) email sent by ACE (Section 8.2). Guidance describing the DAC's recommendations is produced for publication on the ACE website for positive and negative funding decisions (see Section 10). Vaccines

that are recommended for inclusion in the SVL are published on the MOH website on the date of funding implementation. Public healthcare institutions and CHAS GPs are advised of the DAC's recommendations before funding implementation to allow them sufficient time to amend their formularies and make the necessary procurement arrangements.

Procurement of vaccines recommended for funding

Following a positive recommendation from DAC, ALPS Pte Ltd. is responsible for establishing procurement arrangements and securing supply of the vaccine with the supplier for all public healthcare institutions.

ACE will be notified of any changes to the price of a vaccine after it has been recommended for funding and will advise the DAC, who may reconsider the original funding decision.

Price resubmissions

Companies that were unsuccessful in achieving funding for their vaccine on the basis of uncertain or unacceptable cost-effectiveness or budget impact can resubmit a revised price proposal once for the DAC to reconsider using a *Resubmission Form* that will be issued by ACE with the NOO email. It is not mandatory for companies to resubmit prices. Revised price proposals can be submitted during the resubmission period from 1 to 30 November in the next calendar year following the DAC meeting in which the vaccine was evaluated. In some instances, where there is a high unmet clinical need and a lack of alternatives, companies may be contacted for price resubmissions earlier.

Annex 1: Company evidence submission template to support ACE's evaluation

Instructions for companies

This is the template for submission of supplementary evidence to support an evaluation by the Agency for Care Effectiveness (ACE). It is not mandatory for companies to provide 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 funding considerations, irrespective of company involvement. Any evidence provided by the company will be incorporated into ACE's evaluation.

Text in parentheses is intended to inform companies about the type of information they may choose to include in each section and can be removed from the 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

[Evaluation title]

Company evidence submission to support ACE's evaluation

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 current clinical practice to manage the indication under evaluation and list the clinical guidelines (both local and international) which are most commonly used by clinicians in Singapore. Describe any issues relating to current clinical practice, including patients' unmet needs, and any variations or uncertainties in established practice. 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 funded. Estimate how many patients are likely to use the technology in Singapore for the indication under evaluation.]

Summary of clinical effectiveness and safety evidence

[ACE technical staff will have access to all published information to inform their evaluation. Therefore, companies are encouraged to summarise additional (unpublished) information in this section to demonstrate the value of their product and address any clinical uncertainties that may be apparent in the published trials to support ACE's evaluation. Provide a brief overview of the pivotal clinical trials which demonstrate the clinical effectiveness of the technology at its approved 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 2: Request for Information (RFI) template

1. Supplier's profile

Company name:	
Company address:	
Contact person & title:	
Phone:	
Email:	

2. Cost price and volume for Singapore

	Usual cost price per [unit], excluding GST (SGD)	**Number of units sold in the last 12 months [MM YYYY to MM YYYY]**	**Estimated patient numbers in the last 12 months [MM YYYY to MM YYYY]**
[name of drug, strength and pharmaceutical form]			

3. Patient Assistance Programmes (PAPs) (if applicable)

	Please provide details of any existing PAPs, including eligibility criteria, level of funding support and patient numbers on PAP
[name of drug, strength and pharmaceutical form]	

4. Overseas prices

	Published list price per [unit], excluding GST/VAT in local currencies*				
	Australia	**New Zealand**	**United Kingdom**	**South Korea**	**Taiwan**
[name of drug, strength and pharmaceutical form]					

* Please state currency exchange rate.

	Ex-manufacturer price (cost price) per [unit], excluding GST/VAT in local currencies*				
	Australia	**New Zealand**	**United Kingdom**	**South Korea**	**Taiwan**
[name of drug, strength and pharmaceutical form]					

* Please state currency exchange rate.

The Agency for Care Effectiveness was established by the Ministry of Health Singapore to drive better decision-making in healthcare through health technology assessment, clinical guidance, and education.

Drug and Vaccine Evaluation Team
Agency for Care Effectiveness
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