## Record of updates

<table>
<thead>
<tr>
<th>Date</th>
<th>Version</th>
<th>Summary of changes</th>
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<tbody>
<tr>
<td>February 2018</td>
<td>1.0</td>
<td>Publication of initial methods and process guide.</td>
</tr>
<tr>
<td>December 2019</td>
<td>2.0</td>
<td>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.</td>
</tr>
<tr>
<td>June 2021</td>
<td>3.0</td>
<td>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 guidances have also been updated. Additions and amendments throughout the document (including annexes) have also been made to improve the clarity of the text.</td>
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Foreword

The Agency for Care Effectiveness (ACE) is the national health technology assessment (HTA) agency in Singapore residing within the Ministry of Health. It produces evidence-based evaluations of health technologies (e.g. drugs, vaccines and medical technologies) to inform subsidy 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 www.ace-hta.gov.sg/about.

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 government subsidy. This guide is not intended to be a comprehensive academic document or to describe all technical details relating to health economic analyses. Rather, the intention of this guide is to standardise and document the methods that ACE staff follow when conducting drug and vaccine evaluations, and clearly outline ACE’s processes and decision-making frameworks. Procedures and methods that pharmaceutical manufacturers are expected to follow when preparing an evidence submission to ACE through the pilot company-led submission process from January 2021, are outlined in a separate document and are not described here.

While this document forms an important part of the Ministry of Health Drug Advisory Committee’s (DAC) decision-making processes for drug and vaccine subsidy, 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 and pharmaceutical manufacturers who provide evidence and advice to support ACE’s evaluations. ACE will continue to review and update this guide to ensure that it remains a useful resource for the Singapore healthcare system.

ACE would like to thank the following experts for their comments during the development of version 1.0 of this guide (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), The 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 ACE’s HTA methods and processes for the evaluation of 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 manufacturers who submit evidence to inform ACE’s evaluations.

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

Figure 1. Overview of evaluation process

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

2. Topic Selection

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 individual public healthcare professionals. New and emerging drugs that might be suitable for evaluation are also identified through literature searches and horizon scanning by the ACE technical team in conjunction
with pharmaceutical manufacturers, who are invited to share their regulatory pipeline with ACE each year (in December).

Public healthcare institutions are invited to submit applications for the inclusion of drug preparations into the MOH List of Subsidised Drugs on an annual basis (during December to April). 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.

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 which 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 manufacturer 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 topic areas are also currently outside the remit of ACE’s drug evaluations:

- General Sales List (GSL) medications
- Extemporaneous preparations
- Dialysis solutions
- Fertility drugs
- 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 registered 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 subsidy 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).

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.

**Table 1. ACE drug topic selection criteria**

<table>
<thead>
<tr>
<th>No.</th>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Type of gap that drug (intervention) will fill in clinical practice</td>
<td><strong>Chemical gap:</strong> Alternative treatment for the condition of interest is already subsidised but from a different drug class to the intervention. <strong>Therapeutic gap:</strong> No treatment for condition of interest is currently subsidised.</td>
</tr>
<tr>
<td>2.</td>
<td>Unmet clinical need</td>
<td>Extent to which condition is currently being adequately treated in local clinical practice.</td>
</tr>
<tr>
<td>3.</td>
<td>Disease severity</td>
<td>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.</td>
</tr>
<tr>
<td>4.</td>
<td>Size of affected population in Singapore</td>
<td>The estimated size of the patient population that is affected by the underlying health condition and which may be eligible for the intervention.</td>
</tr>
<tr>
<td>5.</td>
<td>Comparative clinical effectiveness (from published literature)</td>
<td>Added or reduced clinical benefit of the intervention compared to alternatives.</td>
</tr>
<tr>
<td>6.</td>
<td>Relative safety (from published literature)</td>
<td>Safety of the intervention compared to alternatives.</td>
</tr>
<tr>
<td>7.</td>
<td>Cost-effectiveness (from published literature)</td>
<td>Dominance or incremental cost-effectiveness of intervention compared to alternatives.</td>
</tr>
<tr>
<td>8.</td>
<td>Resource impact</td>
<td>Estimated annual budget impact required to subsidise technology for condition under evaluation. Cost of additional services, facilities, tests or staff requirements needed if the intervention is subsidised.</td>
</tr>
</tbody>
</table>
3. Technology Evaluation

3.1 Type of evaluation

Information regarding the evaluation process for vaccines under subsidy consideration 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 and pharmaceutical manufacturers, 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 already available as a generic formulation, 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 health system; or
- therapeutically inferior to the comparator but is likely to result in lower costs to the health 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 health system compared to the comparator).

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.

¹ From 2021, under a new pilot company-led process, pharmaceutical manufacturers will be responsible for providing an evidence submission for cancer treatments to ACE to support the DAC’s deliberations instead of ACE staff conducting the technical evaluation in-house. The aim of the new process is to enable drugs to be evaluated close to the anticipated date of regulatory approval by the Health Sciences Authority (HSA) and expedite subsidy considerations to improve patient access to clinically necessary treatments. Initially, only evidence submissions for new oncology products (or new indications of existing oncology products) will be eligible for evaluation through this route. More information about the company-led submission process is available at https://go.gov.sg/company-guidelines.
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

<table>
<thead>
<tr>
<th>Type of evaluation</th>
<th>Types of evidence and analyses included in evaluation</th>
<th>Time Required</th>
</tr>
</thead>
</table>
| Expedited evaluation | - Qualitative written survey of clinical experts (and/or face-to-face meetings) to inform local treatment algorithm, define comparator(s), and describe current use of drug(s) in local practice and patients’ clinical need for drug subsidy  
- Literature search of published clinical and economic evidence (local and international studies) and review of retrieved studies  
- Review of previous assessments by international HTA agencies  
- Cost-minimisation analysis (CMA) may be conducted  
- Value-based pricing proposal from manufacturer  
- Budget impact analysis, including estimated volume and annual cost to government for listing drug(s) on SDL or MAF | 2 to 3 months |
| Full evaluation | - Stakeholder workshop with local healthcare professionals to define the scope of the evaluation  
- Systematic review of published clinical evidence (local and international studies). Indirect comparisons, pairwise meta-analyses and network meta-analyses undertaken if required.  
- Literature search of published economic evidence (local and international studies) and review of retrieved studies  
- Development of economic model (cost-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 manufacturer  
- Budget impact analysis, including estimated volume and annual cost to government for listing drug(s) on SDL or MAF | 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

Overviews of the processes for expedited and full evaluations are shown in Figures 2 and 3 respectively.
Figure 2. Overview of expedited evaluation process for drug topics

1. Topic selected for expedited evaluation
2. ACE develops qualitative survey for clinical experts to define the local treatment algorithm for the condition under evaluation, and the current use of intervention and comparator treatments in Singapore
3. Evaluation framework (PICO elements) defined by ACE in consultation with clinical experts from different public healthcare institutions
4. ACE collates responses from clinical experts for inclusion in evaluation report
5. Value-based pricing (VBP) takes place in parallel, if applicable. Companies may submit a brief (5-page) summary of pivotal clinical evidence as part of their pricing proposal (RFP) to supplement ACE’s evaluation
6. ACE conducts expedited evaluation internally – which includes review of published local and international clinical and economic evidence and a local budget impact analysis
7. ACE completes evaluation report
8. (a) ACE presents evaluation report to MOH Drug Advisory Committee (DAC) for deliberation
   (b) DAC makes subsidy recommendations (subject to financing approval)
9. (a) ACE prepares Drug Guidance and Plain English Summary for publication on website
   (b) Guidance disseminated to public healthcare institutions ahead of implementation to allow sufficient time to revise formularies and make required procurement arrangements
Figure 3. Overview of full evaluation process for drug topics

1. Topic selected for full evaluation
2. ACE identifies clinical experts and forms Expert Working Group
3. ACE develops draft scope and prepares for evaluation
4. ACE conducts Scoping Workshop with Expert Working Group to discuss local treatment algorithm for the condition under evaluation, and the current use of the intervention and comparator treatments in Singapore
5. (a) ACE finalises scope in line with clinical expert feedback
   (b) Scope sent to manufacturer to inform their (optional) evidence submission (35 pages)
6. Manufacturer submits evidence (optional) as supplementary evidence to inform ACE's evaluation
7. Value-based pricing (VBP) takes place in parallel, if applicable. Manufacturer sent Request for Proposal (RFP) for completion.
8. ACE conducts full evaluation internally – which includes systematic review of clinical evidence, local economic evaluation & budget impact analysis
9. ACE may approach manufacturer for clarification after evidence submission and RFP received
10. ACE completes first draft of evaluation report
11. Draft sent to Independent Evidence Review Group (if required) to critique
12. ACE completes final evaluation report
13. (a) ACE presents evaluation report to MOH Drug Advisory Committee (DAC) for deliberation
   (b) DAC makes subsidy recommendations (subject to financing approval)
14. (a) ACE prepares Drug Guidance and Plain English Summary for publication on website
   (b) Guidance disseminated to public healthcare institutions ahead of implementation to allow sufficient time to revise formularies and make required procurement arrangements
3.3 Defining the evaluation framework

Before a technology evaluation commences, the ACE technical team use the PICO framework (population, intervention, comparators, and health outcome 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

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<tr>
<th>P</th>
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<th>C</th>
<th>O</th>
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</thead>
<tbody>
<tr>
<td><strong>Patient/Population</strong></td>
<td><strong>Intervention/Exposure</strong></td>
<td><strong>Comparators</strong></td>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>• Patient or population characteristics</td>
<td>Technology under evaluation</td>
<td>Alternative treatment option(s) to the intervention used in routine clinical practice</td>
<td>Patient-relevant clinically meaningful health outcomes of interest</td>
</tr>
<tr>
<td>• Condition/disease of interest</td>
<td></td>
<td></td>
<td></td>
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</table>

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 (for registered products) or the intended registered indication identified through horizon scanning (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 through a scoping workshop (Section 4.2).

4. Scoping

4.1 Developing the scope

The scope provides a framework for topics which are subject to full evaluation. Using the PICO framework, the scope defines the population, intervention, comparators, and health outcome 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 initial views on the use of the technology in relation to current local clinical practice before the draft scope is finalised and sent to all clinical experts who have confirmed their attendance at the scoping workshop.

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 holds 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.

4.3 Final scope

After the scoping workshop, the ACE technical team finalises the scope, taking into account the discussions by the participants. The final scope is shared with the manufacturer of the technology under evaluation when they receive the Request for Proposal for Subsidy Listing (Section 8.1) to assist them prepare any clinical and/or cost information they intend to provide to support ACE’s evaluation.
5. Evidence Generation and Critical Appraisal

5.1 General principles

Consideration of a comprehensive evidence base is fundamental to the evaluation process. While information from multiple sources may inform the evaluation, 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

<table>
<thead>
<tr>
<th>Evidence type</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| 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 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 for review of 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, is often used to explore areas such as patients' experiences of having a disease and/or specific treatment, and clinicians' views on the role of different types of treatment in local clinical practice. |
| Economic evaluations | • 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 such 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 expert advice

During the course of the evaluation, ACE will seek advice from local healthcare professionals experienced in the management of the indication under review, to confirm local treatment practices and validate the clinical assumptions included in ACE’s evaluation report. Expert advice on the clinical need for the technology under evaluation compared to alternative options (if available) will also be sought. All clinical experts are required to declare any conflicts of interest relating to the technologies under evaluation.

For evaluations of cancer therapies, ACE also seeks clinical expert advice from the MOH Oncology Drug Subcommittee (ODS) which comprises senior public and private clinicians experienced in the management of different cancer types in Singapore. The ODS 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. ODS members are not required to comment on the prices or cost effectiveness of cancer drugs.
5.4. Evidence submissions from manufacturers

For topics which are subject to full evaluation, concise evidence submissions (up to 35 pages) are invited from the manufacturer of the technology under evaluation as supplementary evidence to ACE’s assessment. The information in the submission should be in line with the evaluation framework set out in the final scope issued by the ACE technical team, and provided within the Company evidence submission template to support ACE’s full evaluations (Annex 1). A separate Excel workbook to summarise cost information (Costing template) should also be included alongside evidence submissions for full evaluations. Manufacturers who intend to submit supplementary evidence to inform ACE’s full evaluation, will be given 8-12 weeks to complete the templates depending on the complexity of the topic. The templates should be submitted by manufacturers with their Request for Proposal for Subsidy Listing (see Section 8.1).

For topics which are subject to expedited evaluation, a brief summary (up to 5 pages) of key clinical evidence may be submitted by manufacturers with their Request for Proposal for Subsidy Listing (see Section 8.1). Evidence should be submitted within the Company evidence submission template to support ACE’s expedited evaluations (Annex 2), in line with the PICO framework provided by the ACE technical team, within the required timelines (typically 4-8 weeks).

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

6. The Reference Case

The DAC has to make subsidy 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 for drug evaluations are summarised in Table 5 and in Addendum 2 for vaccines.
Table 5. ACE’s reference case for drug evaluations

<table>
<thead>
<tr>
<th>Component of drug evaluation</th>
<th>Reference Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perspective of the evaluation</td>
<td>• Singapore healthcare system including payments out of the government’s healthcare or insurance (MediShield Life) budget as well as patients’ co-payments including Medisave and out of pocket expenses</td>
</tr>
</tbody>
</table>
| Target population and subgroups | • Consistent with the patient population defined in the evaluation framework  
• Subgroup analyses if appropriate (statistical) justification is provided  
• 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 be used to allow a robust assessment of relative clinical and cost effectiveness  
• Comparator(s) should either reflect the intervention 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 new technology 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 |
| 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 or cost-utility ratios 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
- Health-related quality of life weights based on empirical data from the literature or 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:** 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 technology in the target population (e.g. diagnosis rate, compliance, market share etc.) needs to be considered and justified.
  - **Comparator:** The analysis should calculate the predicted financial impact of subsidising a technology compared to the current situation. Changes in the comparator market share over time following subsidy of the technology under evaluation should be varied in sensitivity analyses.
  - **Outcomes:** No health outcomes are presented in the analysis.
  - **Calculation of costs:** Prices should be kept constant over the years (i.e. not inflated). The cost consequences of the treatment effect, side effects and other short- and long-term consequences (e.g. follow-up treatment) should be included in
If a price reduction or patient assistance programme (PAP) has been proposed by the manufacturer (contingent on a positive subsidy decision), the net cost price after the discount 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. Present the budget impact up to the steady state, with a time horizon of six years (to represent year of subsidy implementation (year 0) and then five years post-subsidy.
- **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 budget 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) budget 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 gain 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 for work or productivity costs), the nature of these characteristics should be clearly explained and if possible the value of the additional benefit should be quantified.

### 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 registered 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 indication 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 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.

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 subsidised. Multiple comparators can be considered if relevant to local clinical practice.

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

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

Each evaluation should include a systematic review of the existing clinical studies on the 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
- the literature is selected on the basis of defined inclusion and exclusion criteria
- the literature is assessed using recognised methodological standards.

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

Once the search strategy has been developed and literature searching undertaken, a list of possible studies should be compiled. Each study must be assessed to determine whether it meets the inclusion criteria of the review. A list of ineligible studies should be produced with the justification for why studies were included or excluded. A flow diagram, specifying the yield and exclusions (with the reason for exclusion) should be presented. Each study meeting the criteria for inclusion should be critically appraised and have its quality assessed.

Consideration of a comprehensive evidence base is fundamental to the evaluation process. While information from many sources may inform the evaluation, randomised controlled trials (RCT) directly comparing the drug under evaluation with relevant comparators are considered to provide the most valid evidence of relative efficacy and safety. However, such evidence may not always be available and may not be sufficient to quantify the effect of treatment over the course of the disease. Therefore, data from indirect comparisons of randomised trials may also be required. Furthermore, data from non-randomised studies may be reviewed to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented. The external validity of study results included in the review, and their applicability to local clinical practice in Singapore should be assessed.
Many factors can affect the overall estimate of relative treatment effects obtained from a systematic review. Some differences between studies occur by chance, others from differences in the characteristics of patients (such as age, sex, severity of disease, choice and measurement of outcomes), care setting, additional routine care and the year of the study. Such potential treatment effect modifiers should be identified before data analysis, either by a thorough review of the subject area, extrapolation from relevant studies, or discussion with experts in the clinical discipline.

6.4.1 Pairwise meta-analysis

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

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

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

6.4.2 Indirect comparisons and network meta-analyses

Data from head-to-head RCTs should be presented in the reference-case analysis 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 conducted by the ACE technical team for both expedited and full evaluations when relevant:

- **Cost-minimisation analysis (CMA)**
  Cost minimisation analyses are used if the effects of two interventions are comparable (i.e., there is a therapeutic claim of non-inferiority). 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 health system; or therapeutically inferior to the comparator but likely to result in lower costs to the health 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;
- 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 discrete event simulation models. The main principle is that a model should be kept as simple as possible while reflecting sufficient clinical reality, and that its internal structure should be consistent with proven or generally accepted relationships between parameters and health
Guidelines for good modelling practices have been developed by the modelling task force of ISPOR (http://www.ispor.org/workpaper/healthscience/tfmodeling.asp), which are followed by the ACE technical team whenever a model is required. Key considerations relating to the development of models are summarised below (Sections 6.5.3 and 6.5.4).

6.5.3 Transformation of evidence

Economic evaluations should ideally be based on studies that report **clinically important, 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 for incorporation into a model. Modelling may require:

- extrapolating data beyond the trial period to the longer term;
- translating surrogate endpoints to obtain final outcomes affecting disease progression, overall survival and/or quality of life;
- generalising results from clinical trials to the Singapore clinical setting; 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 modelling input parameters. All variables in the model and their sources must be documented.

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

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

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

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

For models that extrapolate to longer time periods, such as for chronic conditions or diseases with long-term sequelae, the assumptions used to extrapolate the impact of 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 with respect to the method chosen and in relation to the specific characteristics of the data set in question. These characteristics include the mechanism of crossover used in the trial, the availability of data on baseline and time-dependent characteristics, and expectations around the treatment effect if the patients had remained on the 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\]). When it is not possible to obtain measurements of health-related quality of life directly from patients, data should be obtained from the person who acts as their carer in preference to healthcare professionals. 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 Singaporean preference weights can be used in sensitivity analyses.

Utility values should be derived with a validated instrument (such as EQ-5D). Some valid and reliable instruments which are commonly used in economic evaluations are shown in Table 6.
### Table 6. Generic instruments as measures of utility

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

**Description:** The Assessment of Quality of Life (AQoL) instruments (4D, 6D, 7D, 8D) are multi-attribute tools covering 4, 6, 7 or 8 dimensions from the following: independent living, mental health, relationships, senses, coping, pain, happiness, self-worth, and visual impairment. Scores from the dimensions provide a health profile, but the primary purpose of the instrument is to provide a utility index for quality of life.

**Index score:** AQoL preference values are calculated without the “illness” dimension and are based on multi-attribute utility theory. Within each dimension, each level is assigned a preference value, which is obtained from a random sample taken from the general (Australian) population; these values are then combined in dimension scores, which are also combined.

**Use:** As AQoL is relatively new, experience with the instrument is limited. Nevertheless, there have been a number of comparative studies of AQoL and other utility measures. Users are asked to register their study; see [http://www.psychiatry.unimelb.edu.au/qol/aqol/use_aqol.html](http://www.psychiatry.unimelb.edu.au/qol/aqol/use_aqol.html)

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](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 7.

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 7. Direct costs included in ACE’s drug evaluations

<table>
<thead>
<tr>
<th>Type of costs</th>
<th>Resource consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug/Treatment</td>
<td>• Direct cost of community and hospital medicines, including medicines used to treat adverse reactions and monitoring costs; and</td>
</tr>
<tr>
<td></td>
<td>• Cost of administration</td>
</tr>
<tr>
<td>Hospital inpatient</td>
<td>Diagnostic and investigational services, treatment and/or procedures, hospital capital costs, depreciation and overheads (collectively captured through DRGs)²</td>
</tr>
<tr>
<td>Hospital outpatient</td>
<td>Laboratory services and diagnostics; healthcare professional consultations, hospice visits, treatment administration costs, costs of managing adverse events</td>
</tr>
<tr>
<td>Direct patient healthcare (in primary healthcare setting)</td>
<td>General practitioner visits, patient co-payments, home or continuing care, aged care services</td>
</tr>
</tbody>
</table>

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

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

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

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

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

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

6.11  **Handling uncertainty and testing robustness of results**

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**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.**

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

- **Structural uncertainty** – which includes structural and methodological uncertainty due to the analytical methods chosen to perform the evaluation;
- **Parameter uncertainty** – which includes data uncertainty due to variability in sample data or from uncertainty ranges chosen for non-sample data and uncertainty relating to the variability between patients (heterogeneity) and the generalisability of the study results to other populations and/or other contexts; and
- **Stochastic uncertainty** – which includes the random variability in outcomes between identical patients.
A summary of appropriate methods to address structural and parameter uncertainty is presented in Table 8.

### Table 8. Summary of types of uncertainty encountered in economic evaluations

<table>
<thead>
<tr>
<th>Uncertainty Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter Uncertainty</strong></td>
<td></td>
</tr>
<tr>
<td>Data inputs</td>
<td>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.</td>
</tr>
<tr>
<td>Sample data</td>
<td>Variability of sample data can increase uncertainty. Various samples taken from the same population can result in different data for resource consumption and outcomes.</td>
</tr>
<tr>
<td>Extrapolation</td>
<td>Uncertainty caused by extrapolation from intermediate to final outcomes and uncertainty from extrapolation beyond the study's time horizon.</td>
</tr>
<tr>
<td>Generalisability</td>
<td>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?</td>
</tr>
<tr>
<td><strong>Structural Uncertainty</strong></td>
<td></td>
</tr>
<tr>
<td>Analytical methods</td>
<td>Choice of different analytical methods can lead to uncertainty about the results and conclusions. Methodological uncertainty should be tested using scenario analysis.</td>
</tr>
<tr>
<td>Model structure</td>
<td>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.</td>
</tr>
</tbody>
</table>

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) 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:** 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 targeted population (e.g. diagnosis rate, compliance, market share etc.) needs to be considered and justified.

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

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

**Time horizon:** The time horizon depends on the time needed to reach a steady state. It is recommended to present the budget impact up to the steady state, with a time horizon of six years (to represent year of funding (Year 0) and then five years post-funding).

**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). For topics subject to expedited evaluation, the projected cost to government for subsidising the drug on SDL or MAF is estimated based on current and projected drug utilisation volumes from public healthcare institutions, sales data projections from manufacturers, and clinical expert opinion. Where a price reduction is offered by the manufacturer through the value-based pricing process (see Section 8), multiple budget impact scenarios, using current and proposed prices, may be presented to the DAC to inform their subsidy deliberations.

For topics subject to full evaluation, budget impact models are developed by the ACE team, using either an epidemiological or market share approach depending on the robustness of the prevalence and/or utilisation data available to inform the analysis. An epidemiological approach is usually preferred for generating utilisation and financial estimates if the evaluation indicates a superior therapeutic conclusion. A market share approach is often used if the evaluation suggests a non-inferior therapeutic conclusion. The aim of the analysis is to provide the most likely uptake of the drug in clinical practice if subsidy is recommended, and the cost impact to the government budget. Typically, budget impact analyses are conducted over a 6-year period and take specific considerations into account (Table 9).

In instances where manufacturers choose to submit costing information as part of their evidence submission to ACE (to inform full evaluations), relevant information will be incorporated into ACE’s budget impact analyses.
Table 9. Parameters considered in budget impact analyses for full evaluations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| Target population | • Consistent with the patient population defined in the evaluation framework and/or scope. 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 subsidy 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 and/or scope.  
• Changes in comparator market share over time following subsidy of the technology under evaluation should be modelled and varied in sensitivity analyses.                                                                                                                                                  |
| Health outcomes | • No health outcomes are presented in the analysis.                                                                                                                                                                                                                                                                                                  |
| Costs           | • Only direct healthcare costs should be considered. Indirect costs should not be included.  
• The cost consequences of the treatment effect, side effects and other short and long term consequences (e.g. follow-up treatment) should be included.  
• If a price reduction or patient assistance programme (PAP) has been proposed by the manufacturer in the Request for Proposal for Subsidy Listing (contingent on a positive subsidy decision), the net cost price after the price reduction or PAP is applied should be used in the base case.  
• Any resource costs related to the use of the drug (including staff training, need for companion diagnostics etc.) should be included.  
• 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    | • Analyses should be conducted over a 6-year period (to represent year of subsidy implementation (Year 0), then five years post-subsidy).                                                                                                                                                                                                 |
| Discount rate   | No discount rate should be applied.                                                                                                                                                                                                                                                                                                                |

7. Independent Evidence Review Centres (IERC)

Independent academic centres from overseas institutions which have experience in conducting and appraising HTAs for subsidy decision-making are consulted to review and critique ACE’s evaluation report and accompanying economic model for full evaluations. Expedited evaluations (which do not require a cost-utility analysis), are not typically subject to external review. Review centres are usually given 4-6 weeks to critique ACE’s evaluations, depending on the complexity of the evaluation, and their comments and suggested amendments are incorporated into the final report for 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 subsidy is commensurate with their value in Singapore’s context. The process enables ACE to engage in discussions with manufacturers to determine the price at which their product best represents a cost-effective use of healthcare resources. VBP is conducted for all drugs, including biosimilars, and vaccines evaluated by ACE, unless there are generic formulations registered in Singapore.

Figure 4. Value-based pricing process

- DAC selects the technologies for evaluation
- ACE schedules topics into evaluation work plan
- ACE arranges meetings/phone calls with all manufacturers for technologies scheduled for the upcoming DAC meeting within 3 working days
- ACE issues Request for Proposal (RFP) for Subsidy Listing 4-8 weeks
- Manufacturers submit price proposal to ACE
- ACE presents technical evaluation report, including VBP prices to DAC
- DAC makes subsidy recommendation to MOH
- ACE sends Notification of Outcome to manufacturers who submitted price proposals
- MOH issues Letter of Acceptance within 3 months
- Recommended drugs listed on SDL or MAF
- Recommended vaccines included in the Subsidised Vaccine List (SVL)
8.1 Request for Proposal for Subsidy Listing (RFP)

Manufacturers are invited to submit their best cost prices (i.e. the prices at which the manufacturers sell their products to public healthcare institutions) for their technologies under evaluation and detail any proposed patient assistance programmes in a Request for Proposal for Subsidy Listing template (Annex 3). The impact of any proposed arrangements on the effective cost price should be clearly stated.

Manufacturers 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, and details of any existing patient assistance programmes 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 manufacturers, as well as the meeting schedule of the DAC.

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

8.2 Notification of Outcome

Within 4 weeks after the DAC meeting, a Notification of Outcome (NOO) is sent to **all manufacturers** who submitted price proposals to inform the DAC’s recommendations to provide sufficient lead time for downstream stock supply and inventory management at the public healthcare institutions. Each manufacturer is only informed of the outcome for their product.

Manufacturers of technologies that receive a positive recommendation should not disseminate the information in the NOO in an indiscriminate manner until the subsidy implementation date.

Manufacturers of technologies that are not recommended for subsidy may request to have a post-decision meeting with ACE (via teleconference or in-person) to discuss the clinical and/or economic evidence base that informed the DAC’s decision, key uncertainties in the evidence base deliberated by the DAC and any pricing considerations. Face-to-face meetings are prioritised for manufacturers who wish to address evidence gaps and/or propose a revised price in line with the resubmission process (see section 8.4).

8.3 Letter of Acceptance

The Letter of Acceptance (LOA), that specifies the cost price and conditions of listing on SDL or MAF (for drugs) or on SVL (vaccines), is issued to the **manufacturers of technologies with positive subsidy decisions** shortly before subsidy implementation.
This is a legally binding agreement, signed by the Permanent Secretary (Health) for and on behalf of the Government of the Republic of Singapore, represented by the Ministry of Health, whereby:

- The manufacturer undertakes to sell the drug or vaccine at a cost price not exceeding the negotiated price agreed upon for subsidy listing when supplying it to the public healthcare institutions, and
- MOH lists the drug on SDL or MAF, or the vaccine on SVL, in line with specific clinical criteria.

This agreement sets the cost-effective price for subsidy listing and provides traction against price increases for a subsidised drug or vaccine. From time to time, prices and details of a subsidy listing may be subject to review at ACE’s discretion, 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 listed.

8.4 Resubmission of price proposal following a negative recommendation

Manufacturers are expected to provide their best and final prices for subsidy 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 subsidy is not allowed.

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

Pricing resubmissions are not allowed in the event when the DAC does not recommend a technology for subsidy on the basis of insufficient clinical evidence. Manufacturers may be invited to resubmit only when sufficient new evidence is available for DAC’s reconsideration.

Manufacturers that were unsuccessful in achieving a subsidy listing 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 manufacturers 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 listing), manufacturers may be contacted for price resubmissions earlier.

Manufacturers 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 manufacturers 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 subsidy 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 first drug) may be added, usually no earlier than 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 subsidised. A third drug within the class will only be considered for subsidy on an exceptional basis if it offers substantial benefits over existing subsidised drugs within the class.

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

8.6 Consideration of biosimilars

Manufacturers should inform ACE of the availability of any biosimilar in advance of its introduction into the local market to enable timely evaluation for subsidy consideration. Biosimilars will not automatically be subsidised 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 subsidy deliberations. As part of the evaluation, the manufacturers 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 subsidy 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 subsidised, 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 of Medical Services (DMS). 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 and vaccines 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;
- To appraise the clinical and cost-effectiveness of drugs and vaccines based on available therapeutic, clinical and pharmacoeconomic evidence;
- To provide listing recommendations to MOH, including conditions and/or criteria for subsidy;
- To provide recommendations to MOH and the MediShield Life Council about MediShield Life coverage for cancer treatments; and
- To monitor the impact of ACE guidance on prescribers’ behaviours.

The DAC meets 3 times a year, usually in March/April, July/August and October/November depending on the members’ availability. Additional meetings may be called by the Chairman where necessary, or decisions may be made via email for simple subsidy recommendations (e.g. for revisions to strengths of drugs that are already subsidised). Pre-meetings are also held with the Chairman before each DAC meeting.

A minimum of two-thirds attendance 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 subsidy decisions

The DAC makes subsidy 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
- Estimated annual technology cost and the number of patients likely to benefit from the technology.
Specific factors and judgments which are discussed by DAC when considering each criterion are described in Table 10. Additional factors, including social and value judgments may also inform the DAC’s subsidy considerations.

Table 10. MOH Drug Advisory Committee decision-making framework

<table>
<thead>
<tr>
<th>Core Criteria</th>
<th>Factors considered</th>
<th>Judgement will also take account of:</th>
</tr>
</thead>
</table>
| Clinical need of patients and nature of the condition | • Disease morbidity, mortality and patient clinical disability with current standard of care  
• Impact of the disease on patients’ quality of life  
• Extent and nature of current treatment options | • 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 (or the comparators).  
• Uncertainty generated by the evidence and differences between the evidence submitted for licensing (from clinical trials) and that relating to effectiveness in clinical practice.  
• The possible differential benefits or adverse outcomes in different groups of patients.  
• The balance of clinical benefits and risks associated with the technology.  
• The position of the technology in the overall pathway of care and the alternative interventions that are established in clinical practice. |
| Impact of the new technology | • 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 to current clinical practice  
• Robustness of the current evidence and the contribution the guidance might make to strengthen it | |
| Value for money (Cost effectiveness) | • Technical efficiency (the incremental benefit of the technology under evaluation compared to existing alternatives) | • 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 economic model |
| Cost of the technology and the estimated number of patients likely to benefit | • Estimated annual cost to healthcare system (Singapore government, insurance provider and patient) in the first 6 years of listing | • Any specific groups of people for whom the technology is particularly cost effective  
• Any identified potentially significant and substantial health-related benefits that were not included in the economic model  
• Existing or proposed value-based pricing arrangements |

Additional considerations may also be taken into account for low to moderate cost treatments for rare diseases that are under consideration for subsidy, 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 subsidy 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

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3 Rare is defined as <4 in 10,000 people (i.e. <1600 people with the condition in Singapore).
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 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.

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 the DAC to approve for subsidy.

On the basis of the available evidence, the DAC recommends whether a drug should receive subsidy through listing on the Standard Drug List (SDL) or the Medication Assistance Fund (MAF), or a vaccine should be included on the Subsidised Vaccine List (SVL) (Table 11).

The SDL includes low- to moderate-cost therapies essential for the management of common diseases 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 efficacious 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 registered indications. 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.

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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.
Table 11. Types of recommendations made by DAC

<table>
<thead>
<tr>
<th>Decision</th>
<th>Type of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology provides similar or greater benefits at a lower cost than the comparator(s)</td>
<td>Recommended</td>
</tr>
<tr>
<td>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)</td>
<td>Not Recommended</td>
</tr>
<tr>
<td>Technology provides greater benefits at a greater cost than the comparator(s)</td>
<td>Recommended / Not Recommended depending on the magnitude of incremental benefit, clinical need for treatment and other value judgements that informed the DAC’s decision</td>
</tr>
</tbody>
</table>

10. **Guidance Development and Implementation**

10.1 **Drafting of guidance**

Following the DAC meeting, the ACE technical team draft a guidance document for each topic to outline the subsidy recommendation(s), the DAC’s rationale for the decision, and a summary of the key clinical and economic evidence which informed the DAC’s deliberations. A plain English summary (PES) is also produced to explain subsidy decisions in non-technical language for patients and the public.

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 pricing information. Instead an ICER range is described as follows:

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

The annual budget impact to the government for subsidising the drug under evaluation during the first 3-5 years of listing is also presented in ranges, as follows:

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

The guidances and plain English summaries are typically published on ACE’s website (www.ace-hta.gov.sg) three times per year, when subsidy is implemented.
10.2 Implementation of guidance

Subsidy implementation for recommended drugs and vaccines typically occurs within 4 to 6 months after each DAC meeting once financing is approved by MOH and the LOA is signed (Section 8.3). To assist with the smooth adoption of the recommendations, ACE communicates subsidy decisions to public healthcare institutions after each DAC meeting to allow sufficient time for them to prepare for implementation, including making changes to their hospital formularies, inventories and procurement processes, if necessary. This may be followed by targeted engagements to brief healthcare professionals about the rationale for subsidy decisions, and to work with them to ensure that subsidised drugs and vaccines are made available for those who require them.

For subsidy decisions which are contingent on specific prices agreed with the manufacturer through the value-based pricing process, public healthcare institutions will be instructed to purchase the drug or vaccine through ALPS Pte Ltd, and adhere to a 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 manufacturer are passed onto the patients and selling prices are consistent across the public healthcare institutions. Companies are required to effect new prices one month before subsidy implementation dates.

10.3 Evaluation of post-subsidy drug utilisation

To measure the impact of guidance recommendations, ACE conducts drug utilisation reviews and monitors procurement and selling prices at each institution.

To measure the impact of subsidy and guidance recommendations, ACE examines the utilisation of drugs before and after subsidy implementation to understand if the intended consequences have been achieved e.g. whether reducing the affordability barrier through subsidy 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.

ACE also monitors the maximum selling prices set during the VBP process. Aggregated drug volume and cost data are sourced from public healthcare institutions’ dispensing systems. Where applicable, drug volumes are converted and presented in defined daily doses (DDDs) assigned by the World Health Organization.

10.4 Review of guidance and subsidy 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 undertake a literature search to 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 subsidy 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, or be revised, depending on the DAC’s recommendations. Sometimes guidance documents are withdrawn and superseded by new guidance depending on the number of revisions required.

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

<table>
<thead>
<tr>
<th>Eligibility criteria for medicines considered for inclusion in the RDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicines supported under the RDF should meet <strong>all</strong> of the following criteria:</td>
</tr>
<tr>
<td>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);</td>
</tr>
<tr>
<td>2. Medicine treats a rare, but clinically defined genetic condition that is chronically debilitating or life-threatening;</td>
</tr>
<tr>
<td>- 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;</td>
</tr>
<tr>
<td>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;</td>
</tr>
<tr>
<td>4. There is no cheaper alternative option (including non-drug therapy) for the condition;</td>
</tr>
<tr>
<td>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 (&lt;1,600 patients across all indications); and</td>
</tr>
<tr>
<td>6. The annual cost of the medicine would constitute an unreasonable financial burden on the patient and/or their family or carer.</td>
</tr>
</tbody>
</table>

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\(^5\) 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).
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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 subsidy 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 Working 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 countries/regions (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 4) by ACE to provide local pricing information, and published overseas prices and ex-manufacturer prices in reference countries/regions 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 countries. 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 countries.

**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.
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 methods and processes for vaccines under subsidy 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\(^7\) 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 subsidy

<table>
<thead>
<tr>
<th>Vaccine prioritisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert Committee on Immunisation (ECI) identifies vaccines to be evaluated by ACE based on emerging clinical evidence, local disease burden and international immunisation recommendations.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine evaluation: clinical and cost-effectiveness analysis and value-based pricing</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE conducts technical evaluation with input from local clinical experts. Prices for subsidy listing are negotiated with vaccine companies through the value-based pricing process.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACE completes final evaluation report</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE presents evaluation report to MOH Drug Advisory Committee (DAC) for subsidy deliberation. Outcomes from ACE’s evaluation are shared with ECI.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decision making: subsidy recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAC recommends a clinically and cost-effective vaccine for inclusion on the Subsidised Vaccine List (SVL) (and NCIS/NAIS as appropriate) for a defined population.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Guidance report</th>
</tr>
</thead>
<tbody>
<tr>
<td>A guidance document is prepared by ACE for publication on the ACE website, and disseminated to public healthcare institutions and CHAS GPs to drive vaccine adoption for the eligible population.</td>
</tr>
</tbody>
</table>

\(^7\) NCIS vaccine brands on SVL are subsidised at 100%, while NAIS vaccine brands are subsidised at 50%. Additional means-tested subsidies are provided at polyclinics and CHAS GP clinics for NAIS vaccinations. Individuals may use their MediSave to pay for the co-payment component and non-subsidised brands of vaccines on NCIS and NAIS.
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 subsidy 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 subsidy 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. Manufacturers are invited to submit a price proposal for subsidy 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 IERC to critique (see Section 7), or in situations where complex economic modelling is required (e.g. transmission dynamic models), ACE may engage overseas 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 subsidy deliberations.

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

Table B5. Key additional evidence requirements for vaccines

<table>
<thead>
<tr>
<th>Component of vaccine evaluation</th>
<th>Requirements</th>
</tr>
</thead>
</table>
| 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 manufacturer 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.
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**

<table>
<thead>
<tr>
<th>Evidence supporting likely herd immunity benefits may include any or all of the following factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The proposed vaccine protects against a new infection/disease and/or reactivation of an existing infectious pathogen to cause disease</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

**Decision-making and guidance production**

Vaccine subsidy 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 manufacturers 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 subsidy decisions (see Section 10). Vaccines
that are recommended for inclusion in the SVL are published on the MOH website on the date of subsidy implementation. Public healthcare institutions and CHAS GPs are advised of the DAC’s recommendations before subsidy implementation to allow them sufficient time to amend their formularies and make the necessary procurement arrangements.

**Procurement of vaccines recommended for subsidy**
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 subsidy listing and will advise the DAC, who may reconsider the original subsidy decision.

**Price resubmissions**
Manufacturers that were unsuccessful in achieving a subsidy listing 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 manufacturers 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, manufacturers may be contacted for price resubmissions earlier.
Annex 1: Company submission template to support ACE’s full evaluations

Instructions for companies

This is the template for submission of supplementary evidence to support a full evaluation conducted 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 subsidy considerations, irrespective of company involvement. Any evidence provided by the company will be incorporated into ACE’s evaluation. Following appraisal by the MOH Drug Advisory Committee, in most instances for patented drugs, subsidy through the Medication Assistance Fund (MAF) is considered. Less often, a patented drug may be considered for listing on the Standard Drug List (SDL).

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

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

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

When making an evidence submission, companies must ensure that all confidential information is highlighted and underlined.
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Section 1: The technology

<table>
<thead>
<tr>
<th>HSA approved name and brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registered indication(s) and any restrictions as described in the Package Insert.</td>
</tr>
<tr>
<td>Date of patent expiration</td>
</tr>
</tbody>
</table>

1.1 Administration and costs of the technology

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

Table X: Administration and costs of the technology being evaluated

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pharmaceutical formulation/strength: XXX</th>
<th>Pharmaceutical formulation/strength: XXX</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSA-approved dosing regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average length of treatment course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average cost of a course of treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated average interval between treatment courses</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Estimated number of repeat treatment courses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose adjustments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticipated care setting</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table: Summary of Cost Information

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of units sold in the last 12 months to public healthcare institutions</td>
<td></td>
</tr>
<tr>
<td>Current net** cost price (excluding GST) to public healthcare institutions*</td>
<td></td>
</tr>
<tr>
<td>Revised cost price for subsidy consideration***</td>
<td></td>
</tr>
</tbody>
</table>

* When the registered indication recommends the intervention in combination with other treatments, the cost price of each intervention should be presented.

** Cost price to public healthcare institutions after patient assistance programme, bonusing arrangements or price reductions have been applied

***Revised cost price should be in line with price reduction(s) outlined in value-based pricing Request for Proposal template (Request for Proposal for Subsidy Listing)

### 1.2 Changes in service provision and management

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

### 1.3 Overseas regulatory status

Provide a summary of the regulatory status of the technology in other countries, including Australia, New Zealand, UK, Canada, Taiwan and South Korea. If the technology is already reimbursed/subsidised in these countries, please provide details of the level of subsidy and the indications covered.

### Section 2: Clinical need

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

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

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

Describe current clinical practice to manage the condition and list the clinical guidelines (both local and international) which are most commonly used by clinicians in Singapore. If applicable, describe results from any surveys which have been conducted with local clinicians about current clinical practice. Describe any issues relating to current clinical practice, including variations or uncertainty about established practice.
Explain how the technology under evaluation may change the existing treatment pathway if it is subsidised. Estimate the number of patients who are likely to use the technology in Singapore for the indication under evaluation.

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

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

Section 3: Clinical effectiveness

Section 3 provides guidance on the level of information that should be included in the evidence submission template about the clinical effectiveness of the drug under evaluation. ACE technical staff will have access to all published information to inform their evaluation. Therefore, companies are encouraged to summarise additional (unpublished) information to demonstrate the value of their product and address any clinical uncertainties that may be apparent in the published trials.

3.1 List of relevant trials

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

a. In a table, present the list of relevant RCTs comparing the intervention with other therapies (including placebo) in the relevant patient group. Highlight which studies compare the intervention directly with the appropriate comparator(s) with reference to the final scope. If there are none, state this.

b. All outcome measures listed in the trial protocol, should be identified and completely defined. When outcomes are assessed at several time points after randomisation, indicate the pre-specified time point of primary interest. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant to the final scope. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQoL), and any arrangements to measure adherence. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within Singapore clinical practice). A suggested table format is presented below. The table can be presented in landscape format.]
Table X: List of relevant RCTs

<table>
<thead>
<tr>
<th>Trial number (acronym)</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Primary study reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>[Add more rows as needed]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2 Clinical effectiveness results of the relevant trials

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

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

3.3 Non-randomised and non-controlled evidence

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

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

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

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

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

3.5 Interpretation of clinical effectiveness & safety evidence

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

3.6 Ongoing studies

[Provide details of all completed and ongoing studies from which additional clinical effectiveness evidence is likely to be available in the next 12 months for the indication being evaluated.]
Section 4: Cost effectiveness

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

4.1 Published cost-effectiveness studies

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

Table X: Summary list of published cost-effectiveness studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>Perspective of analysis and country</th>
<th>Type of economic evaluation</th>
<th>Strategies compared</th>
<th>Time horizon</th>
<th>Patient population (average age)</th>
<th>QALYs (intervention, comparator)</th>
<th>Costs (currency) (intervention, comparator)</th>
<th>ICER (per QALY gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
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<td></td>
</tr>
</tbody>
</table>

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

Section 5: Budget Impact

[Section 5 should present budget impact calculations, over a 6-year period, to provide the most likely extent of use of the technology and financial estimates. This section is important for estimating the likely uptake of the proposed technology in clinical practice if subsidy is recommended, and the cost impact on the Singapore Government budget. Any proposed price reductions should be consistent with prices included in the value-based pricing Request for Proposal. The information provided will be used to inform ACE’s budget impact analyses.]

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

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

Ensure that any estimates of the extent of use of the technology in the Singapore setting are consistent with evidence presented throughout. Ensure that uptake of the technology is consistent with its expected use in clinical practice (at appropriate point in local treatment algorithm).
Please complete the Excel workbook ("Costing template") and ensure that all calculations, assumptions and data sources are clearly described. The workbook follows an epidemiological approach; however, it can be modified by the user to capture any other information that is considered important to include to support the submission.

Briefly summarise the results in a table to show 6-year budget impact to the Singapore government (for all clinically eligible patients in line with defined clinical criteria, irrespective of financial eligibility for MAF).

**Section 6: Patient assistance programs**

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

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

**References**

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

**Appendices**
Annex 2: Company submission template to support ACE’s expedited evaluations

Instructions for companies

This is the template for submission of supplementary evidence to support an expedited 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 subsidy considerations, irrespective of company involvement. Any evidence provided by the company will be incorporated into ACE’s evaluation.

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

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

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

<table>
<thead>
<tr>
<th>Contains confidential information</th>
<th>Date of submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes / No</td>
<td></td>
</tr>
</tbody>
</table>

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

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

[Provide details of all ongoing studies from which additional clinical effectiveness evidence is likely to be available in the next 12 months for the indication being evaluated.]
Annex 3: Proposal for Subsidy Listing (RFP template, Form A)

Section 1: Technical Specifications and Costs

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

Table A1: Cost Prices for Subsidy Listing

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Drug, strength and pharmaceutical form</th>
<th>Indication(s)®</th>
<th>Cost price per unit, excluding GST (SGD)</th>
<th>Percentage reduction from usual cost price in public sector (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>[name of drug, strength and pharmaceutical form]</td>
<td>/ [specify units]</td>
<td>/ [specify units]</td>
<td>/ [specify units]</td>
</tr>
</tbody>
</table>

® For use in line with HSA registration. Final subsidy criteria will be based on MOH Drug Advisory Committee's recommendations.

PAP or other arrangements proposed: Yes/No (details in Appendix)

Companion diagnostic test: Yes/No (details in Appendix)

Effective date of new cost price: Click or tap to enter a date.

2 To assist the Authority in assessing this Proposal, we have duly completed and hereby submit the tables and other information in the Appendix for the Authority’s consideration. We confirm and warrant that the information set out in the Appendix is complete, up-to-date, accurate and not misleading. In the event that the Authority seeks clarification on this Proposal, we shall provide full and comprehensive responses within seven (7) days of notification from the Authority.

3 This Proposal is valid for eighteen (18) calendar months from [deadline for submission of the Proposal].

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

Dated this [date] day of [month], [year]

Respondent’s Company or Business Registration No:

Respondent’s postal address:

Respondent’s electronic mail address:

Respondent’s official Stamp:
Section 2: Terms and Conditions

1. ACCEPTANCE OF PROPOSAL

1.1 The issue by the Authority of a letter of acceptance accepting this Proposal (the "Letter of Acceptance") shall create a contract ("Contract") binding the Respondent to offer for sale to all Public Healthcare Institutions and Polyclinics each of the drugs specified in the Letter of Acceptance (each, a "Drug" and collectively, the "Drugs") at a cost price per unit not exceeding the cost price per unit of that Drug set out in this Proposal, on and from the date of the Letter of Acceptance, for as long as that Drug is listed on any Drug List. These Terms and Conditions shall apply to the Contract. Where the Respondent has one or more existing agreements of sale of any of the Drugs with any of the Public Healthcare Institutions and Polyclinics as at the date of the Letter of Acceptance, the Respondent undertakes to take all reasonable steps by the date of the Letter of Acceptance to vary each such agreement so that on and from the date of the Letter of Acceptance, the cost price per unit of that Drug offered to each of the Public Healthcare Institutions and Polyclinics does not exceed the cost price per unit of that Drug set out in this Proposal.

1.2 For the purpose of this Proposal, and any Contract formed upon the Authority’s acceptance of this Proposal:

(a) "Adviser" means:
   (i) ALPS Pte. Ltd. (company registration number: 201805065E); or
   (ii) any of the Authority’s agents, contractors (including subcontractors), consultants or advisers (including legal advisers) engaged in, or in relation to, the performance or management of the Contract;

(b) "Drug List" means the list of drugs eligible for subsidy under the [subsidy] or any other subsidy scheme;

(c) "Parties" means the Authority and the Respondent, and "Party" means any of them;

(d) "Permitted Disclosure" means disclosure of the prices at which the Respondent will sell the Drugs to all or any of the Public Healthcare Institutions and Polyclinics, by the Authority.
(i) to all Public Healthcare Institutions and Polyclinics;
(ii) to the Authority’s Advisers or employees (including any employee of any related body corporate) solely in order to comply with obligations, or to exercise rights, under the Contract;
(iii) to the Authority’s internal management personnel, solely to enable effective management or auditing of Contract-related activities;
(iv) to the responsible Minister;
(v) in response to a request by the Parliament of Singapore;
(vi) to a court, tribunal or other legally constituted enquiry or for the purposes of any alternative dispute resolution process;
(vii) within the Authority, or to and within another Singapore government agency or statutory board, where this serves Singapore’s legitimate interests;
(viii) where required by law to be disclosed;
(ix) for the administration of any Drug List, including the negotiation or administration of any existing or future risk sharing deed or the addition of new drugs onto any Drug List; and/or to the extent such information is in the public domain otherwise than due to a breach of clause 1.4 below;

(e) “Public Healthcare Institutions and Polyclinics” means:

(i) the public healthcare institutions and polyclinics set out in Table A2; and
(ii) each other public healthcare institution or polyclinic as the Authority may notify the Respondent from time to time; and

(f) references to a person include any company, limited liability partnership, partnership, business trust, unincorporated association or government agency (whether or not having separate legal personality).

1.3 In consideration of the above, the Authority shall be bound by the obligations of the Authority under the Contract.

1.4 Save for a Permitted Disclosure, the Authority shall not otherwise make publicly available the prices at which the Respondent will sell the Drugs to all or any of the Public Healthcare Institutions and Polyclinics.

1.5 The Respondent shall continue to comply with the Confidentiality Undertaking signed by it or on its behalf in favour of the Authority, relating to the Ministry of Health’s consideration of the Drugs for inclusion on the list of drugs eligible for subsidy.

1.6 Without prejudice to clause 1.5 above, except with the prior consent in writing of the Authority, the Respondent shall not disclose any information relating to the content of this Proposal or the Contract, or any part thereof, to any third party.

1.7 Clauses 1.4 to 1.6 above shall survive the termination or expiry of the Contract.
2. **PRICE REVIEW AND DETERMINATION OF LISTING**

2.1 From time to time (whether before, on or after the creation of the Contract), including, without limitation, upon the occurrence of any of the following events or circumstances:

(a) the entry or anticipated entry into the Singapore market of a new Biosimilar or a new me-too compound of the same drug class or a new non-inferior clinically comparable drug as that of any Drug;

(b) the entry or anticipated entry into the Singapore market of a new medicine that is indicated for use in combination with any Drug;

(c) upon an expansion to the list of registered indications for any Drug; and

(d) upon the availability of evidence, to the Authority or otherwise, that suggests there are or there will be changes to the cost-effectiveness of any Drug,

the Authority shall have the right to do one or more of the following in its absolute discretion, and the Respondent shall have no claim for any damages or compensation:

(i) call for a re-evaluation of, and re-evaluate, the drugs listed on the Drug Lists (or any of them);

(ii) review prices of one or more of the drugs listed on the Drug Lists (or any of them);

(iii) include or remove any drug (including, without limitation, any one or more of the Drugs) from any one or more of the Drug Lists, and/or amend any one or more of the Drug Lists in any way; and

(iv) notwithstanding Clause 6.1 below, unilaterally amend, supplement and/or add to the conditions or other provisions set out in the Letter of Acceptance by providing not less than 30 days’ written notice of the revision to the Respondent.

2.2 The Authority may terminate the Contract and recover from the Respondent the amount of any loss resulting from such termination, if the Respondent shall have offered or given or agreed to give to any person any gift or consideration of any kind as an inducement or reward for doing or forbearing to do or for having done or forborne to do any action in relation to the obtaining or execution of the Contract with the Authority or for showing or forbearing to show favour to any person in relation to any contract with the Authority, or if the like acts shall have been done by any person employed by the Respondent or acting on its behalf (whether with or without the knowledge of the Respondent) or if in relation to the Contract, the Respondent or any person employed by it or acting on its behalf shall have committed any offence under Chapter IX of the *Penal Code* (Cap. 224) or the *Prevention of Corruption Act* (Cap. 231) or shall have
abettó or attempted to commit such an offence or shall have given any fee or reward the receipt of which is an offence under Chapter IX of the Penal Code or the Prevention of Corruption Act.

3. SUSPENSION AND TERMINATION OF THE CONTRACT

3.1 The Authority shall, after giving seven (7) days prior written notice to the Respondent, have the right to suspend or terminate the Contract if the Authority is affected by any state of war, acts of God or other circumstances seriously disrupting public safety, peace or good order of the Republic of Singapore.

3.2 If the Respondent defaults in its performance of the Contract, the Authority may issue a notice of default to the Respondent informing the Respondent of its default. The Respondent shall, within thirty (30) days of the date of the notice of default, remedy the default. If the Respondent fails to remedy the default, the Authority shall have the right to immediately remove the Drugs (or any one or more of them) from one or more of the Drug Lists, and/or terminate the Contract by way of a written notice to the Respondent, in each case, without the Authority being liable therefor in damages or compensation.

3.3 If on or after the date of the Letter of Acceptance before the Contract is otherwise terminated or expires, the Respondent sells a Drug to any of the Public Healthcare Institutions and Polyclinics (the “Relevant PHI”) at a cost price per unit (each, a “Defaulting Price”) exceeding the cost price per unit of that Drug set out in this Proposal (each, a “Proposal Price”), the Authority shall have the right (in addition to and without prejudice to all other rights or remedies available, including the Authority's right to terminate the Contract pursuant to clause 3.2) to require the Respondent to pay as liquidated damages for each unit of that Drug sold to the Relevant PHI a sum calculated in accordance with the following formula:

\[
\text{Liquidated sum per unit of that Drug} = (\text{Subsidies disbursed})_{\text{Default}} - (\text{Subsidies disbursed})_{\text{Proposal}}
\]

Where:

\((\text{Subsidies disbursed})_{\text{Default}}\) = the average amount of subsidies disbursed by the Authority to the Relevant PHI per unit of that Drug based on that Defaulting Price; and

\((\text{Subsidies disbursed})_{\text{Proposal}}\) = the average amount of subsidies which would have been disbursed by the Authority to the Relevant PHI per unit of that Drug based on that Proposal Price.

3.4 The Authority shall have the right, at its sole discretion, to elect to claim general damages in common law from the Respondent instead of imposing liquidated damages under clause 3.3.

3.5 Clauses 3.3 and 3.4 shall survive the termination or expiry of the Contract.
4. TRA NSFER AND ASSIGNMENT

4.1 The Respondent shall not assign any of its rights or transfer any of its rights or obligations under the Contract except with the prior written consent of the Authority (such consent not to be unreasonably withheld).

4.2 If the Respondent:

(a) is subject to a merger, takeover, re-organisation or any other arrangement which results in it ceasing to supply a Drug in Singapore; or

(b) sells or otherwise disposes of its interest in a Drug to another person, it must:

(c) notify the Authority of that event prior to its occurrence; and

(d) provide the Authority with enough detail of the event to allow the Authority to determine the action it requires.

4.3 On a notice being given pursuant to clause 4.2, the Authority may, in its absolute discretion, notify the Respondent that the Respondent is to, and the Respondent must:

(a) procure the novation of the Contract to the relevant successor on terms acceptable to the Authority; or

(b) procure the relevant successor to enter into a new contract with the Authority on terms acceptable to the Authority.

4.4 Unless the Parties agree otherwise, upon the date specified in the novation or new contract as being the date on which the successor’s obligations will begin, the Respondent is released from its obligations under the Contract.

5. REMEDIES

5.1 The right and remedies of the Parties under the Contract are cumulative and are in addition and without prejudice to any rights or remedies a Party may have at law or in equity. Further, no exercise by a Party of any one right or remedy under the Contract shall operate so as to hinder or prevent the exercise by it of any other right or remedy under the Contract, or any other right existing at law or in equity.

6. VARIATION

6.1 Save as expressly provided in the Contract (including, without limitation, this Proposal, these Terms and Conditions and the Letter of Acceptance), no variation whether oral or otherwise in the terms of this Proposal or the Contract
shall apply thereto unless such variation shall have first been expressly accepted in writing by the authorised signatories of both Parties.

7. **WAIVER**

7.1 In no event shall any delay, failure or omission on the part of either of the Parties in enforcing or exercising any right, power, privilege, claim or remedy, which is conferred by the Contract, at law or in equity, or which arises from any breach by either Party, be deemed to be or be construed as, (a) a waiver thereof, or of any other such right, power, privilege, claim or remedy, in respect of the particular circumstances in question, or (b) operate so as to bar the enforcement or exercise thereof, or of any other such right, power, privilege, claim or remedy, in any other instance at any time or times thereafter.

7.2 No waiver by the Authority of any breach of the Contract shall be deemed to be a waiver of any other or of any subsequent breach.

7.3 Any waiver granted by the Authority under the Contract must be in writing and may be given subject to conditions. Such waiver under the Contract shall be effective only in the instance and for the purpose for which it is given.

8. **ENTIRE AND WHOLE AGREEMENT**

8.1 The Contract contains the entire and whole agreement between the Parties relating to the subject matter of the Contract and supersedes all prior written or oral commitments, representations, arrangements, understandings or agreements between the Parties. Each Party warrants to the other Party that it has not entered into the Contract on the basis of any prior written or oral commitments, representations, arrangements, understandings or agreements between them.

9. **GOVERNING LAW**

9.1 This Proposal and the Contract shall be governed by and construed in accordance with the laws of the Republic of Singapore.

10. **SEVERABILITY**

10.1 In the event any provision in the Contract is determined to be illegal, invalid or unenforceable, in whole or in part, such provision or part of it shall, to the extent it is illegal, invalid or unenforceable, be deemed not to form part of the Contract and the legality, validity and enforceability of the remainder of the Contract shall not be affected.
11. RIGHTS OF THIRD PARTIES

11.1 A person who is not a party to the Contract shall have no right under the Contracts (Rights of Third Parties) Act (Cap. 53B) to enforce any term of the Contract.

12. DISPUTE RESOLUTION

12.1 In the event of any dispute, claim, question or disagreement arising out of or relating to the Contract or its subject matter or formation (a “Dispute”), no Party shall proceed with mediation or any form of dispute resolution unless the Parties have complied with the procedure in this Clause 12.1:

(a) the Parties shall negotiate in good faith with a view to resolution of such Dispute;

(b) if a Dispute is not settled within thirty (30) days of negotiation, or such longer period as the Parties may agree in writing, the Parties shall refer the Dispute to a senior executive or senior officer of each Party respectively (each, a “Senior Executive”) and shall furnish to the Senior Executives the full particulars of the Dispute. Each Senior Executive shall promptly meet with his or her counterparts and shall use his or her best endeavours to settle the Dispute through consultation and negotiation in good faith and in a spirit of mutual cooperation. Any settlement of the Dispute by agreement between the Senior Executives shall be final and binding on the Parties; and

(c) if the Dispute is not settled by agreement between the Senior Executives within 30 days after the date of referral of the Dispute to the Senior Executives, or such longer period as the Parties may agree in writing, any Party may proceed to give the other Party a written request for mediation as contemplated in Clauses 12.2 to 12.4.

12.2 In the event of any Dispute and if no agreement is reached under Clause 12.1 above, no Party shall proceed to any form of dispute resolution unless the Parties have made reasonable efforts to settle the Dispute through mediation in accordance with the mediation procedure of the Singapore Mediation Centre. The Parties shall be deemed to have made reasonable efforts in accordance with this Clause 12.2 if they have gone through at least one mediation session at the Singapore Mediation Centre.

12.3 A Party who receives a written notice for mediation from the other Party shall consent and participate in the mediation process.

12.4 The mediation session is to commence no later than ninety (90) days from the date of the written notice of mediation failing which either Party may proceed to arbitration.
12.5 Failure to comply with Clause 12.2 or 12.3 shall be deemed to be a breach of the Contract.

12.6 In the event of any Dispute and if no agreement is reached under Clause 12.1 or 12.2 above, the Dispute shall be referred to and finally resolved by arbitration in Singapore in the English language by a sole arbitrator in accordance with the Arbitration Rules of the Singapore International Arbitration Centre ("SIAC") for the time being in force which rules are deemed to be incorporated by reference into this Clause. The seat of the arbitration shall be Singapore. The arbitrator shall be agreed upon between the Parties, or on failure to agree within thirty (30) days of a written proposal by one Party to the other Party, to be appointed by the SIAC acting in accordance with the SIAC Rules. This arbitration agreement shall be governed by and construed in accordance with the laws of the Republic of Singapore.

12.7 This clause 12 shall survive the termination or expiry of the Contract.

13. CORRESPONDENCE

13.1 Subject to Clause 13.2, any notice, request, waiver, consent or approval ("Notice") shall be in writing and shall be deemed to have been duly given or made when it is delivered by hand or by prepaid registered post or fax to the Party as follows:

(a) in the case of the Respondent, the Respondent’s postal address set out in Section 1 above; and

(b) in the case of the Authority, the following address:

Agency for Care Effectiveness (ACE)
College of Medicine Building
16 College Road, Singapore 169854.

13.2 Any Notice may be made by the Authority to the Respondent by electronic mail or other electronic means and shall be deemed to have been duly given or made when it is sent to the Respondent’s electronic mail address set out in Section 1 above.

13.3 Either Party may change its address and (in the case of the Respondent) electronic mail address referred to above by giving the other Party written notice of the change.

14. SURVIVING PROVISIONS

14.1 Any provision of the Contract that expressly or by implication is intended to come into or continue in force on or after termination or expiry of the Contract, including Clauses 1.4 to 1.6, 2 (Price Review and Determination Of Listing), 3.3
to 3.5, 5 (Remedies) to 13 (Correspondence) and this Clause 14, shall survive the termination or expiry of the Contract.

**Appendix**

### 1. Volume and current cost price

<table>
<thead>
<tr>
<th>[name of drug, strength and pharmaceutical form]</th>
<th>Number of units sold in the last 12 months in public sector [month/year to month/year]</th>
<th>Usual cost price per unit in public sector excluding GST (SGD)</th>
<th>Number of units sold in the last 12 months in private sector [month/year to month/year]</th>
<th>Usual cost price per unit in private sector excluding GST (SGD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[specify units]</td>
<td></td>
<td>[specify units]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 2. Patient Assistance Programmes (PAPs) currently in place (if any)

<table>
<thead>
<tr>
<th>[name of drug, strength and pharmaceutical form]</th>
<th>Please provide details (eligibility criteria, level of subsidy, differences among Public Healthcare Institutions and Polyclinics and patient numbers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3. Existing agreements to sell the Drugs to Public Healthcare Institutions and Polyclinics listed in Table A2 (if applicable)

<table>
<thead>
<tr>
<th>Contracting Party</th>
<th>Date of expiry of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>[name of drug, strength and pharmaceutical form]</td>
<td></td>
</tr>
<tr>
<td>[name of drug, strength and pharmaceutical form]</td>
<td></td>
</tr>
</tbody>
</table>
### Annex 4: Request for Information (RFI template)

#### 1. Supplier’s profile

<table>
<thead>
<tr>
<th>Company name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Company address:</td>
<td></td>
</tr>
<tr>
<td>Contact person &amp; title:</td>
<td></td>
</tr>
<tr>
<td>Phone:</td>
<td></td>
</tr>
<tr>
<td>Email:</td>
<td></td>
</tr>
</tbody>
</table>

#### 2. Cost price and volume for Singapore

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

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

<table>
<thead>
<tr>
<th>Please provide details of any existing PAPs, including eligibility criteria, level of funding support and patient numbers on PAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>[name of drug, strength and pharmaceutical form]</td>
</tr>
</tbody>
</table>

#### 4. Overseas prices

| Published list price per [unit], excluding GST/VAT in local currencies* |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Australia                   | New Zealand     | United Kingdom  | South Korea     | Taiwan China    |
| [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.
Agency for Care Effectiveness
College of Medicine Building
16 College Road, Singapore 169854

Email    ace_hta@moh.gov.sg
Web      www.ace-hta.gov.sg

Driving better decision-making in healthcare