

# MEDICAL TECHNOLOGIES EVALUATION METHODS AND PROCESS GUIDE

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## Record of updates

Date	Version	Summary of main changes
October 2018	1.0	Publication of initial methods and process guide.
March 2022	2.0	<ul style="list-style-type: none"><li data-bbox="644 472 1385 573">• Included a new annex on Medical Technology Subsidy List (MTSL) and the processes for new item addition of implants onto MTSL.</li><li data-bbox="644 573 1385 607">• Updated the topic identification and selection process.</li></ul>

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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](http://www.ace-hta.gov.sg/about).

The *ACE Medical Technologies Evaluation Methods & Process Guide* outlines the core technical methodology and processes underpinning ACE's assessment of clinical and economic evidence for medical technologies 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 medical technology evaluations, and clearly outline ACE's processes and decision-making frameworks.

While this document forms an important part of the Ministry of Health (MOH) Medical Technology Advisory Committee's (MTAC) decision-making processes for subsidy of medical technologies, it is only a guide – ACE and MTAC 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 manufacturers who provide evidence and advice to support ACE's evaluations, where applicable. 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 this guide:

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# 1. Introduction

Health technology assessment (HTA) is an established scientific research methodology to help inform policy and clinical decision-making on the relative value of new health technologies, such as drugs, devices and medical services, when compared with existing standards of care. HTAs are conducted using analytical frameworks, drawing on clinical, epidemiological and health economic information, to help inform 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 medical technologies available in Singapore. It introduces the general methodological concepts underlying each stage of the evaluation process that can be applied in the assessment of most technologies. The methods for evaluating diagnostics are not detailed in this guide but are referred to in line with ACE’s reference HTA agencies such as the National Institute for Health and Care Excellence (NICE), UK, and the Medical Services Advisory Committee (MSAC), Australia.

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

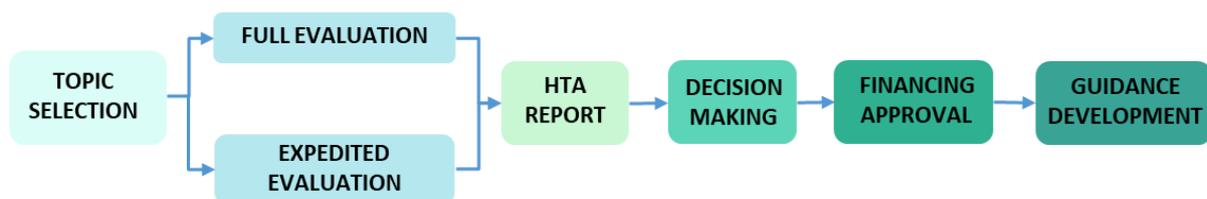


Figure 1: Overview of medical technology evaluation process

## 1.1 Characteristics of medical technologies

For the purpose of this guide, medical technologies can include, but are not limited to, medical devices, diagnostics, and medical services or procedures. A medical device is generally defined as those used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability; and
- investigation, replacement or modification of the anatomy or of a physiological process.

Diagnostics are defined as any medical technology with a diagnostic purpose, and are a sub-set of medical technologies. They do not include tests based on clinical sign detection as part of regular clinical examination not involving the use of instruments or devices. A co-dependent diagnostic technology, where the primary purpose of the technology is to identify patients who respond best to new drugs, may be evaluated concurrently or in parallel with the ACE drug evaluation programme together with the concomitant drug. Whereas, a hybrid technology (e.g. drug-eluting stents or photodynamic therapy for treating skin diseases) combines different characteristics of different health technologies within a single product and is within the purview of this guide.

Medical technologies are different from other medical interventions (e.g. drugs) in many ways:

- Technologies may be modified frequently over time in ways that change their effectiveness.
- Clinical evidence on technologies, especially for new technologies, is often limited, particularly randomised controlled trials comparing appropriate alternative treatments or diagnosis.
- The clinical outcomes resulting from the use of technologies often depend on the training, competence, and experience of the user (e.g. the 'learning curve').
- The healthcare system benefits of adopting medical technologies often depend on organisational factors, such as the setting in which the technology is used or the staff who use it, in addition to the benefits directly related to the technology.
- When the technology is a diagnostic test, improved clinical outcomes also depend on the subsequent delivery of appropriate healthcare interventions, instead of only the test itself.
- Direct evidence of the effect of diagnostic tests on clinical outcomes is often not available.
- Some technologies are indicated in managing or investigating a medical condition by different healthcare professionals and in a variety of healthcare settings, so the outcomes can vary.
- Costs of medical technologies often comprise both procurement costs (including associated infrastructure) and running costs (including maintenance and consumables).
- A new technology may influence costs by its effect on various aspects of the care pathway, in addition to costs directly related to the use of the technology.

## 2. Technology Evaluation

### 2.1 Evaluation process

The technology evaluation process includes six broad stages and is supported by the Medical Technology Advisory Committee (MTAC) and special working groups if necessary. Figure 2 gives a high-level view of the overall process. The details on each stage of the evaluation are described in the following sections

### 2.2 Type of evaluation

The choice of evaluation method will vary depending on the clinical novelty of the technology, amount of evidence available, complexity of the topic, potential budget impact and timeline of the evaluation. ACE mainly conducts two types of evaluation – full and expedited evaluations (Table 1). Typically, a full evaluation may be conducted if the technology of interest shows superior outcomes compared with its comparator(s) and there is lack of recent good-quality economic study which is judged to be applicable to the local context. A full evaluation will take 6 to 9 months to complete. Otherwise, an expedited evaluation will be conducted over 3 to 4 months.

**Table 1: Type of evaluation report**

Deliverable	Description	Target audience	Time required
<b>Full evaluation report</b>	A comprehensive literature review and critical appraisal of all relevant or higher level evidence, evaluating the safety and clinical effectiveness of the technology. Cost-effectiveness of using the technology (de novo economic modelling) and financial impact are evaluated. Any organisational, ethical and social considerations from using the technology are also considered.	MTAC	6 to 9 months
<b>Expedited evaluation report</b>	A review of only highest level evidence or of most recent (e.g. last 10 years) evidence, evaluating the safety and clinical effectiveness, cost-effectiveness (from literature), financial and organisational impact of using the technology. <i>Optionally</i> , the evaluation may include an appraisal of the quality of the evidence and can address other relevant considerations from using the technology.	MTAC	3 to 4 months

The timelines are indicative. Actual timelines vary depending on the complexity of topic and indication(s) included in each evaluation.

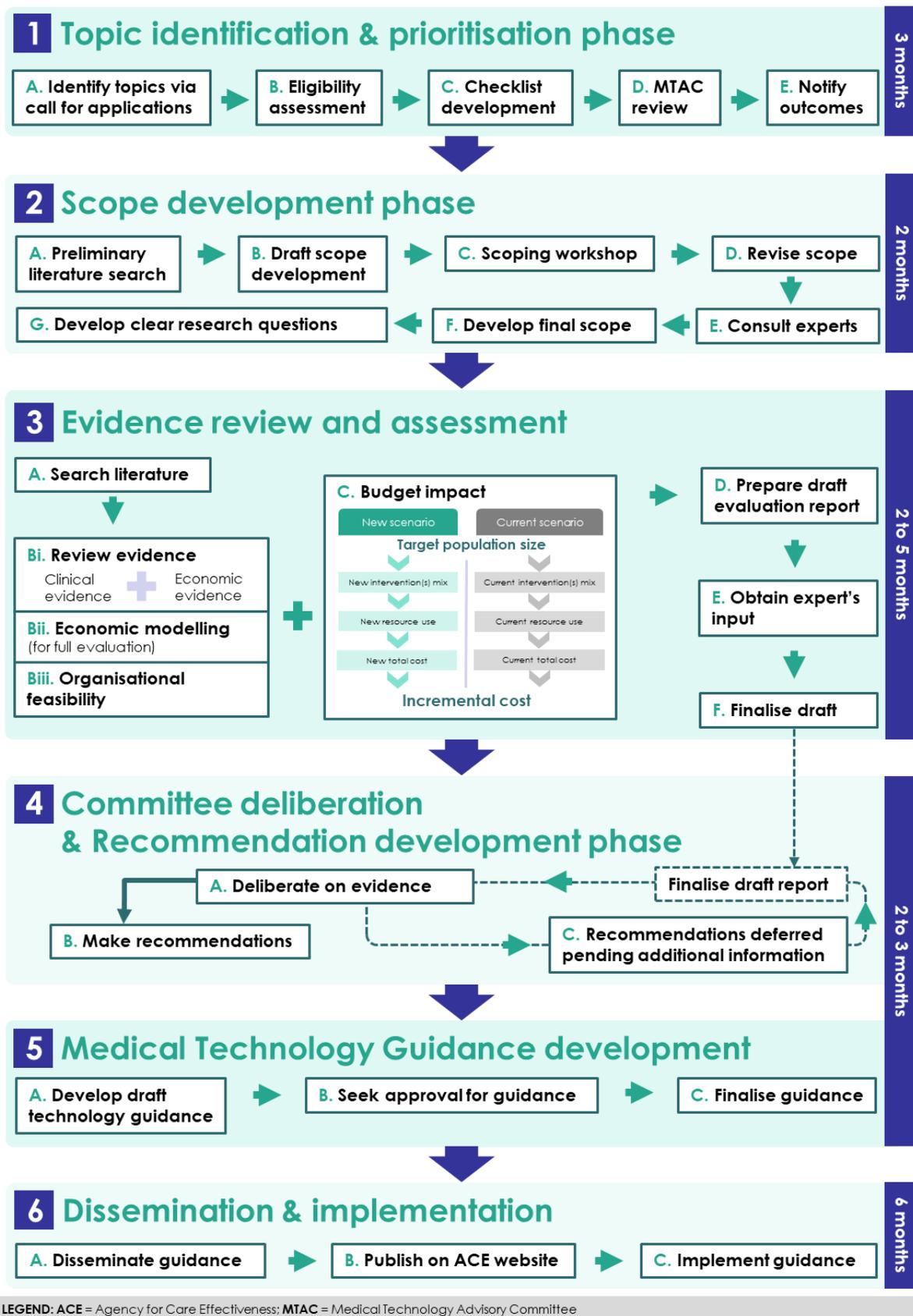


Figure 2: Overview of medical technology evaluation process

## 3. Topic selection

### 3.1 Topic identification and prioritisation

This section describes the methods used for selecting topics that are suitable for evaluation by ACE. This process ensures that the medical technologies selected address disease areas with high burden to society that will improve population health.

#### 3.1.1 Identifying topics

Evaluation topics are identified through a number of channels, such as (i) annual call for applications from the public healthcare institutions (PHIs), (ii) horizon scanning of novel technologies, (iii) topics referred to ACE by other divisions within MOH, and (iv) industry submission for implants (refer to Annex 1 for more details).

For the annual call for topics, PHIs have approximately two months to submit applications for subsidy consideration. All applications need to be endorsed by their respective Chairman of the Medical Board (CMB) and verified by the Chief Finance Officer (CFO) before submission to the MTAC Secretariat within ACE.

The ACE technical team conducts an eligibility check on all applications in line with inclusion and exclusion criteria (Annex 2). In general, applications for medical devices, diagnostic tests or medical services for the indication(s) of interest are considered suitable for evaluation to inform MTAC's subsidy deliberations if:

- The technology is new or an innovative modification of an existing technology with the potential for substantial benefits in terms of patient and/or healthcare system outcomes over the comparator(s) for the indication(s) of interest; and
- The technology has major cost implications; and
- The technology has been, or is ready to be used in the PHIs; and
- There is sufficient clinical evidence for a meaningful HTA evaluation based on a preliminary assessment of published evidence.

All medical technologies used in the provision of medical services must be assessed by relevant regulatory agencies in Singapore, such as the Health Sciences Authority (HSA), and included in the Singapore Medical Devices Register (SMDR) when applicable. Generally, ACE will only assess medical technologies that are included in the SMDR and support public funding for indications which have been approved by the regulatory authorities.

Infrequently, ACE may accept evaluation applications before a technology is approved by HSA, provided that the regulatory process for the technology has commenced. ACE will only finalise its appraisal of the technology and present to MTAC for subsidy deliberation once HSA approval is confirmed for the indication(s) of interest.

The following medical technologies are currently outside the scope of evaluation:

- Technologies that are still in the research stage of development;
- Models of care (the way health services are delivered, which outlines best practice of care and services for the patient cohort as they progress through the stages of a condition);
- IT systems (i.e. a software platform for pre-operative surgery planning);
- Telemedicine;
- Population screening tests;
- Contraceptives;
- Dental technologies or services; and
- Cell and tissue therapy (under a different workstream).

Topics which are considered eligible for evaluation will then be prioritised.

### **3.1.2 Selecting topics through prioritisation**

#### **3.1.2.1 Developing need scores**

When prioritising topics, in general, the ACE technical team gathers supporting evidence to inform the prioritisation criteria for each topic and completes a checklist (Annex 3) to generate a 'need score'.

Topics are more likely to receive a moderate to high need score and be selected for evaluation if the technology is expected to provide significant benefits to patients and/or the healthcare system, and based on preliminary assessment, there is sufficient evidence to support an evaluation.

In some instances, a technology which has the potential to incur high costs may still be evaluated, despite a low need score. In contrast, for some topics which have a high need score due to strong ethical issues surrounding the use of a technology (e.g. filling a high unmet need), an HTA may have limited impact on decision-making and therefore may not be prioritised.

#### **3.1.2.2 Estimating potential budget impact**

The budget impact associated with funding a medical technology is calculated with an intention of estimating the potential annual costs to the MOH. For a technology which requires high up-front investment for the acquisition of a piece of equipment and modification of infrastructure, more uncertainty may be associated with the cost estimates and is also taken into consideration. The following are some examples illustrating the general rules applied when estimating potential budget impact of topics being considered for evaluation:

- For a technology which has been used in the PHIs: if the unit charge (including the set-up and running costs) for use of the technology has been provided, together with any other procedure/service costs (if applicable), these can be used together with the estimated eligible patient numbers to work out the total budget;
- For a new technology (especially those with large up-front capital costs for equipment and/or facilities): the unit charge may be unknown and is often uncertain given the associated set-up and running costs of the technology. Budget impact may be estimated based on best available

information on costs related to the consumables, procedures or services, excluding the capital costs of the equipment deployed in the hospitals.

## 4. Scoping

### 4.1 Scope development

The first step of conducting an HTA is developing the scope, or focus of the evaluation. The purpose of the scoping process is to ensure that the topic for evaluation is well defined and relevant, and that the evaluation is achievable within the time and resources available. A well-defined scope, including a clear clinical care pathway, provides a focused framework for evaluating a medical technology. It also identifies important evidence and any other issues relevant to the evaluation.

#### 4.1.1 Drafting scope

The draft scope is developed by scanning the relevant literature, including HTA reports, published studies, and other grey literature (defined as documents produced by government, academics, business and industry in print or electronic formats). Various local clinical and content experts are consulted to help refine the scope, either through a formal stakeholder workshop or through individual consultations. When necessary, other stakeholders (e.g. industry) may be consulted to provide input on the scope.

The ACE technical team uses the PICO framework (**P**opulation, **I**ntervention, **C**omparators, and **O**utcome measures) to define the key elements of interest and the research question that the evaluation is intended to address. This serves to clearly define the purpose and boundaries of the evaluation, and to assist the ACE team formulate clear search terms and yield more precise search results (Table 2). Determining the care pathway in the scope is also essential to define the sequence and time frame for the interventions covered and key steps leading to final outcomes. The care pathway is particularly important for diagnostics as it should cover the entire sequence of tests and treatments relevant to the topic. It may also include tests or treatments that are performed to deal with the adverse effects of the tests and treatments in the pathway. The care pathway can vary depending on the patient's characteristics and the hospital's practice pattern. A flowchart or diagram to illustrate the pathway may be included in the scope description.

**Table 2: PICO framework**

<b>Population</b>	People affected by a condition for which the medical technology under review is used
<b>Intervention</b>	The medical technology under evaluation
<b>Prior test*</b>	Prior testing results
<b>Comparator</b>	The alternative(s) to the medical technology under review
<b>Outcome</b>	Relevant patient and/or healthcare system outcomes expected to result from using the technology under review

\* mainly applies to diagnostics

If relevant, the health care setting and time frame in which the medical technology is used (e.g. hospital, primary care, community) are also additional considerations included in the evaluation framework.

The scope may also include other questions raised by MTAC during the prioritisation stage, which may relate to the technology's ease of use, training and expertise required, its ability to generate the claimed benefits to patients or healthcare system in the local context, or organisational, ethical or societal factors that may influence its use in clinical practice.

In the case of diagnostics, it is often not obvious where in the care pathway the diagnostic technology is best placed (e.g. different points in the pathway, in sequence or in combination etc.), so different options in terms of treatment strategies or sequencing may be assumed and evaluated. Refer to Section 10 for more details on specific considerations for evaluating diagnostic technologies.

#### **4.1.2 Target population and condition**

The ACE technical team identifies information on the prevalence and/or incidence of the health condition of interest, focusing on data from Singapore if available, and specifies the population affected by the condition. The information may include the stage of the condition (e.g. acute, chronic, or palliative), age of the patients, results of prior tests (to include or exclude patients in the proposed population), and other characteristics. Among the affected population, the ACE technical team estimates the proportion who would be eligible to use the technology.

#### **4.1.3 Intervention**

The key features of the medical technology under evaluation are described, including its primary components, intended indications, different versions of the medical technologies that exist, mode of delivery, appropriate frequency and intensity of use.

In addition, the registration status of the medical technology in Singapore is checked to obtain the current registered indication(s) for its approved use, and a list of all registered products together with their licensed manufacturers. Any discrepancy between the intended and the approved indication(s) is highlighted.

#### **4.1.4 Comparator**

Comparators provide a reference against which the benefits and costs of the medical technology under evaluation are compared within the context of the Singapore healthcare system. Comparators may include drugs, surgical procedures, or one or more alternative medical technologies. Sometimes, standard of care consists of no treatment, or there may be more than one comparator. The main comparator is defined, if possible, as that which is most likely to be replaced in clinical practice by the technology under evaluation, and is typically the current standard of care for the health condition being reviewed.

The use of the technology as a replacement or addition to the comparator(s) is also assessed. Reviews of diagnostic tests may also identify both the reference standard, which may not necessarily represent standard of care, and the relevant comparator test(s) in the context of the clinical pathway.

#### 4.1.5 Health outcomes

The ACE technical team, in consultation with clinical experts, identifies health outcomes that are important and meaningful to people living with the health condition being reviewed, focusing on those outcomes that measure the direct impact of the technology on patient survival and quality of life. In addition, outcomes which are clinically important to patients and/or to the health system are also considered as valid measures of the benefits of the medical technology under evaluation.

Since medical technologies are often claimed to be resource-releasing which may translate to benefits for other patients or improved system efficiency, system benefits including cost savings are also an outcome of interest.

#### 4.1.6 Setting and timing

When necessary, the scope of the evaluation may include the setting in which the technology is administered (e.g. hospital, primary care, community), and will define the care provider (e.g. family physician, specialist). Furthermore, specific timings of when the medical technology should be used in patients with the health condition under evaluation may also need to be specified in the scope (e.g. in relation to the progression of the condition or recovery pathway).

#### 4.1.7 Other considerations

The scope of the evaluation may also need to take into consideration any ethical, legal or social issues associated with the use or adoption of the medical technology under evaluation, as well as any organisational factors (e.g. policies or legislation) that may influence or impact the technology's implementation or use in clinical practice in Singapore.

#### 4.1.8 Stakeholder workshop

To ensure that the evaluation framework is appropriately defined with relevance to local clinical practice and patient need, ACE may hold a stakeholder workshop with typically 8 to 10 healthcare professionals with expertise in the disease area or the use of the medical technology under evaluation. Other stakeholders outside the healthcare sector may be included when deemed necessary. Stakeholder workshops are conducted for all full evaluations and select expedited evaluations.

The main aims of the workshops are to:

- Ensure that the scope is appropriately defined;
- Seek verification and/or modification of the care pathway; and
- Identify important evidence and any other issues relevant to the evaluation such as any guidance implementation barriers on the use of the medical technologies.

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

#### **4.1.9 Final scope**

After the stakeholder workshop, the ACE technical team finalises the scope, taking into account the experts' inputs. The final scope is shared with the stakeholders involved.

After finalising the scope, the ACE technical team clearly defines the clinical, economical, and organisational research questions and any other relevant aspects of the medical technology under evaluation to guide evidence generation and appraisal.

## 5. Evidence generation and critical appraisal

The aim of the evidence review is to retrieve and collate published evidence comprehensively, and critically appraise and synthesise all relevant evidence on the technology under review in order to provide a comprehensive summary of benefits and issues related to its use in the form of a HTA report. The most appropriate review approach for a topic is guided by the research questions and the type of evaluation undertaken (e.g. a full evaluation may require a systematic review). The main components of an ACE HTA report are:

- Clinical: to assess the clinical evidence on the safety and effectiveness of the technology under evaluation;
- Economic: to evaluate the value for money and the budget impact of adopting a technology; and
- Organisational: to assess the changes required to adopt a technology into local health system.

Typically, the ACE HTA report relies primarily on publicly available literature. However, other valid evidence (e.g. unpublished local data) identified as being relevant to the scope of the assessment may be considered to improve the robustness of the evaluation. In general, clinical and economic evidence from randomised trials which directly compare the proposed technology with the main comparator are preferred. As trials are not always available, lower levels of evidence relevant to the intended use and claimed benefits of the technology without design or quality threshold restrictions are often considered. In these instances, an indirect comparison of randomised trials (across two or more sets of randomised trials involving one or more common reference) and non-randomised trials may be required to inform the evaluation.

### 5.1 Clinical evidence

The objective of the clinical evidence review is to synthesise the relevant evidence on the benefits and harms of a medical technology to patients and/or healthcare system. The evidence review is based on comprehensive review methodologies to systematically collate, appraise and synthesise all relevant published evidence to provide an unbiased summary.

Typically, the ACE technical team starts with a review of existing HTA reports and/or published systematic reviews. If recent HTAs/systematic reviews which meet the selection criteria are identified, the team may adapt or update the review, rather than conduct a new HTA and replicate the existing evidence base. However, any issues on the applicability of the published reviews to the local context in terms of patient population, care pathways and available technologies are highlighted.

### 5.2 Literature search

The primary objective of the literature search is to collate all relevant trials that compare the proposed technology with the main comparator(s) for the proposed population. The search typically covers clinical efficacy, effectiveness, and safety outcomes. Any health economic studies identified during the search are also assessed for suitability. A comprehensive literature search is conducted by searching:

- HTA reports from the reference HTA agencies;
- Published literature, including systematic reviews with/without meta-analysis; and
- Reference lists of all included studies (manual checking).

A search of the registers of clinical trials is also conducted to identify any ongoing trials which may assess the benefits of the technology under evaluation. Unpublished data may be used as supplementary evidence to support a narrative review of the technology. Manufacturers may also be asked to provide relevant data/reports to supplement the evidence base.

Typically, the population (e.g. health condition) and intervention (e.g. the technology) or its intended use form the basis for the literature search terms in the medical databases. The comparator(s) may be used as additional search terms if necessary. A combination of Medical Subject Headings [MeSH] terms (or equivalent) and keywords as text words are used in the search. At a minimum, the following databases are searched:

- PubMed (Medline)
- Embase.com
- Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials).

Additional databases may be searched if appropriate to the topic. The ACE technical team may also use additional search filters to limit the results by specific study designs, publication date, target age groups, etc. Generally, language is limited to English only.

The methods used to search the published literature are important to assess the comprehensiveness of the overall search and to enable an independent replication of the search if required. Thus, the details of the search strategies are also reported including:

- The databases and registers of clinical trials searched;
- The period of search;
- The complete search strategies used, including the search terms;
- Any supplementary searches conducted, especially manual checking of references in the included papers.

Identified studies are then downloaded to a reference management system (e.g. EndNote) and duplicates removed before study selection occurs.

### 5.3 Study selection

Studies are selected according to the eligibility criteria specified in the scope document. The selection criteria may include relevant PICO criteria, study design, year of publication, setting and timing of using a technology, sample size, and minimum follow-up period. English language and full-text publications are a general requirement for evidence which will inform ACE's evaluations. Study designs included in the clinical evidence depend on the following factors:

- The approach taken, e.g. review of primary studies or overview of HTA reports/systematic reviews;
- The evidence needs of the specific research questions, e.g. well conducted cross-sectional studies with a blinded comparison with a valid reference standard are considered high-level evidence for diagnostic accuracy studies; and
- The availability of evidence.

A hierarchical approach is sometimes necessary where consideration is first given to the most appropriate study design for the research questions. When the evidence is limited, alternative study designs may be considered appropriate. Typically, the ACE technical team will initiate an evaluation including comparative studies only; however, after reviewing the available evidence, the evaluation selection criteria may be expanded to include non-comparative studies.

Patient-relevant health outcomes such as quality of life, mortality, morbidity and adverse events are preferred over other surrogate outcomes. Valid surrogate outcomes that have established links to important clinical outcomes may also be included. Other relevant outcomes are determined based on requirements for the economic model (e.g. resource use).

The basic steps in the study selection process include the following:

1. Scan of study titles and abstracts to remove studies not meeting inclusion criteria;
2. Full-text review of studies appearing to meet inclusion criteria; and
3. A check of reference lists of included studies for relevant studies not identified by database search.

Study selection is performed by either a single reviewer or two independent reviewers (for full evaluations). In the latter case, any discrepancies between the two reviewers are resolved through discussion. If agreement cannot be reached, a third reviewer will independently assess the eligibility of the studies in question.

The study selection process and results, including data sources, number of studies screened and included at each stage, and a high-level summary of the reasons for exclusion at the full-text stage are reported in the evaluation report in a PRISMA flow diagram.

## 5.4 Evidence appraisal

When appraising evidence, the ACE technical team considers two main components:

1. Level of evidence; and
2. Quality of evidence.

Each study design is assessed according to its place in the research hierarchy. The hierarchy reflects the best study types for the research question and is specifically concerned with the risk of bias in the presented results that is related to study design. The ACE technical team assigns evidence levels to

each included study according to the Australian National Health and Medical Research Council (NHMRC) designations of levels of evidence (Annex 4).

Quality of evidence, on the other hand, reflects how well the studies were conducted in order to eliminate bias. Quality assessment is conducted either by two reviewers independently or by a single reviewer using a set of checklists, depending on the type of evaluation (e.g. full vs expedited), and staff resources and time available, to determine the internal (risk of bias) and external validity of the studies. The checklists are adopted or modified from valid, widely used checklists from various international agencies which assess the main biases including:

- Selection bias;
- Measurement bias;
- Performance bias;
- Reporting bias; and
- Confounding.

In addition to risk of bias, the consistency of findings across different studies, the precision of the effect estimates, and the applicability of the study results to local context are also considered when defining the study quality. Based on the assessment, the overall quality of evidence is described for each study as “High”, “Moderate”, or “Low”. The quality rating reflects the level of confidence in the effect estimates reported in the study.

## 5.5 Evidence synthesis

Depending on the quantity and quality of the available evidence base, data from the included studies may be synthesised quantitatively or qualitatively to determine the relative clinical effectiveness of the technologies.

When there is sufficient similarity among a group of included studies with regard to their clinical (e.g. PICO) and methodological (e.g. study design) characteristics, study results may be combined using meta-analysis to obtain a summary of effect estimates and to undertake sensitivity analysis. If appropriate, indirect and mixed treatment comparisons (network meta-analysis) may be used to provide pooled effect estimates, especially for model inputs. Generally, the methodological approach outlined in the Cochrane Handbook for Systematic Reviews or Cochrane Handbook for Diagnostic Test Accuracy Reviews is followed.

Where there is significant heterogeneity among studies, either clinical or methodological, meta-analysis is not appropriate. The ACE technical team will provide a qualitative synthesis of study results, which includes a description of the study findings, an exploration of the patterns of data and variation in results among the studies.

## 5.6 Expert consultation

Clinical or content experts will contribute to the evaluation by providing additional knowledge, opinions and experience. They are involved in the whole evaluation process from scope development, to feedback on the evaluation report and implementation of technology guidance. Expert opinion is also useful in judging the clinical meaningfulness of any differences detected between the intervention and comparator(s) in the evaluation.

In addition, experts can help contextualise the results from the reviewed evidence. The information provided can relate to the technical specification of the technology which may affect its capability in delivering the claimed benefits, the training and experience required to use the technology, and organisational factors that may influence the technology's performance or use in clinical practice.

## 6. Economic evaluation

The objective of the economic evaluation is to determine the relative costs and consequences of adopting a medical technology compared with its alternatives. The evaluation includes a review of published economic evidence from available literature. For a full evaluation, a primary economic analysis is conducted to estimate the cost-effectiveness of the technology in the local context.

The ACE technical team will review the available economic literature to summarise the evidence relevant to the technology, determine the validity of the study results and assess its applicability to Singapore healthcare system.

The literature search for economic evidence is aligned with the PICO framework which informed the clinical evidence search, and is generally conducted alongside the clinical searches using the same medical databases and filtration processes. Additional databases (e.g. EconLit) may be searched for further economic literature if needed.

The ACE technical team assesses the validity of the study results based on whether the structure and assumptions of the models used are reasonable, the outcomes represent patient-relevant final outcomes, and all necessary resources and costs are included and appropriate. The major limitations and/or uncertainties on the reliability of the cost-effectiveness evidence are highlighted. The quality of the economic evidence may be conducted and guided by the prevailing version of Consolidated Health Economic Evaluation Reporting Standards (CHEERS). The results of any sensitivity analysis reported in the study, if available, should be mentioned and any key drivers of the economic model and areas of uncertainty identified by the sensitivity analysis should be included in the evaluation report.

The ACE technical team will also assess the extent to which the published evidence reflects the decision problem in the local context. In determining the applicability of the available evidence, the following questions are considered:

- Are the study population, intervention and comparator(s) similar to those proposed in the research question?
- Is the perspective(s) taken appropriate to the local context?
- Is the health system in which the study was conducted similar to Singapore's context?
- Are estimates of treatment effect likely to be realised in the local context, taking into consideration resource availability and variation in clinical practice?
- Are all relevant costs and consequences considered and included?

Based on the results of the clinical and economic evidence review, the ACE technical team determines whether there is a need to conduct a primary economic evaluation. A primary CEA is generally not necessary in the following cases:

- When the clinical evidence review finds insufficient evidence to claim superior outcomes for the technology compared with its comparator(s); and

- When the economic literature review identifies a recent study without major limitations and is judged to be applicable to the local context based on the abovementioned considerations.

When a published economic evaluation is assessed to be applicable to local context, its conclusions can provide information on the potential cost-effectiveness of the technology locally. In some instances, the published model from overseas may be adapted to the Singapore context with an updated analysis.

## 6.1 Primary economic analysis

The objective of the primary economic analysis is to assess the cost-effectiveness of the technology in Singapore for the specific patient population. A CEA is generally only carried out for full evaluations if the proposed medical technology is clinically superior to the main comparator(s).

The type of analysis for the primary economic evaluation is based on the nature of the research question, the health condition, and the availability of relevant data. Typically, a CEA, which compares both the costs and consequences of the medical technology under evaluation to its main comparator(s), is preferred. It measures the incremental cost per unit of health outcome gained. The result is expressed as an incremental cost-effectiveness ratio (ICER).

Health outcomes are measures of benefit and may be reported in natural units such as life years gained, lives saved, heart attacks avoided; or quality of life measures such as quality-adjusted life years (QALY). Generally, the QALY is preferred since it is a comprehensive measure of health taking into consideration both the length of life and the health-related quality of life (as used in cost-utility analysis), allowing results to be compared across different technologies and diverse disease areas. However, when certain data (e.g. utility weights) are not available, outcome measures in natural units may be used.

Some technologies may only have healthcare system benefits. Examples are imaging technologies with nearly equivalent diagnostic performance, or laboratory equipment with nearly equivalent analytical and clinical validity but improve system throughputs. If there is evidence of equivalence with existing alternatives, the economic evaluation may concentrate on healthcare system outcomes.

Other types of economic evaluations may be conducted (albeit uncommonly) when appropriate. Examples are 1) cost-minimisation analysis, where the proposed technology has been demonstrated to be no worse than its main comparator(s) in terms of effectiveness and safety, so the difference between the service and the appropriate comparator(s) can be reduced to a comparison of costs only; 2) cost-consequence analysis, if the proposed medical technology is demonstrated to have a different profile of effects that are not adequately captured by a single outcome measure (as used in CEA) and there might be trade-offs between the two therapeutic medical services in terms of the directions of changes in effectiveness and safety.

Once the economic model structure is finalised, the ACE technical team identifies and obtains model inputs (e.g. clinical benefits, costs, utilities) from relevant sources, including published literature, other available information and expert opinion. Most model inputs have a point estimate, representing the

most likely value, and a distribution around the point estimate to quantify uncertainty or variation in the value.

### 6.1.1 Clinical effectiveness inputs

Clinical effectiveness inputs for the model typically include transition probabilities (e.g. the probability of a patient transitioning from one health state to another) and treatment effects (e.g. relative risks, odds ratios, hazard ratios). The inputs are obtained from relevant best-quality clinical studies.

When identifying the estimates for clinical effectiveness, the following is considered:

- Quality of the evidence: based on the assessment of risk of bias described in section 5.4. Generally high-quality studies are preferred when available;
- Relevance of the evidence: based on the assessment of the similarity between the local healthcare system and those in which the evidence is generated (e.g. the care pathways, the expertise of medical and healthcare staff); and
- Comprehensiveness of the evidence: based on whether the estimates are representative of the clinical literature as a whole. When available, systematic reviews or meta-analysis of high-quality studies directly comparing the technology with relevant comparator(s) are preferred for base-case analysis. Estimates from a single study may be used in cases where there is sparse clinical literature, where only a single high-quality study is available, or where there is one study, among available studies with significant heterogeneity, that is most generalisable to the local context.

When the effectiveness estimates are based on short-term data from clinical trials, the ACE technical team extrapolates the time horizon beyond those used in the trials to estimate longer-term outcomes. Extrapolation methods depend on data available. Surrogate or intermediate outcomes may be used if there is an established link between them and patient-relevant final outcomes. In addition, the modelling exercise should attempt to capture the complexities specific to the effectiveness of the technology such as surgical expertise (e.g. imperfect procedures) and adverse events (e.g. harms) by modifying the model structure to include these.

Sensitivity analyses are performed to assess the impact of these considerations and their limitations on the result, such as inputs from experimental or observational studies, intention-to-treat analysis or per protocol analysis, different quality studies, or different follow-up periods.

### 6.1.2 Cost inputs

Cost inputs depend on the perspective taken in the model. A healthcare payer perspective, which includes government, health insurers and patients, should be taken. Costing should be performed following the general guidelines for economic evaluation set out by Canadian Agency for Drugs and Technologies in Health (CADTH) and MSAC. The ACE technical team systematically identifies and estimates all costs resulting from or associated with the use of the technology using total costs to the patient (i.e. charge), including acquisition and maintenance costs and costs related to infrastructure modification. Some costs typically included in the model are the following:

- Use of the medical technology (including acquisition and infrastructure);
- Clinician and other healthcare staff services;
- Diagnostic and/or laboratory tests;
- Medical/surgical procedures;
- Hospitalisation;
- Emergency care;
- Outpatient clinic visits;
- Rehabilitation;
- Home care;
- Long-term care; and
- Assistive devices.

Costing is generally conducted by estimating the resource quantities in natural units and applying a price (unit cost) to each item. ACE technical team specifies the data sources used for estimating resource quantities and unit costs, together with the methods by which they were collected. Resource use may be obtained from literature or an existing MOH database (e.g. casemix). Unit costs may be derived from administrative databases (e.g. costing using diagnosis-related groups [DRGs] for inpatient stays), or information from costing exercises conducted by MOH Health Finance division, or costs provided by the clinicians or other relevant departments within the hospitals, published literature, or the manufacturer.

### 6.1.3 Valuing health effects

Health outcomes used in the economic evaluation may be expressed in quality of life measures such as QALY or in natural units such as life years gained. Generally, quality of life measures are preferred. However, when they are not available, natural units may be used.

Economic evaluations typically report a QALY outcome, which is a comprehensive measure of health that takes into account both length of life and health-related quality of life. It can be applied across different patient populations and disease areas to enable comparison among multiple alternatives. QALY weights (utilities) for health states are typically measured on an interval scale with death valued at 0 and perfect health at 1. QALYs are calculated by multiplying the utility weight by the time spent in the health state being evaluated. The weights for a given health state are best elicited through preference-based measures (e.g. time-trade-off, standard gamble), which may be generic or disease-specific. Utility values should be derived with a validated instrument. Some valid and reliable generic measures of quality of life which are commonly used in economic evaluations are EQ-5D, SF-36, HUI Mark 3, and AQL. Scenarios with validated disease-specific measures for health-related quality of life can be presented as supplementary analyses. However, disease-specific measures may limit policy-makers' ability to compare trade-offs between competing investments in different disease states, and can undermine comparability and consistency in decision-making. 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>).

Utility values associated with each health state or event are generally obtained from published literature. The justification for choosing a particular data set should be clearly provided. 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. When necessary, mapping valuations from other generic or disease-specific quality of life measures to utility-based measures is only recommended if mapping functions are based on validated and well-defined algorithms. Sensitivity analyses to explore variation in the use of the mapping algorithms on the outputs should be presented.

#### 6.1.4 Uncertainty and variability

In general, two key types of model uncertainty are considered: 1) parameter uncertainty, which refers to the precision of input parameters and their estimates; and 2) structural uncertainty, which relates to the correct model structure and its assumptions. In addition, methodological uncertainty (e.g. discount rates, time horizon) and heterogeneity (e.g. mix of sub-groups in trial population) may also be sources of uncertainties. To explore uncertainties, several methods may be used:

- One-way sensitivity analyses: used to assess the imprecision and impact of each key model input parameters (e.g. costs, probabilities, utilities, treatment effects) on costs and effect outcomes one at a time.
- Probabilistic sensitivity analyses (PSA): used to examine the joint effects of uncertainty in all input parameters simultaneously. The results are presented in the form of a cost-effectiveness acceptability curve. The curve represents the probability that the medical technology is cost-effective at a particular threshold compared with the existing alternative and reflects the robustness of the model and confidence in its conclusion.
- Scenario analyses: used to explore the implications of potential changes to the model and/or estimates, either for structural uncertainty, methodological uncertainty or subsets of parameter uncertainty. Typically, the base case presents the most probable scenario, and a number of other relevant scenarios may also be conducted.

In addition to uncertainty, there may be variability in the target population due to variation in individual response to an intervention. When the individual differences in responses can be attributed to patient heterogeneity, it should be addressed by subgroup analysis. Important patient subgroups are identified at the scope development stage or, alternatively, at the beginning of the economic evaluation.

In validating the evaluation, the model and its assumptions should be verified and clearly stated in the report. The face validity of the model is ensured through communications with clinical experts, and having the results cross-checked with published economic evaluations addressing similar decision questions. Key areas of uncertainty and the main variables affecting the cost-effectiveness conclusions should be highlighted.

# 7. Budget impact analysis

The objective of budget impact analysis (BIA) is to estimate the utilisation and incremental costs to the government for subsidising the medical technology in the public healthcare system in Singapore. The analysis is conducted from MOH’s perspective.

The general approach taken is to identify the current mix of interventions in a specific disease area and predict how subsidising the new technology may impact utilisation changes and the overall budget. The budget impact of introducing the new technology is estimated by calculating the cost difference between the new scenario (anticipated clinical practice altered by the new technology) and the current scenario (current clinical practice) (Figure 3). The BIA may be accompanied by a cost-effectiveness analysis or as a standalone analysis. The budget impact is typically projected over a five-year time horizon.

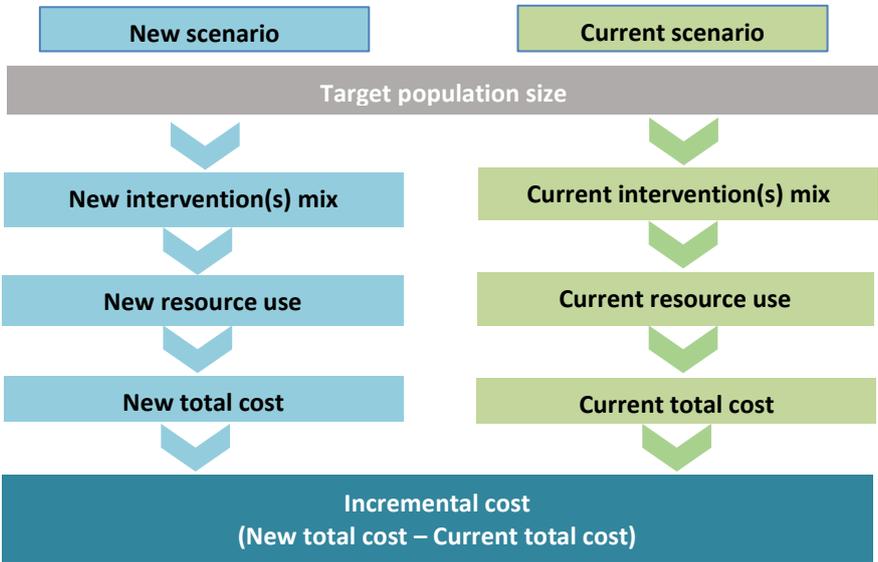


Figure 3: Flowchart of budget impact analysis

## 7.1 Population size

The target population consists of all Singapore citizens and permanent residents who are eligible to receive the technology for the indication(s) of interest. The size of the eligible population can be estimated based on prevalence data or historical utilisation data. For prevalence-based BIA, the size of the target population can be estimated using epidemiological data such as the prevalence and incidence of the disease under evaluation. The changes in target population and, when appropriate, disease severity mix over the time horizon are also estimated. Often only a subset of the eligible population will form the target population for the technology under evaluation. If historical utilisation data are used, the size of the target population can be forecasted based on the number of historical cases.

In general, BIA based on epidemiological approach is preferred especially for novel technologies when reliable local utilisation data are lacking. However, given prevalence-based analyses often require

many assumptions to derive the final target population, local utilisation data, if available, are used to supplement or validate the estimates based on epidemiological approach.

## 7.2 The intervention mix

Multiple interventions are generally available for a particular condition in the healthcare system at any time point. However, they are often used at different rates referred to as intervention mix. In BIA, the alternatives are the new technology and the comparator(s), typically standard of care, defined in the scope and, when available, consistent with those included in the economic evaluation. The ACE technical team estimates the current and potential future mix of interventions. The future mix of interventions depends on how quickly the new technology is likely to be adopted (e.g. uptake rate) and the extent to which it would replace the current intervention. The future intervention mix and uptake rate of the new technology may be extrapolated from current available data, either local or published overseas, or informed by experts.

## 7.3 Resource use and costs

Depending on the perspective of the analysis and the indication of the technology, the resource use and associated costs may include those of the technology, the related procedures, monitoring, treatment-related adverse events, and disease progression. In BIA accompanied by a cost-effectiveness analysis, costs associated with both the technology and disease are included. For standalone BIA conducted for expedited evaluations, only costs associated with the use of the technology and some key drivers of resources consumption in disease management are typically included.

## 7.4 Uncertainty

Similar to the economic evaluation, both the parameter uncertainty of the input values and the structural uncertainty of the assumptions made in the analysis should be addressed. Where possible, the nature of uncertainties and their impact on the overall budget should be explained, and the level of uncertainty should be estimated. Budget impact under different scenarios may be conducted. In addition, sensitivity analyses which vary the price of the new technology, the market size, and market share of the alternatives are also performed. In general, two types of uncertainty should be differentiated:

- Usage that differs from expectations: generally arises from uncertainty within and across particular variables in the analysis. Sensitivity analyses should be performed to examine the impact of this source of uncertainty; and
- Usage that extends beyond the restricted indication: generally arises from the uncertainty as to whether the requested restriction would achieve its intended objective. This raises questions on the overall cost-effectiveness of the proposed technology where the intention of restriction is to exclude its subsidised use in non-cost-effective restrictions. Scenario analyses may be presented to examine the impact of this uncertainty.

The BIA should be presented by the population size and costs for both the new and current scenarios for each year over five years. For costs, when possible, both total costs and disaggregated costs by various components (e.g. costs associated with the device, treatment, administration) over the time horizon should be presented. The major limitations related to the parameter inputs and sources should be discussed.

## 8. Diagnostic technologies

Diagnostics may be used for various purposes but are mainly used for diagnosis, staging, monitoring, screening (e.g. early detection, risk stratification) and prognosis (e.g. prediction of future events and outcomes). Some diagnostic technologies are used with concomitant treatments. Population screening tests are outside the scope of ACE evaluation. ACE only evaluates screening tests that are used to detect patients who are already suspected of having a disease.

The approach to evaluate diagnostics involves estimating the outcomes that the patient will experience as a result of using the diagnostic test, estimating the costs to the healthcare payers (government, patient, insurer), and determining the cost-effectiveness of using the technology. The outcomes and costs typically include those arising from treatments following the use of the diagnostic technology and cover the relevant section of the care pathway. It is often not obvious where in the care pathway the diagnostic technology is best placed, so different options are assumed and evaluated.

Regardless of their use, evaluation on diagnostics has some similarities and differences when compared to evaluation on treatments. They are similar because both are interventions aimed at improving the quantity and quality of life of the patient. However, there are several important differences between them in the evaluation. The most important difference is that the benefits of diagnostic tests are typically indirect, meaning that outcomes affecting the patient are from treatments rather than directly from diagnostic procedures. The other important difference is that tests are frequently used in conjunction with other tests, meaning it is a composite of a series of tests that is used in clinical decision-making. These make the evaluation of diagnostics more complex. Rarely do studies of diagnostic tests follow patients through treatment to final outcomes. In addition, evaluation of diagnostics usually requires information on the impact of diagnostics on clinical management decisions and the effects of treatment. If these are not known, analyses can be performed, but the validity of the results will be less certain. All these increase the uncertainty in the decision-making process for diagnostic tests.

The accuracy of most diagnostic tests is assessed by comparing the test with a reference standard at a particular point in time, which can be in addition to an appropriate comparator since the reference standard may not be routinely used in clinical practice. However, for tests that generate predictions of future events (prognostic information), studies should follow the patients for a longer time period to determine if the predicted events actually occur. Alternatively, linked evidence may be used, if available, in the absence of direct evidence.

Diagnostic tests can affect health in several ways. The outcomes of a diagnostic test are primarily information, which may affect treatments and the resultant outcomes. The test may also have direct effects such as side effects, for example injury from invasive tests, reaction to contrast media, discomfort from the test preparation or the test itself, radiation overdose, anxiety from the test results, or direct benefits when the test provides treatment. A test result can lead to follow-up tests, which can be invasive and have potential for further side effects. Most benefits from diagnostics are those arising from treating the identified disease, together with its potential adverse effects. Unnecessary treatment can be avoided in patients with negative test results. However, diagnostic errors (false

negatives and false positives) may incur harmful effects through different means such as delayed treatment, unnecessary interventions and their associated side effects.

Typically, the preferred evidence for diagnostic technologies is studies that follow patients from testing, through treatment, to final outcomes (so called 'end-to-end studies'). However, in most cases end-to-end studies are rarely available for a diagnostic technology. A linked evidence approach is therefore taken which includes the following three components:

- Evidence on diagnostic accuracy;
- Evidence on impact of diagnostics on management decision; and
- Evidence on the effectiveness of treatment as a result of diagnostics.

A comprehensive literature review using a pre-defined protocol for studies related to the three components abovementioned should be undertaken. If recent high-quality systematic reviews that meet the inclusion criteria are available, a de novo review is not necessary.

In principle, the approach to assessing the cost effectiveness of diagnostic technologies is similar to treatment assessments. However, due to the differences highlighted previously, more extensive modelling is often required, including the initial testing, follow-up testing, treatment and monitoring. The same model is often used to estimate both the clinical effectiveness (e.g. patient outcomes) and cost-effectiveness.

For detailed methods on evidence review and economic modelling of diagnostics, the ACE technical team refers to NICE (2011) part III: Methods used for decision-making in "Diagnostics Assessment Programme manual" ([www.nice.org.uk](http://www.nice.org.uk)).

## 9. The reference case

MTAC makes subsidy decisions across different medical technologies and disease areas. It is therefore important that analyses of clinical and cost effectiveness undertaken follow a consistent approach. To allow this, a 'reference case' is defined to ensure quality analysis and encourage consistency in analytical approaches. The key elements of analysis using the reference case are summarised in Table 3.

Although the reference case specifies the preferred methods followed by ACE, it does not preclude MTAC's consideration of non-reference-case analyses if appropriate. However, the reasons for the use of non-reference-case analyses should be clearly specified and justified, and the likely implications quantified if possible.

For more details on the reference case for conducting cost-effectiveness analysis, please refer to the ACE Drug and Vaccine Evaluation Methods and Process Guide at [www.ace-hta.gov.sg](http://www.ace-hta.gov.sg).

**Table 3: ACE's reference case for medical technology evaluations**

Component of medical technology evaluation	Reference case
<b>Perspective of the evaluation</b>	<ul style="list-style-type: none"> <li>• Singapore healthcare system including payments out of the government's healthcare or insurance budget as well as patients' co-payments including Medisave and out-of-pocket expenses.</li> <li>• If characteristics of a technology have value to people independent of any direct effect on health, the nature of these characteristics should be clearly noted and, if possible, the value of the additional benefit should be quantified.</li> </ul>
<b>Target populations and subgroups</b>	<ul style="list-style-type: none"> <li>• Consistent with the patient population defined in evaluation scope. Characteristics of the patient cohort may include demographics, specific conditions, disease severity, comorbidities and risk factors.</li> <li>• Epidemiological data for Singapore presented for the entire target population and relevant subgroups, if available.</li> <li>• Subgroup analyses if appropriate (statistical) justification is provided.</li> </ul>
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• Consistent with the comparator(s) defined in the evaluation scope.</li> <li>• Comparator(s) should reflect either the intervention that is most likely to be replaced by the new technology or, in the case of add-on interventions, the current intervention without the add-on technology. In circumstances where mixed comparators are preferred or required, a reasonable percentage (e.g. &gt;20%) of patients using the intervention is required for inclusion as a comparator.</li> <li>• For diagnostics where there are multiple test sequences in common use, they should all be included as comparators. Any other relevant test variants such as the cut-off values, the timing of the tests and their place in the clinical pathway may be included in the assessment.</li> </ul>
<b>Systematic review</b>	<ul style="list-style-type: none"> <li>• Systematic reviews of the existing clinical studies on the intervention and comprehensive search of published economic studies provide 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.</li> </ul>

Component of medical technology evaluation	Reference case
	<ul style="list-style-type: none"> <li>• Provides reproducible search strategy, transparent selection criteria and selection procedures, and critical appraisal and quality assessment of the evidence.</li> </ul>
<b>Economic evaluation</b>	<ul style="list-style-type: none"> <li>• For interventions which are non-inferior (comparable effectiveness and safety) to their comparator(s), a cost-minimisation analysis (CMA) should be undertaken.</li> <li>• 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.</li> <li>• 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.</li> <li>• Results should be expressed as incremental cost-effectiveness ratios (ICERs) with their associated upper and lower limits.</li> <li>• 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.</li> </ul>
<b>Calculations of costs</b>	<ul style="list-style-type: none"> <li>• Only direct healthcare costs should be included.</li> <li>• The identification, measurement and valuation of costs should be consistent with the perspective of the Singapore healthcare payer (government, insurance provider and patient health costs).</li> <li>• Non-healthcare costs or unrelated healthcare costs generally should not be included in the reference case analysis, but can be included in scenario analyses.</li> </ul>
<b>Measuring and valuing health effects</b>	<ul style="list-style-type: none"> <li>• Final, clearly defined, patient-relevant, clinically meaningful outcomes should be presented.</li> <li>• Life expectancy estimates based on recent Singapore age-specific and gender-specific life tables.</li> <li>• For cost-effectiveness analyses (CEA) involving chronic conditions and acute conditions with long-term sequelae or a relevant short-term outcome for acute conditions with no long term consequences, QALYs gained and life years gained should be presented.</li> <li>• Health-related quality of life weights based on empirical data from the literature on patients with the condition (e.g. trial data) or general population (preferably based on UK data, which ideally have been accepted by NICE).</li> <li>• Quality of life weights derived with validated instrument (e.g. EQ-5D).</li> </ul>
<b>Time horizon</b>	<ul style="list-style-type: none"> <li>• 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.</li> </ul>
<b>Discount rate</b>	<ul style="list-style-type: none"> <li>• Costs and health outcomes are discounted at an annual rate of 3%.</li> <li>• Other scenarios can be presented to test sensitivity of results to the discount rate applied.</li> </ul>

Component of medical technology evaluation	Reference case
<b>Handling uncertainty</b>	<ul style="list-style-type: none"> <li>• Explore all relevant structural, parameter source, and parameter precision uncertainty.</li> <li>• One-way deterministic sensitivity analysis should be presented for all uncertain parameters.</li> <li>• Multivariate probabilistic sensitivity analysis may also be performed to examine simultaneous impact of all uncertain parameters.</li> </ul>
<b>Budget impact analysis</b>	<p>Budget impact analyses should follow these principles:</p> <ul style="list-style-type: none"> <li>• Target population: The analysis should estimate the potential size of the target population and its potential evolution over time with justifications provided.</li> <li>• Comparator: The analysis should calculate the predicted financial impact of subsidising the new technology compared to the current situation. Changes in the comparator market share over time should be varied in sensitivity analyses.</li> <li>• Calculation of costs: Prices should be kept constant over the years (i.e. not inflated). If a price reduction has been proposed by the manufacturer (contingent on a positive subsidy decision), the net cost price after the discount is applied should be used in the base case.</li> <li>• Time horizon: The time horizon depends on the time needed to reach a steady state. Present the budget impact up to the steady state, typically with a time horizon of five years.</li> <li>• Discount rate: Future costs and savings should not be discounted.</li> </ul>

## 10. Organisational feasibility

The objective of organisational feasibility assessment is to identify potential barriers and enablers of adopting the medical technology into the Singapore public healthcare system, and any organisational factors that might influence the technology's performance or use in clinical practice. Potential solutions to overcome the barriers should be highlighted.

Adopting a medical technology can have far-reaching impact on the system beyond the department where the technology is deployed. Many of these may generate costs to the system which should be included in the economic evaluation. Some of the potential impacts are:

- Changes in the organisation of care, other existing services or clinical units, workforce considerations;
- Modification in property or facility (e.g. capital works) and software requirements;
- Additional resources in terms of staff and other resources required to provide the service;
- Additional training and credentialing requirements for service providers and whether the manufacturer will provide sufficient training, including onsite support for the technology; and
- Any other organisational factors which may influence the technology's performance or use in clinical practice.

Wide consultation with appropriate stakeholders to identify main issues regarding the adoption of the technology should be conducted alongside the evaluation. If many system-level changes need to be made and/or there are many resource gaps for the medical technology to be successfully adopted, adoption is likely to take more time and effort.

## 11. Independent Evidence Review Centres (IERC)

For full evaluations, independent academic centres from overseas institutions which have experience in conducting and appraising HTAs for medical technology subsidy decision-making can be consulted to review and critique ACE's evaluation reports and accompanying economic models. Expedited evaluations (which do not require economic modelling) can also be subject to external review. Review centres are typically given 4 to 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 MTAC's consideration.

## 12. Value-based pricing (VBP)

The need for VBP for each technology under evaluation is at MTAC's discretion. For selected medical technologies, ACE will conduct VBP in parallel with medical technology evaluations to ensure that the cost of the technology being considered for subsidy is commensurate with its value in Singapore's context. The process enables ACE to engage in discussions with manufacturers to determine the price at which the technology best represents a cost-effective use of healthcare resources. Note that medical implants are usually subjected to VBP (refer to Annex 1 for details).

The overall principles and process for VBP, including the request for proposal, notification of outcome, and letter of acceptance, are consistent with those used for drugs. Please refer to the ACE Drug and Vaccine Evaluation Methods and Process Guide at [www.ace-hta.gov.sg](http://www.ace-hta.gov.sg) for details on the VBP processes.

## 13. Decision-making

### 13.1 Medical Technology Advisory Committee (MTAC)

Subsidy decisions for medical technologies are made by the Medical Technology Advisory Committee (MTAC) which comprises 18 members with a range of expertise including senior clinicians who develop and use health technologies, and individuals from health services and finance divisions within MOH who provide a lay perspective of the issues affecting patients and the systems in the public healthcare institutions. Members are appointed for a three-year term by the Chairman and may be re-appointed to serve more than one term. MTAC is chaired by the MOH Director of Medical Services (DMS).

The terms of reference of MTAC are:

- To identify and prioritise medical technologies with potential to address care gaps, deliver significant improvements in health outcomes and/or patients' experience, ease of operator use, and/or improvements in the efficient use of resources for evaluation;
- To deliberate and serve as lead discussant, if needed, on evidence including comparative safety, effectiveness, cost-effectiveness and total cost of the medical technology and organisational feasibility;
- To recommend whether public funding should be provided for a medical technology and, if so, the conditions and the criteria for subsidy; and
- To monitor the impact of ACE guidance on prescribers' behaviour; and
- To act as champions to drive adoption of MTAC-recommended medical technologies, in support of subsidy decisions based on principles of health technology assessment.

Committee members meet three times per year. All members are required to submit a declaration of interests every year, and to declare any conflicts of interest at each Committee meeting.

### 13.2 Decision framework

Based on the findings from ACE's HTA, MTAC makes a subsidy recommendation, through a deliberative process, for the medical technology under evaluation. The decision-making process is guided by an international decision determinant framework (Table 4). The framework provides five key criteria for consideration in developing a recommendation:

1. Clinical need of patients and nature of the condition;
2. Overall benefit of the technology for the patient and/or the system;
3. Cost-effectiveness (value for money), which covers the incremental benefit and cost of technology compared to existing alternatives;
4. Estimated annual technology cost and the number of patients likely to benefit from the technology;
5. Organisational feasibility, which covers the potential impact of adopting the technology, especially barriers for diffusion.

The Committee will consider other important factors, such as equity, ethical and political issues which pertain to the use of a technology, in reaching its recommendation. These criteria are not assigned weights, as the relative importance of each criterion is specific to the individual technology under evaluation.

**Table 4: MTAC decision-making framework**

Criteria	Definitions
<b>Clinical need</b>	The size of the affected population potentially benefiting from the technology and the severity of the condition. Whether there are unmet needs, in terms of alternative technologies and their limitations, for the affected population.
<b>Overall benefit</b>	Potential of the proposed technology to prevent disease or to produce beneficial changes for patients over alternatives, in terms of better safety and effectiveness, and/or better efficiencies for the system.
<b>Cost-effectiveness (value for money)</b>	The potential of technology to be cost-effective or cost-saving (after VBP where applicable).
<b>Estimated annual technology cost</b>	The net annual incremental cost to the MOH related to the start-up and recurrent costs to subsidise the technology for the intended indication(s).
<b>Organisational feasibility</b>	The potential impact of adopting the technology in the healthcare system, in terms of resource requirements and barriers to diffusion (e.g. capital, operational, regulatory considerations).
<b>Additional considerations</b>	Any ethical, societal, political or other issues related to the adoption of the technology.

**13.2.1 Clinical need**

Consideration of the clinical need for a medical technology for the indication(s) of interest is informed by:

- The burden of the disease: the size (e.g. incidence, prevalence) of the affected population by the target condition who would benefit from the proposed technology and the severity of the condition under evaluation; and
- The availability of an effective alternative to the proposed technology, and its limitations.

The target population is often only a subset of the total population affected by a health condition, and sometimes the size of the target population is not easily identifiable. Relevant literature and inputs from local experts provide the basis for the estimates.

**13.2.2 Overall benefit**

The overall benefits (or harms) of a technology and the magnitude of the effects are informed by ACE’s review of the effectiveness and safety of the proposed technology, compared with the available alternatives, to the patients and/or the healthcare system.

Since medical technologies are often claimed to be resource-releasing and more convenient for end users (either clinicians or patients) relative to current management, system benefits are often given

equal consideration to patient benefits if there is sufficient evidence of equivalence/non-inferiority of the technology compared with current management, and no potential compromise to patient outcomes.

### **13.2.3 Cost-effectiveness (value for money)**

The Committee considers whether the cost of the new technology represents value for money and is an efficient use of resources, compared with an alternative intervention for the same condition under review, based on ACE's findings from the review of the economic literature and/or an in-house economic model, if available.

MTAC does not use a precise maximum acceptable ICER above which a medical technology would automatically be defined as not cost effective or below which it would (i.e. an ICER threshold), but the ICER will be used as a component of the deliberative decision making process. ICERs are not precise values and are associated with a degree of uncertainty. MTAC considers the upper and lower limits of the ICER range, in addition to the base-case point estimate when determining whether a medical technology represents good value for money.

### **13.2.4 Estimated annual technology cost**

ACE's BIA generates the most likely utilisation and financial estimates to the MOH related to the costs of providing the proposed technology. MTAC assesses the incremental cost to subsidise the technology with the intended indication(s) compared with the currently available alternative(s).

### **13.2.5 Feasibility of technology adoption in the public health system**

Apart from economic feasibility (budget impact), the organisational feasibility of adopting a technology into the Singapore public healthcare system is also considered by MTAC. To do this, they assess the impact on currently available healthcare resources of adopting the technology, and health system barriers and enablers for diffusion of the technology such as:

- Resource gaps (e.g. additional staff or training/credentialing requirements) that need to be addressed; and
- System-level changes (e.g. infrastructure modification, subsidy framework changes) that need to be made; and
- Organisational factors (e.g. change of care pathway) that might influence the technology's technical performance or use in clinical practice.

When there are significant resource gaps or many system-level changes required, the adoption is likely to be more difficult. Therefore, MTAC is likely to be more cautious about recommending the use of a technology when the level of system change required is very high especially in circumstances where improved outcomes are not expected to be significant.

### 13.2.6 Other ethical, social and political considerations

Apart from the five main criteria abovementioned (Table 4), MTAC also takes into consideration other potential ethical, societal and political issues that are important to the use of the technology under review, that may impact its use. Evidence from literature and real-world experience of clinicians, patients and their families or caregivers provide the basis for examining the actual and potential impact of the technology.

### 13.3 MTAC recommendation

Following committee deliberation on the findings of ACE's HTA report, MTAC prepares a recommendation consisting of a statement regarding the subsidy decision for the technology under review and a brief rationale for the recommendation. MTAC is more likely to recommend a medical technology for subsidy if there is clear evidence that the technology is clinically and/or cost effective to the patient population under consideration.

Recommendation statements usually take one of the following forms:

- The MTAC has recommended subsidy for [medical technology] in patients with [health condition];
- The MTAC has not recommended subsidy for [medical technology] in patients with [health condition].

The Committee may add supplementary recommendations that provide additional guidance or clinical restrictions on the subsidy. Sometimes, MTAC may defer recommendations pending additional information related to any aspects of the evaluation, including evidence or revised pricing proposals for the technology.

## 14. Developing and implementing medical technology guidance

### 14.1 Guidance development

Following each MTAC meeting, Technology Guidance may be developed for positive and negative recommendations, where needed. Guidance outlines:

- Conditions/criteria of subsidy;
- Clinical need and a brief summary of the clinical and cost-effectiveness evidence which informed the Committee's deliberations and rationale for decision-making; and
- Estimated annual cost of subsidising the service based on the number of patients likely to benefit from the technology;
- Any organisational issues which may impact on the implementation of the service.

For full evaluations, where an economic model is developed by ACE, the actual base case ICERs are reported in ranges as described below:

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

Similarly, the annual cost to the government of subsidising the service under evaluation is reported in ranges, as follows:

- Cost saving;
- <\$1 million;
- \$1 million to <\$3 million;
- \$3 million to <\$5 million;
- ≥\$5 million to <\$10 million;
- ≥\$10 million.

### 14.2 Implementation of guidance

Subsidy implementation typically takes effect within 6 to 15 months after each MTAC meeting once financing is approved by MOH. To assist with the smooth adoption of the recommendations, ACE communicates subsidy decisions to public healthcare institutions after each MTAC meeting to allow sufficient time for them to prepare for implementation, including making changes to facilities, care pathways, and procurement processes, if necessary.

The ACE adoption team is involved at the early stage of technology evaluation, especially for technologies which may have significant barriers to adoption, to identify these barriers and to develop resources to support implementation in the event of a positive recommendation. The adoption team is likely to focus their resources on topics where there is a high potential for system benefit and/or

substantially improved outcomes. This is done through working directly with the public healthcare institutions and clinicians with experience of, or who are currently using the technology.

For technologies where VBP is conducted, subsidy decisions are contingent on the target price being met by the manufacturer. The public healthcare institutions will be instructed to adhere to a recommended maximum selling price to ensure that the savings generated from price reductions from the manufacturer are passed on to the patients.

To monitor clinician adherence to ACE guidance, MOH may track the actual (vs predicted) utilisation and the uptake rate of subsidised technologies, and monitor whether there is a commensurate reduction in alternative technologies, if the subsidised technology is intended to replace the alternative(s). Where required, educational audits will be conducted in the institutions by MOH to improve adherence to the guidance recommendations. In addition, outcome evaluation post-subsidy implementation may also be conducted for selected technologies, especially those with anticipated high impact on patient outcomes and healthcare system, to assess whether the intended outcomes are achieved.

### **14.3 Review of guidance and subsidy recommendations**

The guidance may be considered for review 2 to 5 years after publication, if deemed necessary. At that time, the ACE technical team will undertake a literature search to determine whether any new evidence that has become available is likely to have a material effect on the subsidy decision and guidance recommendations.

Where considerable clinical or economic evidence has become available, the topic may be scheduled in ACE work plan for re-evaluation as a full or expedited topic, depending on the amount of new evidence that has become available. The process for full or expedited evaluations will be followed for all topics subject to re-evaluation. Following MTAC's consideration of the new evidence, the existing guidance may be revised, depending on the recommendations made.

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## Annex 1: The MedTech Subsidy List (MTSL)

The MTSL is a national list of medical technologies that has received subsidy recommendations from MTAC. Implants will be the first group of medical technologies to be included on the MTSL.

Implants are a subset of medical technologies defined by the Health Products (Medical Devices) Regulations 2010 as any medical device which is intended by its product owner:

- to be wholly introduced into a human body, or to replace a human epithelial surface or the surface of a human eye, by surgical intervention, and to remain in place after the surgical intervention; or
- to be partially introduced into a human body by surgical intervention, and to remain in place for at least 30 days after the surgical intervention, and includes any such medical device that is wholly or partially absorbed by the human body, epithelial surface or eye.

### Architecture of the MTSL for implants

A classification system was developed to group implants by their biomechanical actions and patient outcomes. The five-tier classification system classifies implants by clinical function, clinical category, product category, product groups, and products, as shown in Figure 4. Reasonable prices and subsidy criteria are set at product group level. Prices determined to be reasonable for each product group are an internal price guide based on the respective local prices and overseas reimbursement prices, subject to review from time to time. Overseas prices are from a basket of reference jurisdictions such as Australia, Belgium, France, New Zealand, South Korea, and Taiwan. Subsidy criteria specify the population eligible for subsidy. Although subsidy criteria for many product groups usually reflect the HSA-registered indication(s), a more restrictive subsidy criteria may be developed in consultation with local clinician experts for selected product groups, taking into consideration the cost of technology, potential for misuse, and clinical and economic evidence. Patients will be eligible for subsidy of listed implants when they are used as per subsidy criteria.

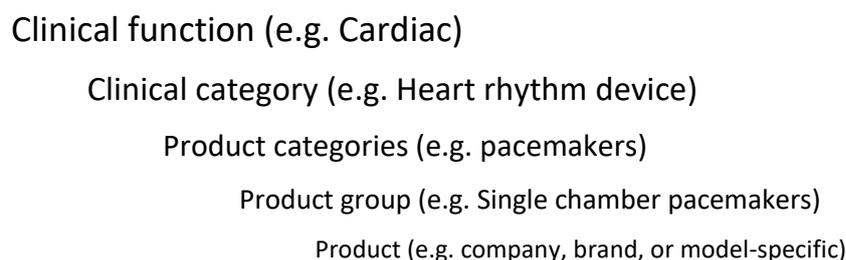


Figure 4: Five-tier classification system of the MTSL

#### i. Clinical functions

The primary classification is based on anatomical areas and therapeutic specialties offered as clinical services in Singapore. These are termed “clinical functions” such as cardiac, cardiothoracic, ophthalmic, orthopaedic, or vascular surgery. A general miscellaneous section captures implantable medical devices not included in the other clinical functions.

## **ii. Clinical categories**

For each clinical function, clinical categories are assigned based on the types of clinical interventions available for different conditions concerned. For example, the “cardiac” clinical function includes clinical categories of heart rhythm devices, interventional cardiology, structural heart, etc.

## **iii. Product categories**

Under each clinical category, different product types are further classified into product categories to address a certain clinical condition. For example, under the “heart rhythm device” clinical category, product categories include pacemakers, defibrillators, electrodes, etc.

## **iv. Product groups**

Under each product category, different product groups are assigned based on similar implant function and the expected clinical outcomes. Products with different features addressing unique clinical needs and demonstrating incremental clinical benefits may justify a separate product group. For example, under the “pacemaker” product group, dual chamber pacemakers are in a separate product group from single chamber pacemakers.

## **Process of reviewing and updating MTSL**

The MTSL is a dynamic list that will be updated three times a year to incorporate new market entrants and any updates to existing implants resulting from newly published evidence, or change in reimbursement status in ACE’s reference jurisdictions. This section explains the general process on reviewing and updating MTSL, mainly in the addition of newly HSA-registered implants to the MTSL (

Figure 5). Each implant item listed on MTSL can be a standalone implant model or package.

#### **i. Identification of implants for MTSL listing**

New implants for MTSL listing are identified through industry submissions.

#### **ii. Inclusion of the implants and their related products on the MTSL**

All implants considered for inclusion in the MTSL must first be registered with the HSA for the intended indication(s) in Singapore. For example, implants used outside the approved regulatory indication (i.e. off-label use), supplied through special access schemes routes, or exempted from HSA-registration, are excluded from the evaluation and are not eligible for MTSL listing.

#### **iii. Determination of MTSL product group and proposed price**

In the industry submission, manufacturers are required to clearly indicate the product group under which a new implant can be grouped and the proposed price. Different pathways apply:

- Where an existing product group applies and the proposed price is deemed to be reasonable, an expedited approval pathway can be expected which includes ACE's due diligence to check the validity of the proposal. The timeline is approximately 6 months to addition onto MTSL; or
- Where a new product group is proposed, a full approval pathway is expected as the implant may be subjected to an in-depth review of comparative evidence on the product's safety, clinical-, cost-effectiveness, and additional consultations with clinical experts. The types and method of evaluation may vary and are determined based on the criteria described in the main body of this methods guide (see Section 2). The timeline is approximately two years to addition onto MTSL.

#### **iv. MTAC decision**

Information submitted by the industry to support MTSL listing consideration, together with ACE's assessment including product group, proposed prices and subsidy criteria will be submitted to MTAC for subsidy recommendation. Following the recommendation, the MTSL will be updated if needed within a suitable timeframe for implementation.

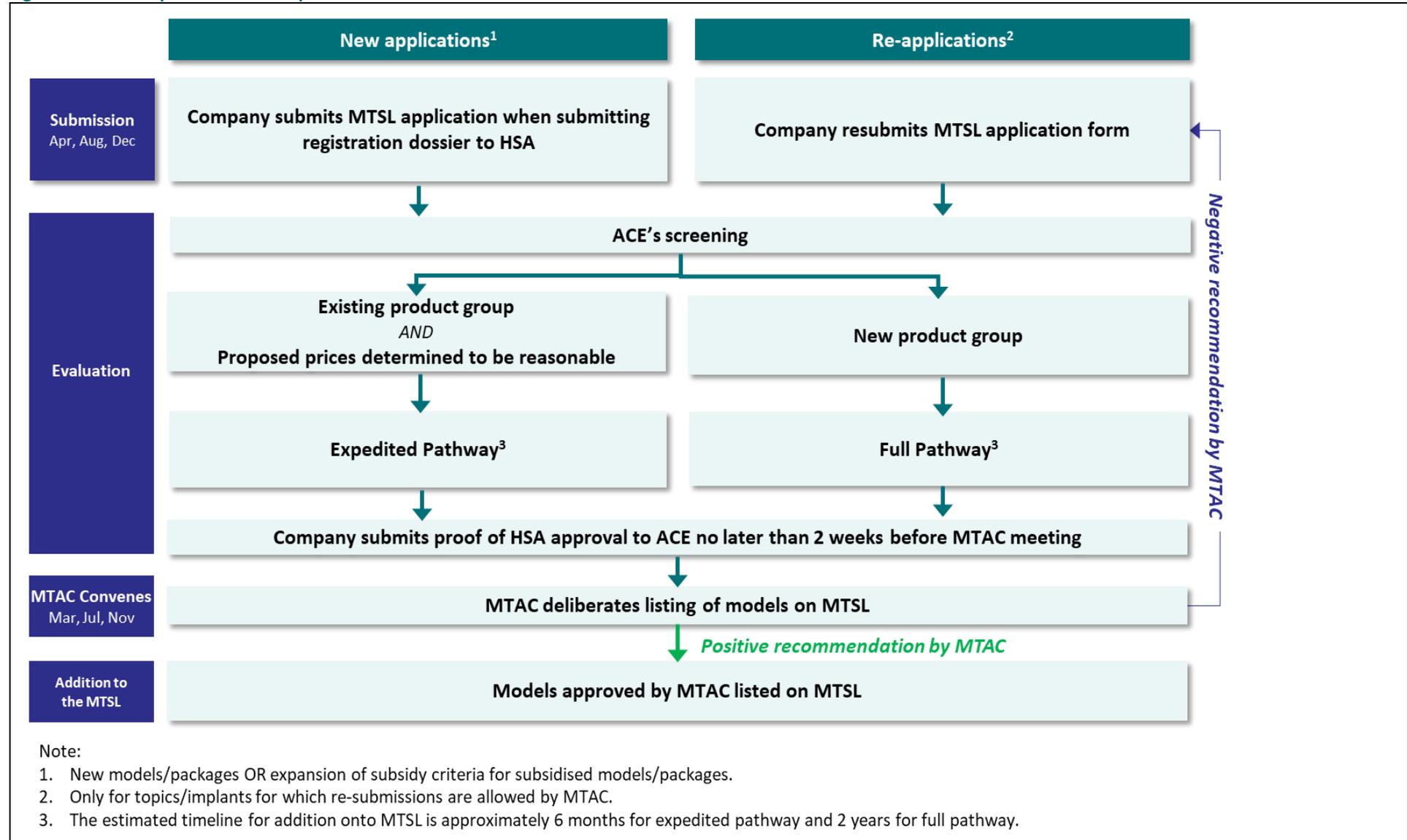
### **Subsidy implementation**

For implants and/or implant packages that are recommended for subsidy, an undertaking that specifies the price and conditions for subsidy listing will be issued to the relevant vendor by ACE. The Undertaking 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 vendor undertakes to sell each implant or implant package specified within the Undertaking at the accepted price when supplying that implant or implant package to the public healthcare institutions; and
- MOH lists each implant and/or implant package in line with specified clinical criteria.

The listed implants will be added to the respective national procurement contracts at the next scheduled update where feasible, to effect procurement contracts in tandem with subsidy implementation. The updated MTSL will be disseminated to the public healthcare institutions and uploaded to Ministry of Health website. Technology Guidance may be developed for selected implants considered for MTSL listing, as deemed necessary.

Figure 5: Inclusion process of the implants in the MTSL



## Annex 2: Medical technology eligibility criteria for evaluation

Eligibility criteria	Detail
<b>Within the remit of MTAC</b>	The technology is suitable to be evaluated by ACE (within the definition of a medical technology or diagnostic technology) and is not currently subsidised in the PHIs.
<b>A new or existing technology seeking subsidy</b>	Any medical devices, diagnostic tests, or medical services which are either new or an existing technology with potential benefits in terms of patient and/or healthcare system outcomes over the comparator(s), and the technology has been or is ready to be used in the PHIs.
<b>Appropriate timing</b>	Where registration or licensing with MOH or the Health Sciences Authority (HSA) is required, the medical technology must first be registered or licensed prior to ACE's evaluation.
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• The medical technology is currently subsidised in the PHIs;</li> <li>• Technologies that are still in the research stage of development;</li> <li>• Models of care (i.e. the way health services are delivered, which outlines best practice of care and services for the patient cohort as they progress through the stages of a condition);</li> <li>• IT systems e.g. Automated systems to reduce waiting time at outpatient pharmacy;</li> <li>• Telemedicine;</li> <li>• Population screening tests;</li> <li>• Contraceptives;</li> <li>• Dental technologies or services; and</li> <li>• Cell and tissue therapy (under a different workstream).</li> </ul>

## Annex 3: Prioritisation criteria

### Checklist for prioritisation for medical technologies

Name of the technology	Manufacturer	Medical device class	Registration number	Registration date
Proposed indication				
Purpose of use (for diagnostics only)				

Stopping criteria		
Registration status of the technology for the indication(s) requested	If required, has the medical technology been registered with relevant regulatory bodies (e.g. HSA) for the indications requested?	<b>Not Applicable</b> <b>No</b> (stop the checklist) <b>Yes</b> (proceed to the following)
Regulatory approval for service provision	If relevant, have the relevant Health Regulatory Group and/or Health Services Group within MOH given approval for the service to be provided in the PHIs?	<b>Not Applicable</b> <b>No</b> (stop the checklist) <b>Yes</b> (proceed to the following)
Sufficient literature findings to enable a meaningful HTA to be undertaken	Is there sufficient literature to enable a meaningful HTA to be undertaken, taking into consideration the number of clinical studies available, the level of evidence and the total patient numbers included?	<b>No</b> (stop the checklist) <b>Yes</b> (proceed to the following)

Please give a score for each of prioritisation criteria for the CLINICAL NEED section, based on the information provided in the Details column.

Prioritisation criteria	Details
<b>CLINICAL NEED</b>	
<b>1. Disease burden</b>	
Size of affected population	The size of the population with the condition (e.g. prevalence and incidence of a condition) who may potentially benefit from the intervention. This is <i>often a subgroup</i> of the affected population with greater clinical benefit from intervention.
Disease severity	Severity of the disease treated with the proposed technology with respect to mortality, morbidity, disability, function, impact on quality of life, etc.
Unmet needs	Are there any alternative technologies currently in use for the condition? If so, are there major limitations with the current technologies?

Prioritisation criteria	Details
<b>2. Claimed benefits (based on literature scan)</b>	
(Comparative) Safety	Potential of the proposed technology to produce a reduction in intervention-related adverse effects (consider their clinical significance) compared to with alternatives
(Comparative) Clinical benefits for patients	Potential of the proposed technology to produce benefit over alternatives, focusing on patient-reported health outcomes (e.g. quality of life, prolonging life, diagnostic speed/accuracy & convenience) Taking into consideration of the magnitude of the effect.
(Comparative) Healthcare system benefits	Potential of the proposed technology to reduce resource use, e.g. to facilitate outpatient treatment, or to require fewer staff, or to reduce hospital stay.
<b>3. Organisational consideration</b>	
Organisational feasibility	The potential impact of adopting the technology on changes in the organisation of care, workforce, facility and training/credentialing requirement.
<b>4. Reimbursement internationally</b>	
Reimbursement/subsidy status in reference countries	Whether the technology has been recommended for reimbursement/subsidy in our reference countries / regions
<b>COST CONSIDERATION</b>	
Direct cost of the technology	Costs related to the set-up the service (e.g. acquisition cost, implementation or significant infrastructural requirements) and recurrent costs (e.g. maintenance & operational costs). If shortlisted, other health-related costs may be considered in the full assessment.
<b>ADDITIONAL CONSIDERATIONS</b>	
Impact of the HTA	Indicate whether a recommendation based on the HTA is likely to influence subsidy decision, taking into account other <u>ethical and political</u> considerations.

#### Attachment 1: Subsidy/Reimbursement status of technology in reference agencies

CADTH	HQO	MSAC	NICE

**Attachment 2: Summary table of studies identified during scoping search**

<b>Type of study</b>	<b>Total no. of patients and follow-up</b>	<b>Study conclusion</b>
e.g. HTA, Systematic review, RCT, non-randomised comparative studies, case series, etc.		

## Annex 4: National Health and Medical Research Council (NHMRC) designations of ‘Levels of Evidence’ according to type of research question

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening intervention
I	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternative collation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternative allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> <li>▪ Non-randomised experimental trial</li> <li>▪ Cohort study</li> <li>▪ Case-control study</li> <li>▪ Interrupted time series with a control group</li> </ul>	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> <li>▪ Non-randomised experimental trial</li> <li>▪ Cohort study</li> <li>▪ Case-control study</li> </ul>

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening intervention
III-3	<p>A comparative study without concurrent controls:</p> <ul style="list-style-type: none"> <li>▪ Historical control study</li> <li>▪ Two or more single arm study</li> <li>▪ Interrupted time series without a parallel control group</li> </ul>	Diagnostic case-control study	A retrospective cohort study	A case-control study	<p>A comparative study without concurrent controls:</p> <ul style="list-style-type: none"> <li>▪ Historical control study</li> <li>▪ Two or more single arm study</li> </ul>
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

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