MEDICAL TECHNOLOGIES EVALUATION METHODS AND PROCESS GUIDE

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ACE
agency for
care effectiveness

Record of updates

Date	Version	Summary of main changes
October 2018	1.0	Publication of initial methods and process guide.
March 2022	2.0	Updated the topic identification and selection process. A new addendum was added on Medical Technology Subsidy List (MTSL) and the processes for new item addition of implants onto MTSL.
March 2024	3.0	Guide was updated to include more information on topic selection, value-based pricing, and how patients provide input to inform ACE's evaluations. Updated information on Implant Subsidy List (ISL) (previously known as MTSL) and related processes.
December 2025	4.0	Updated to include a new addendum on evaluation methods and processes for digital health technologies (DHTs) under subsidy consideration. Minor additions, wording changes and amendments of figures throughout the document have been made to improve the clarity of the text and streamline processes.

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Foreword

Established by the Ministry of Health (MOH), the Agency for Care Effectiveness (ACE) is the national health technology assessment and clinical guidance agency in Singapore. It produces evidence-based evaluations of health technologies (e.g. drugs, vaccines and medical technologies) to inform funding decisions by MOH committees, and publishes technology guidance documents for public hospitals and institutions in Singapore to promote the appropriate use of clinically effective and cost effective treatments. ACE also conducts horizon scanning to provide early alerts concerning new and emerging health technologies with the potential to significantly impact the healthcare system. Find out more about ACE at 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 being considered for funding. This guide intends to standardise and document the framework and methods that ACE follows when conducting medical technology evaluations, and to increase transparency of our processes and decision-making frameworks. It is not a comprehensive academic or technical document.

Alongside ACE, various Ministry of Health technology advisory committees, such as the Medical Technology Advisory Committee (MTAC), may use this process guide. However, they are not bound to adhere to it in every detail, or in every case.

Information in this guide may also be useful for relevant stakeholders who provide evidence and advice to support ACE's medical technology 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 contributions to the development of versions 1.0 (all experts), 2.0, 3.0 (Prof Terry Campbell only) and 4.0 (Prof Andrew Wilson, Prof Jonathan Craig, Prof Tim Shaw) of this guide. The appointments listed were current at the point of expert consultation:

- **Prof Jonathan Craig**, Chair, Commonwealth Medical Services Advisory Committee (MSAC); Vice President and Executive Dean, College of Medicine and Public Health, Flinders University, Australia
- **Prof Ron Goeree**, Professor Emeritus, Department of Health Research Methods, Evidence and Impact, McMaster University, Canada
- **Prof Carole Longson**, Chief Scientific Officer, Association of the British Pharmaceutical Industry UK and Scientific Adviser on HTA, NDA Advisory Services Ltd. [former Director of the Centre for Health Technology Evaluation, National Institute for Health and Care Excellence (NICE), United Kingdom]
- **Prof Paul Scuffham**, Director, Centre for Applied Health Economics (CAHE), Griffith University, Australia
- **Prof Mark Sculpher**, Centre for Health Economics, University of York, United Kingdom
- **Prof Robyn Ward**, Executive Dean, Faculty of Medicine and Health, University of Sydney, Australia
- **Prof Terry Campbell,** Chair, Prostheses List Advisory Committee (PLAC), Commonwealth of Australia; Emeritus Professor of Medicine, University of New South Wales (UNSW), Australia [Since July 2023, PLAC has been renamed Medical Devices and Human Tissue Advisory Committee (MDHTAC).]

- **Prof Andrew Wilson**, Co-Director, Leeder Centre for Health Policy, Economics and Data, School of Public Health, The University of Sydney, Australia
- **Prof Tim Shaw,** Professor of Digital Health and Director of Research in Implementation Science and eHealth (RISe), Faculty of Medicine and Health, The University of Sydney, Australia; Research Leader, Digital Health Cooperative Research Centre

1. Introduction

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

This document provides an overview of the HTA methods and processes that ACE uses when evaluating new and existing 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 medical technologies. The methods for evaluating investigative technologies are not detailed in this guide but are 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 evidence generation, decision-making, and the development of ACE's guidance (Figure 1).

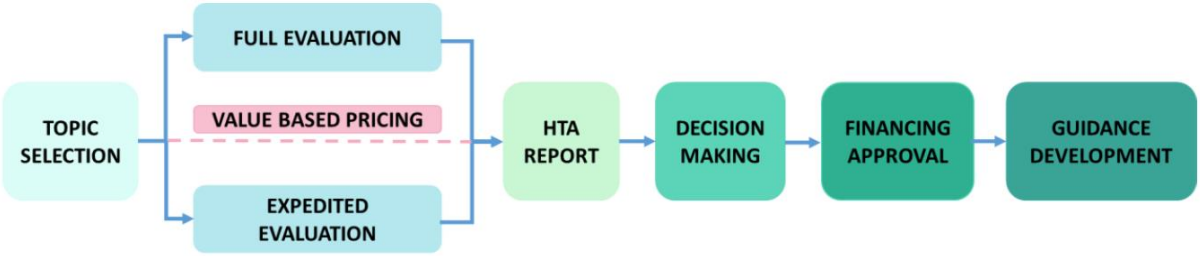

Figure 1. Overview of evaluation process for medical technologies

1.1. Characteristics of medical technologies

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

- 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 a physiological process for medical purposes.

Medical technologies can have a therapeutic or investigative purpose. The aim of a therapeutic technology is to directly improve the health outcomes of the person receiving it without the need to render anything else. On the other hand, an investigative technology improves health outcomes indirectly, as it functions to generate clinically relevant information about the individual using it. To

achieve an improvement in health outcomes, the information must lead to a change in the clinical management of a patient. Investigative technologies are also known as diagnostics or tests.

Medical technologies differ from drugs in several ways which can increase the complexity of their evaluation:

- Medical technologies may be modified frequently over time in ways that change their effectiveness.
- Clinical evidence for medical technologies is often limited, especially when novel or emerging. This is particularly so for randomised controlled trials (RCT) comparing the new technology with appropriate alternative therapeutic or investigative technologies.
- Healthcare system benefits from adopting a medical technology are often dependent on organisational factors, such as the setting where the technology will be used as well as the training, competence, and experience of the user (e.g. the 'learning curve').
- Direct evidence of the effect of investigative technologies on clinical outcomes is often not available.
- For investigative technologies, improved clinical outcomes depend on the subsequent delivery of appropriate healthcare interventions, not only the technology.
- Some medical technologies can be used for therapeutic or investigative purposes depending on the healthcare professionals using them and the clinical scenarios they are used for.
- Costs of medical technologies often include procurement costs (i.e. associated infrastructure) and running costs (i.e. 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 its use.

Health technologies are technologies used in a healthcare system and can include medical technologies and drugs. Health technologies are codependent when health outcomes related to the use of a therapeutic technology is improved by the use of another technology. As the combined use of these technologies leads to the intended clinical effect, they should be assessed together. An example of a codependent technology is an investigative test used to identify patients who respond best to certain drugs, and it may be evaluated together or in parallel 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. Codependent technology and hybrid technology are within the purview of this guide.

2. Topic selection

Topic selection is the process for deciding which medical technologies and clinical indications (medical technology topics) are appropriate for evaluation by ACE. The process has been designed to ensure that the medical technologies chosen will address priority issues and clinical gaps that help improve population health, and support healthcare professionals to provide appropriate care. Information regarding the selection of digital health technologies (DHTs) for evaluation is described in Addendum 3.

2.1. Topic identification

Potential evaluation topics are identified through several channels, including (i) an annual call for applications from public healthcare institutions, patients, carers and patient organisations, (ii) horizon scanning of novel medical technologies, (iii) company applications for the MOH Implant Subsidy List (ISL) listing consideration, and (iv) topics referred to ACE by other divisions within MOH. The topics may include new medical technologies or those already in use locally, but not subsidised.

Every year (typically between March and May), public healthcare institutions are invited to submit applications for potential medical technology evaluation topics. At the start of each application cycle, an invitation is sent to the Chairman of the Medical Board (CMB) or equivalent body of each institution from the MOH Medical Technology Advisory Committee (MTAC) Secretariat within ACE. All applications are required to be submitted to the CMB (or equivalent body) of each institution for endorsement and verification by the Chief Finance Officer (CFO) before sending to the MOH MTAC Secretariat. During the application cycle, applicants may approach ACE for preliminary feedback on whether their submitted topic is within ACE's evaluation remit, before deciding to proceed with the application form.

Every year (typically between October and January), patients, carers and patient organisations are invited by the ACE Consumer Engagement and Education (CEE) team to submit applications for potential medical technology evaluation topics. More information about patient involvement in the topic selection process is described in a separate guide.

New and emerging medical technologies potentially suitable for evaluation are also identified through literature searches and horizon scanning by the ACE technical team. More information about ACE's horizon scanning efforts for potential topics is described in a separate guide.

As part of the ISL work, companies can apply for funding consideration for their implant products either during the request for proposal (RFP) exercise in collaboration with the national public healthcare supply chain agency, or during the model update process (MUP). More details are in Addendum 1.

From time to time, ACE also receives topic suggestions from other divisions within MOH.

2.2. Filtering of medical technology topics

Elimination criteria filter out topics unsuitable for evaluation. A topic will typically not be considered for evaluation by ACE if:

- the medical technology is not registered for use in Singapore by the Health Sciences Authority (HSA) and/or any other relevant regulatory agencies; or
- it is identical or similar to a topic that has been recently evaluated by ACE (e.g. last two years) with no material change in evidence or local clinical management; or
- there is insufficient evidence available to conduct an evaluation.

All medical technologies that provide medical services must be assessed by relevant regulatory agencies in Singapore, such as HSA, and included in the Singapore Medical Device Register (SMDR) where applicable. Generally, ACE will only assess medical technologies that are included in the SMDR and support public funding for indications approved by the regulatory authorities. Infrequently, ACE may accept evaluation applications before a medical technology is approved by HSA, provided that the regulatory process for the product has commenced. ACE will only finalise its appraisal of the medical technology and present it to MOH MTAC for funding deliberation after HSA approval is confirmed for the indication(s) of interest.

The following medical technologies are not eligible for application by public healthcare institutions, patient organisations, and companies:

- Medical technologies that are currently subsidised in the public healthcare institution(s);
- Medical technologies that are not registered or not requiring registration with HSA and/or other relevant regulatory entities;
- Medical technologies that are still in the research stage of development;
- 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);
- Screening tests;
- Vital sign monitoring devices;
- Contraceptive, fertility and cosmetic technologies;
- Dental technologies or services;
- Proton beam therapy.

2.3. Selection of medical technology topics

After filtering, the need to evaluate each topic is considered against specific prioritisation criteria. These criteria measure disease burden and unmet need, claimed benefit over alternative treatments, organisational considerations, overseas recommendation status, potential budget impacts and value that ACE could add by conducting an evaluation.

For each potential topic, the ACE technical team gathers supporting evidence to complete a checklist (Annex 1) to generate a 'need score', estimate the potential budget impact, and apply additional considerations (e.g. subsidy implementation feasibility), if necessary.

In general, medical technologies topics are considered suitable for evaluation to inform MOH MTAC's funding deliberations if:

- The medical 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;
- The medical technology has major cost implications;
- The medical technology has been, or is ready to be used in public healthcare institution(s);
- There is sufficient clinical evidence for a meaningful HTA evaluation based on a preliminary assessment of published evidence; and
- A HTA evaluation is likely to influence funding decision-making.

Developing need scores

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

In some instances, a medical technology with a low need score may still be evaluated if it has the potential to incur high costs or has specific concerns (e.g. safety). In contrast, a medical technology with a high need score may not be prioritised if HTA has limited impact on funding decision-making.

Estimating potential budget impact

The budget impact associated with funding a medical technology is intended to estimate the potential annual costs to MOH. For a medical technology with high upfront capital cost for the acquisition of equipment and modification of infrastructure, more uncertainty may be associated with the cost estimates, and this uncertainty is also taken into consideration.

When estimating the potential budget impact of topics being considered for evaluation, the following general rules are applied:

- For a medical technology used in one or more public healthcare institution(s)
    - If the unit charge (includes setup and running costs) for use of the technology has been provided, together with any other procedure/service charge (if applicable), these can be combined with the estimated eligible patient numbers to estimate the potential budget impact;
- For a new technology (especially those with high upfront capital costs for equipment and/or infrastructure)
    - The unit charge may be unknown and is often uncertain. Budget impact may be estimated based on best available information for costs related to the consumables, procedures or services. The capital costs and maintenance costs, where relevant, can be reflected separately, if available.

3. Technology evaluation

Medical technology topics prioritised for evaluation by the MOH MTAC would proceed to HTA evaluation. Evaluations are usually conducted internally by the ACE technical team with supporting evidence provided by local healthcare professionals from public healthcare institutions, patient organisations, and medical technology companies, where required.

Information regarding the evaluation methods and process for DHTs is provided in Addendum 3.

3.1. Type of evaluation

Evaluations are conducted at two levels – full or expedited – depending on the:

- clinical novelty of the technology;
- complexity of the topic;
- extent of evidence available for evaluation;
- estimated budget impact;
- uncertainty around the clinical and cost parameters, and
- availability of ACE technical resources to evaluate within the expected timeframe for the evaluation.

Typically, a full evaluation may be conducted if the technology for the indication(s) of interest shows superior outcomes compared with its comparator(s) and there is a lack of recent, good-quality economic studies applicable to the local context.

A summary of the evidence sourced for each evaluation type, the analyses undertaken by ACE, and the average time to complete each evaluation is shown in Table 1.

Table 1. Type of evaluation report

Type of evaluation	Types of evidence and analyses included in evaluation	Time required[a]
Full evaluation	• Stakeholder workshop with or without written survey of clinical experts, to define the scope of the evaluation, inform local treatment algorithm, define comparator(s), and describe current use of the technology in local practice. • For wearable and home-based medical devices, patient inputs through qualitative written surveys to define the clinical need for the technology under evaluation and patients' preferences for new technologies. • A comprehensive systematic literature review and critical appraisal of all relevant or higher-level evidence (local and international studies) evaluating the safety and clinical effectiveness of the technology. • Literature search of published economic evidence (local and international studies) and review of retrieved studies. • Synthesis of relevant and available evidence to summarise safety, clinical effectiveness, and cost effectiveness of technology.	6 to 9 months

Type of evaluation	Types of evidence and analyses included in evaluation	Time required[a]
	• Development of economic model, using local data inputs where available. Scenario analyses and sensitivity analyses also undertaken to model the uncertainty of key model parameters. • Review of previous assessments by international HTA agencies. • Budget impact analysis, including estimated volume and annual cost to the healthcare system. • Any organisational, ethical and social considerations from using the technology are also considered.	
Expedited evaluation	• Stakeholder workshop and/or written survey of clinical experts to inform local treatment algorithm, define comparator(s), and describe current use of the technology in local practice. • For wearable and home-based medical devices, patient inputs through qualitative written surveys to define the clinical need for the technology under evaluation and patients' preferences for new technologies. • Literature search of highest level or most recent (e.g. last 10 years) published clinical and economic evidence (local and international studies). *Optionally*, the evaluation may include a critical appraisal of the evidence. • Synthesis of relevant and available evidence to summarise safety, clinical effectiveness, and cost effectiveness of technology. • Review of previous assessments by international HTA agencies. • Budget impact analysis, including estimated volume and annual cost to the healthcare system. • Any organisational, ethical and social considerations from using the technology are also considered.	3 to 4 months

[a] The timelines are indicative. Actual timelines vary depending on the complexity of topic and number of medical technologies/indication(s) included in each evaluation.

Abbreviation: HTA, health technology assessment.

3.2 Evaluation process

Figure 2 provides a high-level view of the overall evaluation process for medical technology topics. The details of each stage are described in the following sections.

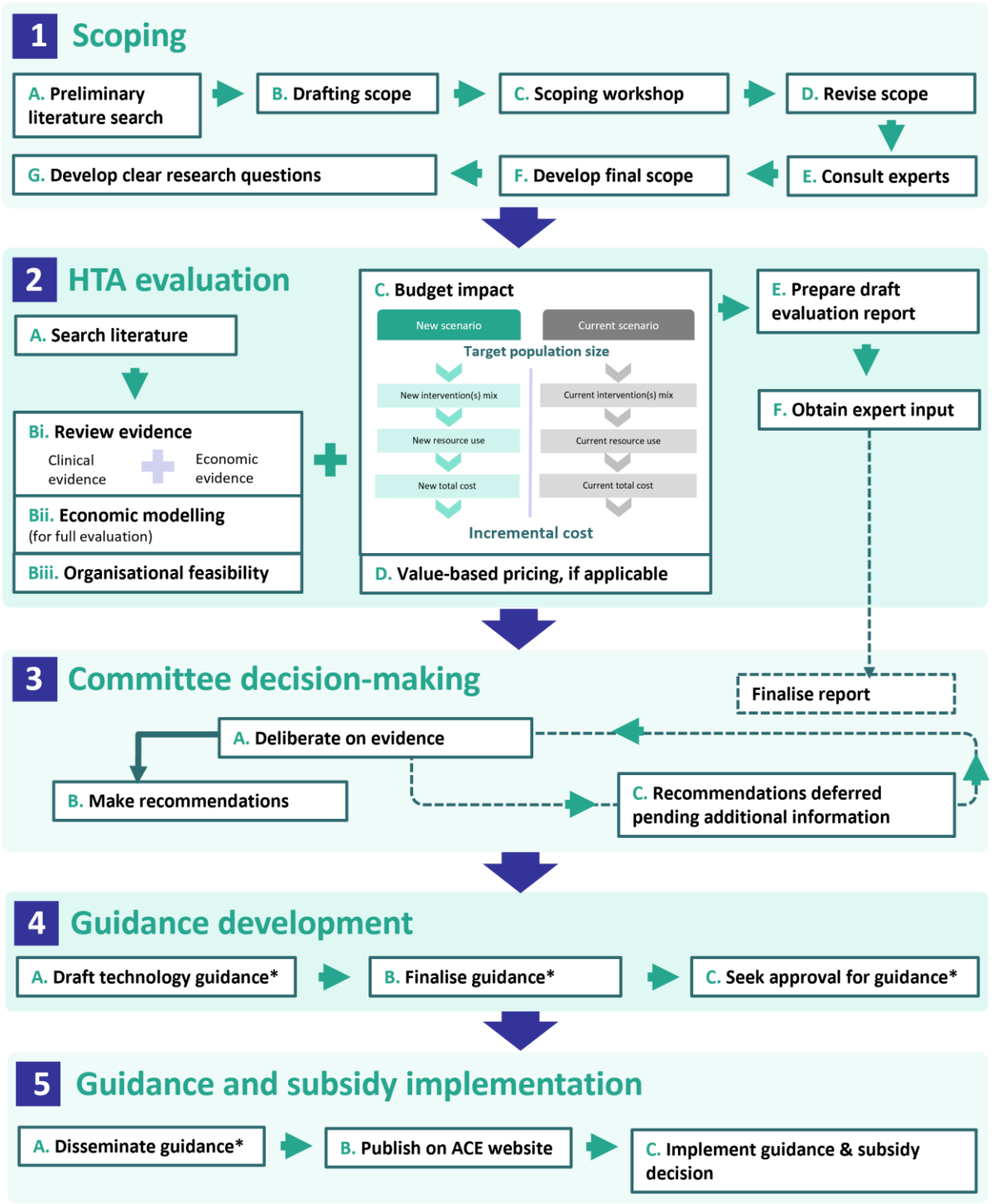

Figure 2. Overview of medical technology evaluation process
*** Guidance may be accompanied by plain English summary for wearable and home-based medical devices.**

4. Scoping

4.1. Developing the scope

The first step of conducting a HTA is developing the scope or focus of the evaluation. The purpose of the scoping process is to ensure 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.

The ACE technical team uses the PICO framework (**P**opulation, **I**ntervention, **C**omparators, and health **O**utcome measures) to define the key elements of interest and the research question that the evaluation is intended to address. This serves to clearly define the purpose and boundaries of the evaluation, and to assist the ACE team in formulating clear search terms and yielding more precise search results (Table 2).

More details on developing the scope for DHTs are provided in Addendum 3.

Table 2. PICO framework

Domain	Description
Population	People of certain characteristics affected by a condition that uses the medical technology under evaluation
Intervention	Medical technology under evaluation
Prior test*	Prior testing results
Comparator	Alternative(s) to the intervention used in routine clinical practice
Outcome	Patient-relevant clinically meaningful health outcomes of interests and/or healthcare system outcomes expected from using the medical technology under review

* Applies mainly to investigative technologies

4.2. Drafting the scope

The draft scope is developed by the ACE technical team. This entails 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 scoping workshop or through individual consultations. When necessary, other stakeholders (e.g. industry) may be consulted to provide inputs to the scope.

Determining the care pathway in the scope is also essential. This helps define the sequence and timeframe for the interventions covered and the key steps leading to final outcomes. The care pathway is particularly important for investigative technologies, 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 other tests and treatments in the pathway. The care

pathway can vary depending on the patient's characteristics and the clinical practice norms across public healthcare institutions. A flowchart or diagram to illustrate the pathway should be included in the scope description.

If relevant, the health care setting where the technology will be used (e.g. inpatient or outpatient use within a hospital, primary care, community) and the timeframe are additional considerations for the scope.

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

For investigative technologies, the optimal position in the care pathway is not always obvious (e.g. different points in the pathway, in sequence or in combination), so different permutations of treatment strategies or sequencing may need to be assumed and evaluated. Refer to Addendum 2 for more details on specific considerations for evaluating investigative technologies.

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 may also estimate the proportion of patients who are likely to be eligible for the medical technology being evaluated. Patient subgroups in whom the medical technology might be particularly clinically- and/or cost-effective are also be considered.

Intervention

The key features of the medical technology under evaluation are described. This can include its primary components, mechanism of action, 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 in Singapore and a list of registered products and corresponding manufacturers and/or distributors. Any discrepancy between the intended and the approved indication(s) is highlighted.

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, the standard of care may involve more than one comparator, or no treatment. The main comparator is defined, if possible, as that which is most likely to be replaced in clinical practice by the medical technology under evaluation, and is typically the current standard of care for the health condition being reviewed.

The use of the medical technology as a replacement or addition to the comparator(s) is also assessed. Reviews of investigative technologies may also identify the reference standard and the relevant comparator test(s) in the context of the care pathway. The reference standard may not necessarily represent the standard of care.

Health outcomes

The ACE technical team, in consultation with clinical and patient 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 clinically important to patients and/or to the health system are also considered valid measures of the benefits of the medical technology under evaluation. Where relevant, the length of time over which the benefits and costs apply will be considered.

As medical technologies may have resource-releasing claims that translate to benefits for other patients or improved healthcare system efficiency, system benefits including cost savings are also an outcome of interest.

Setting and timing

When necessary, the scope of the evaluation may include the setting in which the medical technology is administered (e.g. hospital inpatient or outpatient, primary care or community), and also define the user (e.g. medical 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 (i.e. use in relation to the progression of the condition or recovery pathway).

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 implementation or use of the technology in clinical practice in Singapore.

4.3. Stakeholder workshop

To ensure that the evaluation framework is appropriately defined and relevant to local clinical practice and patient need, ACE may hold a stakeholder workshop with healthcare professionals who have expertise in the disease area or the use of the medical technology under evaluation. Stakeholders outside the healthcare sector may be included when deemed necessary. All participants are required

to sign a non-disclosure agreement to safeguard any confidential information, and declare any conflict of interest prior to the workshop.

The aims of the workshop are to:

- Ensure that the scope is appropriately defined;
- Seek further advice from healthcare professionals on:
    - Variations between groups of patients, in particular, differential baseline risks of the condition and the potential for different patient subgroups to benefit;
    - Appropriate, patient-relevant outcomes and surrogate outcome measures;
    - Significance of side effects or adverse events, and clinical benefits that are expected or realised in local clinical practice;
    - Relevant potential comparators;
    - Requirements to implement guidance on use of the medical technology, including need for additional staff or equipment, education and training requirements, and ways in which uptake may be affected;
    - Versions of the medical technology that are relevant to evaluation;
    - Verification of existing and new care pathways; and
- Identify important evidence and any other issues relevant to the evaluation such as potential implementation barriers or pitfalls in the use of the technology.

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.

4.4. Finalising the scope

After the workshop, the ACE technical team finalises the scope, taking into account discussions held by the stakeholders. The finalised scope is then shared with the stakeholders involved.

The finalised scope clearly defines the clinical, economic, and organisational research questions and any other relevant aspects of the medical technology under evaluation that will guide evidence generation and appraisal.

5. Evidence generation and critical appraisal

Consideration of a comprehensive evidence base is fundamental to the evaluation process. The evidence review aims to retrieve and collate published evidence, and critically appraise and synthesise all relevant evidence on the medical technology under review, to provide a comprehensive summary, in the form of a HTA report, of benefits and issues related to use of the technology. 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).

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 evidence from RCTs which directly compare the proposed technology with the main comparator are preferred, as they are considered to provide the most valid evidence of relative efficacy. As RCTs are not always available, lower levels of evidence without design or quality threshold restrictions are often considered, if they are relevant to the intended use and claimed benefits of the technology. In these instances, indirect RCT comparisons (across two or more sets of RCTs, involving one or more common reference) and non-randomised studies may also inform the evaluation.

A summary of the different types of evidence used to inform ACE's technical evaluations, and the considerations made by ACE when using each type of evidence are shown in Table 3. More details on the evaluation methods for investigative technologies and DHTs are provided in Addendum 2 and Addendum 3, respectively.

Table 3. Types of evidence considered in ACE evaluations

Evidence type	Considerations
Randomised controlled trials	• RCTs are appropriate for measures of relative and absolute treatment effects. If randomisation is conducted properly, observed and unobserved characteristics should be balanced between the randomised groups, so the effect of the treatment versus the control on the observed outcomes can be inferred. • The relevance of RCT evidence to the evaluation depends on both the external and internal validity of each trial: ○ Internal validity is assessed according to the design and conduct of a trial and includes blinding (when appropriate), the method of randomisation and concealment of allocation, and the completeness of follow-up. Other important considerations are the size and power of the trial, the selection and measurement of outcomes, and analysis by intention to treat. • External validity is assessed according to the generalisability of the trial evidence; that is, whether the results apply to wider patient groups (and over a longer follow-up), Asian populations, and to routine clinical practice in the local context.
Non-randomised evidence	• In non-randomised studies (such as observational or epidemiological studies), the treatment assignment is non-random, and the mechanism of assigning patients to alternative treatments is usually unknown. Hence, the estimated effects of treatment on outcomes are subject to treatment selection bias, and this should be recognised in the interpretation of the results. • Inferences will necessarily be more cautious about relative treatment effects drawn from studies without randomisation or control groups than those from RCTs. The potential biases of non-randomised studies should be identified, and ideally quantified and adjusted for.

Evidence type	Considerations
	• Evidence from non-randomised sources is often used to obtain non-clinical model parameters such as costs and utility values. Non-randomised studies may also provide useful evidence about long-term outcomes, rare events and populations that are typical of real-world practice. As study quality can vary, critical appraisal and sensitivity analyses can be helpful when reviewing these study outcomes.
Test performance / diagnostic accuracy evidence	• In the absence of high quality evidence, direct from test to health outcomes, an assessment of an investigative technology would need a linked evidence approach. • Studies on test performance or diagnostic accuracy are used to inform the linked evidence approach. • The ability to appropriately categorise patients by the test (i.e. test accuracy) is important to help understand how the proposed test would change patient management and its likely impact on patient health outcomes.
Real world data	• In its broad definition, real world data encompasses all non-randomised evidence and can include data generated as part of pragmatic controlled trials; however, in HTA, it typically presents as observational data from patient registries, administrative databases, electronic medical records and surveys. • The quality of real-world data can vary across different data types and sources. To mitigate potential bias, careful study design is needed, and an analysis plan should be created prior to retrieving and analysing real world data.
Qualitative research	• Qualitative research, in the form of questionnaire or survey responses from clinical professionals and patient experts, is often used to explore areas such as patients' experiences of a disease and/or specific treatment(s), and clinicians' views on the role of different treatments in local clinical practice.
Economic evaluations	• Evidence on the cost effectiveness of the technology under evaluation may be obtained from de novo analyses conducted by the ACE technical team (for full evaluations); however, a comprehensive search of published, relevant evidence on the cost effectiveness of the technology is also conducted to inform the evaluation. • Economic evaluations should quantify how the treatments under comparison affect disease progression and patients' health-related quality of life, and value those effects to reflect the preferences of the general population.
Unpublished evidence	• To ensure that the evaluation does not miss important relevant evidence, attempts are made to identify evidence that is not in the public domain. Such evidence includes unpublished clinical trial data in clinical study reports (which is preferred over data in poster or abstract form only). • If unpublished evidence is used to populate an economic model, such information should be critically appraised and, when appropriate, sensitivity analysis conducted to examine the effects of its inclusion or exclusion on the results.

5.1. Clinical evidence

The objective of a clinical evidence review is to synthesise the relevant evidence about the benefits and harms a medical technology has on patients and/or the healthcare system. Comprehensive review methodologies are followed to ensure that all relevant published evidence is systematically collated, appraised and synthesised, to provide an unbiased summary.

When sourcing information, secondary studies, such as systematic reviews and assessments of published information (including HTA reports and clinical guidelines) are typically retrieved before primary studies (individual trials). If recent HTA reports or systematic reviews meeting the selection criteria are identified, the ACE technical team may adapt or update the review, rather than conduct an evidence review from only primary studies 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 clinical trial registers is also conducted, to identify any ongoing trials that 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 the 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. The following databases are typically 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 refine the results by specific study designs, publication dates, or target age groups, amongst others. Generally, only studies published in English are included.

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

- The databases and registers of clinical trials searched;
- The period of the 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 are removed before study selection occurs.

5.3. Study selection

Studies are selected according to the eligibility criteria specified in the scope document, which may include relevant PICO criteria, study design, year of publication, setting and timing of technology usage, sample size, and minimum follow-up period. English language and full-text publications are general requirements for evidence used to 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:

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

Study selection is performed by either one or two reviewers. For the latter (usually for full evaluations), any discrepancies 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 the level of evidence; and 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 2).

Quality of evidence, on the other hand, reflects how well the studies were conducted 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), 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 concerning 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 advice

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

Experts may be involved in the whole evaluation process, from scope development to feedback on the evaluation report and implementation of any technology guidance. Their opinion is also useful in ascertaining the clinical value of the medical technology and the clinical meaningfulness of any differences detected in the evaluation between the intervention and comparator(s). In addition, experts can also help contextualise the results from the reviewed evidence. The information they provide can relate to technical specifications of the technology which may affect its ability to deliver the claimed benefits, the training and experience required to use the technology, and organisational factors which may influence how the technology performs or is used in clinical practice.

5.7. Evidence submissions from companies

During the evaluation, ACE may invite the company of the technology of interest to submit a summary of key clinical evidence to supplement ACE's assessment. Only companies invited by ACE can submit relevant evidence. The evidence should be provided using the company evidence submission template (see Annex 3), within the required timelines stipulated by ACE.

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

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 relevant evidence, determine the validity of the study results and assess the applicability of the technology to the Singapore healthcare system.

The literature search for economic evidence is aligned with the PICO framework that 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.

For each study, the ACE technical team assesses the validity of the results based on whether the structure and assumptions of the models used are reasonable, whether the outcomes represent final patient-relevant outcomes, and whether all necessary resources and costs are included and appropriate. 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 healthcare 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 cost-effectiveness analysis (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 as 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.

More details on conducting an economic evaluation for DHTs are provided in Addendum 3.

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 is preferred, as it compares both the costs and consequences of the medical technology under evaluation to its main comparator(s). 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, 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 (CUA)), 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 improved 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:

- cost-minimisation analysis (CMA), where the proposed technology has been demonstrated to be no worse than its main comparator(s) in terms of clinical effectiveness and safety (in both nature and magnitude), so the difference between the proposed technology and the appropriate comparator(s) can be reduced to a comparison of costs to the healthcare system;
- cost-consequence analysis (CCA), if the proposed 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 are 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 and study healthcare systems (e.g. the care pathways, the expertise of medical and healthcare staff).
- Comprehensiveness of the evidence – based on whether the estimates are representative of the clinical literature as a whole. When available, systematic reviews or meta-analyses 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 available data. Surrogate or intermediate outcomes may be used if there is an established link between them and any 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

The Singapore healthcare system perspective, which includes government, insurance provider and patients, should be taken. The ACE technical team systematically identifies and estimates direct costs resulting from or associated with the use of the technology, using total costs to the patient (i.e.

charge). Direct costs include acquisition and maintenance costs, and costs related to infrastructure modification. Some costs typically included in the model are:

- 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. The ACE technical team specifies the data sources and collection methods used for estimating resource quantities and unit costs. Resource use may be obtained from literature or an existing MOH database (e.g. case mix). Unit costs may be derived from administrative databases (e.g. costing using diagnosis-related groups [DRGs] for inpatient stays), from MOH Healthcare Finance division costing exercises, or from costs provided by clinicians and relevant hospital departments, published literature, or the company.

Indirect healthcare costs or non-healthcare costs should not be included in the reference case analysis. Indirect patient costs, which relate to lost productivity of the patient due to treatment, illness or death, of that of family members due to time off work for caring, should not be included in the reference case analysis, but can be considered as supplementary evidence, if justifiable.

6.1.3. Valuing health effects

Health outcomes used in the economic evaluation may be expressed as quality of life measures (such as QALY) or in natural units (such as life years gained). If available, quality of life measures are generally preferred.

ACE 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 from 0 (death) to 1 (perfect health). 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. Generic measures of quality of life that are valid, reliable and commonly used in economic evaluations include EQ-5D, SF-36, HUI Mark 3, and AQoL. 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 website.

Utility values associated with each health state or event are generally obtained from published literature. Clear justification for choosing a particular data set will be provided. When more than one plausible set of utility data is available, sensitivity analyses will be carried out to show the impact of the alternative utility values. 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. The ACE technical team use sensitivity analyses to explore how variation in the use of the mapping algorithms impacts outputs.

6.1.4. Uncertainty and variability

In general, two key types of model uncertainties 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 parameter (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 differences in individual responses to an intervention. Differences attributable to patient heterogeneity 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.

When 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 by 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 a budget impact analysis (BIA) is to estimate the utilisation and incremental costs to the government if the medical technology was funded in the public healthcare system in Singapore. The analysis is conducted from MOH's perspective.

The general approach taken by the ACE technical team is to identify the current mix of interventions in a specific disease area and predict how funding the new technology may impact utilisation changes and the overall budget. Figure 3 outlines how 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). The BIA may be standalone or accompanied by a cost-effectiveness analysis. The budget impact is typically projected over a five-year time horizon.

More details on conducting a BIA for DHTs are provided in Addendum 3.

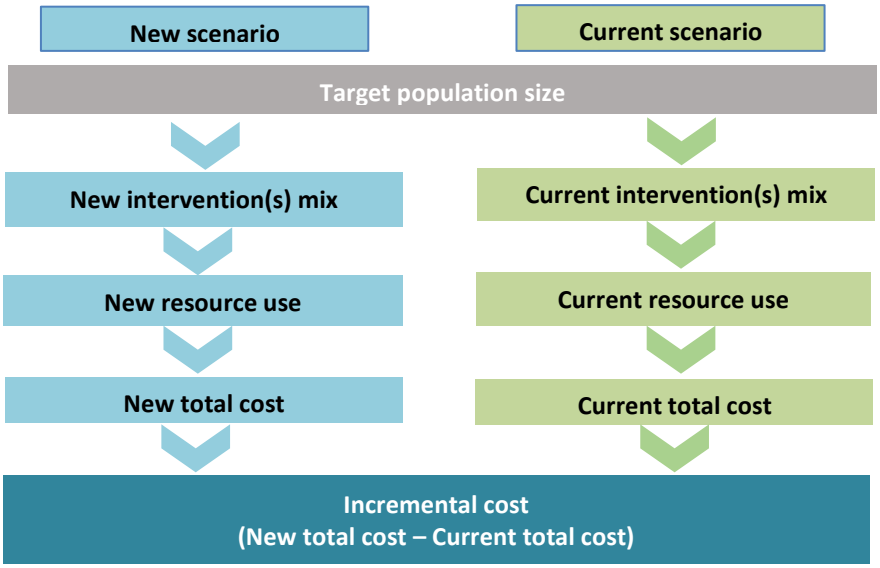

Figure 3: Flowchart of budget impact analysis

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. 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, a BIA based on an epidemiological approach is preferred for novel technologies, as reliable local utilisation data are lacking. However, given that 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 an epidemiological approach.

7.2. The 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. At any point in time, there are usually multiple interventions available in the healthcare system to treat a particular condition. However, they are often used at different rates, referred to as intervention mix. The ACE technical team estimates the current intervention mix as well as the potential future mix, which depends on how quickly the new technology is likely to be adopted (e.g. uptake rate) and the extent to which it would replace any current intervention. The future intervention mix and uptake rate of the new technology may be extrapolated from currently available data (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 new technology, resource use and associated costs may include those associated with the technology, as well as any related procedures, monitoring, treatment-related adverse events, and disease progression. In a BIA accompanied by a cost-effectiveness analysis, costs associated with both the technology and disease are included. For a 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 BIA should be addressed. Where possible, the nature of the 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. Sensitivity analyses which vary the price of the new technology, the market size, and the market share of the alternatives, are also performed. In general, there are two types of uncertainty that 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 uncertainty around whether the requested restriction would achieve its intended objective. This raises questions on the overall cost-effectiveness of the proposed technology where restriction intends 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. The Reference case

The MOH MTAC makes funding decisions across different medical technologies and disease areas. It is therefore crucial that analyses of clinical- and cost-effectiveness undertaken to inform the evaluation adopt a consistent approach. To allow this, ACE has defined a 'reference case' to promote quality analysis and encourage consistency in analytical approaches.

Although the reference case specifies the preferred methods followed by ACE, it does not preclude MOH MTAC's' consideration of non-reference-case analyses, if appropriate. The reasons for the use of non-reference-case analyses should be clearly specified and justified, and the likely implications quantified if possible. The key elements of the reference case are summarised in Table 3.

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.

Table 3. The ACE reference case for medical technology evaluations

Component of medical technology evaluation	Reference case
Perspective of the evaluation	• Singapore healthcare system, including payments from government healthcare or insurance (MediShield Life) budgets, as well as patients' co-payments including MediSave and out-of-pocket expenses. • 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.
Target populations and subgroups	• 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. • Epidemiological data for Singapore presented for the entire target population and relevant subgroups, if available. • Subgroup analyses if appropriate (statistical) justification is provided.
Comparators	• Consistent with the comparator(s) defined in the evaluation scope. • 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. For investigative technologies 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.
Outcomes	• Consistent with the outcomes defined in the evaluation framework. • Health outcomes should be patient-relevant and valued from a Singapore healthcare system perspective.

Component of medical technology evaluation	Reference case
Systematic review	• 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. • Provides reproducible search strategy, transparent selection criteria and selection procedures, and critical appraisal and quality assessment of the evidence.
Economic evaluation	• For interventions which are non-inferior (comparable effectiveness and safety) to their comparator(s), a cost-minimisation analysis (CMA) should be undertaken. • A cost-effectiveness analysis (CEA) should be carried out for full evaluations if the technology is clinically superior to the comparator. It should be undertaken to establish whether differences in expected costs between treatment options can be justified in terms of changes in expected health effects. • Cost-utility analysis (CUA) is the preferred method and should be used if the technology has an impact on health-related quality of life that is significant to the patient or if there are multiple patient-relevant clinical outcome parameters expressed in different units. • Results should be expressed as incremental cost-effectiveness ratios (ICERs) with their associated upper and lower limits. • Economic models should be based as much as possible on data from clinical studies comparing the intervention and the comparator, on data from validated databases and/or from published literature. Model inputs and outputs should be consistent with existing data and have face validity. Justification of model structural assumptions and data inputs should be provided. When there are alternative plausible assumptions and inputs, sensitivity analyses of their effects on model outputs should be undertaken.
Calculations of costs	• Only direct healthcare costs should be included. • The identification, measurement and valuation of costs should be consistent with the perspective of the Singapore healthcare system (government, insurance provider and patient health costs). • Indirect healthcare costs or non-healthcare costs should not be included in the reference case analysis, but can be included in secondary analyses.
Measuring and valuing health effects	• Final, clearly defined, patient-relevant, clinically meaningful outcomes should be presented. • CUA: quality-adjusted life years (QALYs) gained. • Life expectancy estimates based on recent Singapore age-specific and gender-specific life tables. • For 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. • EQ-5D-3L utility weights estimated based on the general population in the UK (which ideally have been accepted by NICE) should be used in the scoring algorithm to calculate utility weights, where available. • Singapore-based preference weights can be used in sensitivity analyses. • Quality of life weights derived with validated instrument (e.g. EQ-5D).
Time horizon	• The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the treatments being compared.
Discount rate	• Costs and health outcomes are discounted at an annual rate of 3%.

Component of medical technology evaluation	Reference case
	• Other scenarios can be presented to test sensitivity of results to the discount rate applied.
Handling uncertainty	• Explore all relevant structural, parameter source, and parameter precision uncertainty. • One-way deterministic sensitivity analysis should be presented for all uncertain parameters. • Multivariate probabilistic sensitivity analysis may also be performed to examine simultaneous impact of all uncertain parameters.
Budget impact analysis	Budget impact analyses should follow these principles: • Target population: The analysis should estimate the potential size of the target population and its potential evolution over time with justifications provided. • 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. • 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 funding decision), the net cost price after the discount is applied should be used in the base case. • Time horizon: The time horizon depends on the time needed to reach a steady state. Present the budget impact up to the steady state, typically with a time horizon of five years. • Discount rate: Future costs and savings should not be discounted.

9. Organisational feasibility

Adopting a medical technology can have far-reaching impacts on the healthcare 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.

The objective of an organisational feasibility assessment is to identify potential barriers and enablers to adopting the medical technology into the Singapore public healthcare system. Potential solutions to overcome the barriers should be highlighted.

Some potential impacts are:

- Changes to the organisation in terms of care, other existing services or clinical units, workforce considerations;
- Modification to property or facility (e.g. capital works) and software requirements;
- Additional resources (including staff) 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 that may influence the technology's performance or use in clinical practice.

More details on organisational feasibility assessment for DHTs are provided in Addendum 3.

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

10. Evidence Review Centres (ERCs)

Academic centres (usually from overseas institutions) with experience in conducting and appraising HTAs for medical technology may be consulted to review ACE's evaluation reports and accompanying economic models for full evaluations. Expedited evaluations are not typically subject to external review. ERCs are usually given 4 to 8 weeks to review ACE's evaluations, depending on the complexity of the evaluation, and their comments and suggested amendments are incorporated into ACE's final evaluation report for MOH MTAC's consideration.

11. Value-based pricing (VBP)

At the discretion of MOH MTAC, ACE will conduct VBP in parallel with the evaluation of selected medical technologies, to ensure that the cost of the technology being considered for funding is commensurate with its value in the context of the Singapore healthcare system. The process enables ACE to engage in discussions with companies to determine the price at which the technology best represents a cost-effective use of healthcare resources.

11.1. Request for Proposal

Companies are invited to submit their best cost prices (i.e. the prices at which the companies sell their products to public healthcare institutions) for medical technologies under evaluation and to detail any other proposed arrangements. The impact of any proposed arrangements on the effective cost price should be clearly stated.

Companies are also required to provide additional sales information, such as:

- the current cost prices for their technology;
- the number of units sold during the past period (up to 36 months) to patients in public healthcare institutions (if applicable); and
- details of any existing pricing arrangements in Singapore.

The deadline for submission is typically 4 to 8 weeks or based on predetermined submission windows (see Addendum 1). Any request for an extension is considered exceptional and is subject to approval by ACE on a case-by-case basis. Submission validity is generally 24 months unless otherwise stated, on balance of acceptability to companies and the meeting schedules of the MOH MTAC.

Proposed prices are used to inform ACE's evaluation, economic analyses (where applicable) and budget impact assessments. In instances where a company is required to submit more than one proposal during the evaluation process, any new proposal submitted shall supersede previous proposal(s), unless otherwise specified.

Where relevant, to confirm commitment to the proposal, the company is required to sign an agreement before the MOH MTAC meeting where their proposal is being considered. The agreement cannot be executed until the MOH MTAC has issued a positive recommendation.

11.2. Notification of Outcome

A Notification of Outcome (NOO) is sent to all companies who submitted proposals to advise them of MOH MTAC's recommendations, and to provide sufficient time for downstream stock supply and inventory management at the public healthcare institutions. Each company is only informed of the outcome for their product(s). Companies that receive a positive recommendation for their product(s) should not disseminate the information in the NOO in an indiscriminate manner until the date of funding implementation.

11.3. Establishment of Agreement

In general, legally binding agreements such as a Letter of Undertaking (LOU) are issued to companies of technologies with positive funding decisions. They specify the cost price and conditions of listing, and any terms for other pricing or access arrangements.

These agreements are signed by the Permanent Secretary (Health) for and on behalf of the Government of the Republic of Singapore, represented by the Ministry of Health, whereby:

- the company undertakes to sell the technology at a cost price not exceeding the negotiated price agreed upon for funding when supplying it to the public healthcare institutions; and
- MOH lists the technology in line with specific clinical criteria.

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

11.4. Resubmission of price proposal following a negative recommendation

Companies are expected to provide their best and final prices for funding consideration of their product in their submission. Immediate resubmission of a price proposal, in response to the NOO email, for technologies that have not been recommended for funding is not allowed. If a medical technology is recommended for delisting (i.e. removal of funding), it will not be considered for re-listing for at least 3 years.

Pricing resubmissions are not allowed if the MOH MTAC did not recommend a technology for funding based on insufficient or unfavourable clinical evidence. Companies may be invited to resubmit only at the discretion of the MOH MTAC, when sufficient new evidence is available for their reconsideration. Any resubmission is also at MOH MTAC's discretion.

At an appropriate time determined by MOH MTAC, companies unsuccessful in achieving funding for their products based on uncertain or unacceptable cost-effectiveness or budget impact may resubmit a revised price proposal for the MOH MTAC to reconsider.

Revised price proposals can be submitted no earlier than 6 to 12 months from receiving the NOO for the topic. Generally, for eligible medical technologies, ACE accepts resubmissions three times a year via the Model Update Process (MUP), during the first 15 days of April, August and December, in line with the submission application windows for updating existing funded medical technologies. The MUP is currently open to companies that have implants listed on the ISL. In the event of a submission being delayed, the proposal will be considered at a later MOH MTAC meeting.

Revised pricing proposals will be scheduled for the MOH MTAC's consideration at the next available deliberation depending on the timing of existing procurement agreements between companies and public healthcare institutions for the technology under evaluation and/or its comparators.

12. Decision-making

12.1. MOH Medical Technology Advisory Committee (MTAC)

Funding decisions for medical technologies are made by the MOH MTAC.

The MOH MTAC is an expert committee comprising members with a range of expertise including senior clinicians who use medical technologies, and senior regulatory affairs and healthcare finance representatives from MOH who provide a lay perspective of the issues affecting patients and the systems in the public healthcare institutions. It is chaired by the MOH Director-General of Health (DGH). Members are appointed for a 3-year term by the Chairman and may be re-appointed to serve for more than one term.

The MOH MTAC is responsible for providing evidence-based advice to the MOH so that funding decisions for medical technologies are made in an equitable, efficient and sustainable manner. The terms of reference of MOH MTAC are to:

- Identify and prioritise medical technologies with potential to address care gaps, deliver significant improvements in health outcomes and/or patients' experience, offer ease of operator use, and/or improvements in the efficient use of resources for horizon scanning and/or evaluation;
- Deliberate and serve as lead discussant, if needed, on evidence including comparative safety, clinical effectiveness, cost effectiveness and total cost of the medical technology and organisational feasibility;
- Recommend whether early adoption should be supported or funding should be provided for a medical technology and if so, the conditions and the criteria for funding;
- Monitor the impact of ACE guidance on prescribers' practice; and
- Act as champions of MOH MTAC-recommended medical technologies, in support of early adoption and funding decisions based on principles of HTA.

The MOH MTAC usually meets three times a year. Additional meetings may be called by the Chairman. Pre-meetings are also held with the Chairman before each MOH MTAC meeting.

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

All MOH MTAC members are required to submit a declaration of interest every year, and to declare any conflict of interest at each Committee meeting.

12.2. Factors informing funding decisions

The MOH MTAC makes funding recommendations informed by ACE's technical evaluations through a deliberative process. When forming recommendations, five core decision-making criteria are considered:

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) – the incremental benefit and cost of the technology compared to existing alternatives;
4. Budget impact; and
5. Organisational feasibility – the potential impact of adopting the technology, especially barriers for diffusion.

Specific factors and judgments discussed by MOH MTAC when considering each criterion are described in Table 4. Additional factors, such as ethical, societal and political issues, and other value judgements may also inform the MOH MTAC's funding considerations. These criteria are not assigned weights, as the relative importance of each criterion is specific to the individual medical technology under evaluation.

Table 4. MOH Medical Technology Advisory Committee decision-making framework

Criteria	Factors considered	Judgement will also take account of:
Clinical need of patients and nature of the condition	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.	• The nature and quality of the evidence, and expert views from clinicians, patients and carers on the lived experiences with the condition and the technology • The nature and quality of the evidence and the views expressed by clinical experts on the experiences of patients with the condition and those who have used the technology • Uncertainty generated by the evidence and differences between the published evidence and that relating to effectiveness in clinical practice
Overall benefit of technology	Potential of the proposed technology to prevent disease or produce beneficial changes for patients over alternatives, in terms of better safety and	

	effectiveness, and/or better efficiencies for the system.	• The possible differential benefits or adverse outcomes in different groups of patients • The balance of clinical benefits and risks associated with the technology • The position of the technology in the overall pathway of care and the alternative interventions that are established in clinical practice
Cost-effectiveness (value for money)	The potential of technology to be cost-effective or cost-saving (after VBP, where applicable)	• Robustness of costing information • Key drivers of cost-effectiveness • Uncertainties around and plausibility of assumptions and inputs in the model • Any specific groups of people for whom the technology is particularly cost effective • Any identified potentially significant and substantial health-related benefits that were not included in the economic model • Existing or proposed value-based pricing (VBP) arrangements
Budget impact	The net annual incremental cost to the MOH related to the start-up and recurrent costs to fund the technology for the intended indication(s).	
Organisational feasibility	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).	• Any variation in existing technology adoption or readiness of adoption across various public healthcare institutions. This can include different versions of the medical technology under evaluation.
Additional considerations	Any ethical, social or other issues related to the adoption of the technology.	

The MOH MTAC has the discretion to take account of the full range of clinical and economic evidence available, including RCTs, non-randomised studies and qualitative evidence related to the experiences of local healthcare professionals and patients who have used the medical technology or are familiar with the condition under evaluation.

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

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 clinical experts provide the basis for the estimates.

Overall benefit of technology

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

Since medical technologies can 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 there is no potential compromise to patient outcomes.

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. These considerations are based on ACE's findings from their review of the economic literature and/or an in-house economic model, if available.

The MOH MTAC does not use a precise maximum acceptable ICER (i.e. an ICER threshold) to determine if a medical technology is cost effective. ICERs are not precise values and are associated with a degree of uncertainty. Therefore, the MOH MTAC considers sensitivity analyses, in addition to the base-case point estimate when determining if a technology represents good value for money.

Budget impact

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

When assessing the annual cost of the technology to the healthcare system, the MOH MTAC is not restricted to making recommendations below a certain budget impact threshold; however, technologies with a large budget impact will be subject to additional scrutiny and the MOH may take longer to approve funding.

Organisational feasibility

Apart from economic feasibility (budget impact), the organisational feasibility of adopting a medical technology into the Singapore public healthcare system is also considered by MOH MTAC. To do so,

they assess how adopting the technology will impact currently available healthcare resources, and also consider the healthcare 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, funding 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, adoption is likely to be more difficult. Therefore, MOH MTAC is likely to be more cautious in recommending the use of such technologies, especially in circumstances where improved outcomes are not expected to be significant.

Other ethical, social and political considerations

Apart from the five core decision-making criteria mentioned above, MOH MTAC also considers potential ethical, societal and political issues important to the use of the technology under review and that may impact its use. Evidence from literature and experiences of clinical experts, patients and their families or caregivers can be used to examine the actual and potential impact of the medical technology.

Based on the available evidence, the MOH MTAC recommends to MOH whether a medical technology should receive funding, through inclusion on the MOH ISL or via another funding mechanism.

13. Guidance and funding implementation

13.1. Drafting ACE guidance

Following the MOH MTAC meeting, the ACE technical team may draft a Technology Guidance for a topic that received positive or negative funding recommendation. The purpose of this document is to outline:

- MOH MTAC's recommendations;
- Conditions/criteria of funding;
- Clinical and patient expert advice, clinical need and a brief summary of the key clinical and cost-effectiveness evidence that informed the Committee's deliberations and rationale for decision-making;
- Budget impact of funding the service based on the number of patients likely to benefit from the technology; and
- Any organisational issues which may impact implementation of the service.

Guidance documents are published on the ACE website when funding decisions are implemented. A plain English summary (PES) is also produced for patients and the public and uses non-technical language to explain MOH MTAC's recommendations for wearable and home-based medical devices.

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

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

The annual budget impact to the government, for funding the medical technology under evaluation, is also presented as ranges:

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

13.2. Funding implementation

Funding implementation for recommended medical technologies typically occurs 6 to 9 months after each MOH MTAC meeting, once the agreement is signed by the company and financing is approved by MOH. To assist with the smooth adoption of the recommendations, ACE communicates funding decisions to public healthcare institutions after each MOH MTAC meeting. This gives them sufficient time to prepare for implementation, including making changes to facilities, workflows, care pathways, and procurement processes, if necessary. This may be followed by targeted engagements to prepare public healthcare institutions for the implementation of the funding and ensure that the correct funding is accorded to eligible patients.

The ACE technology adoption and implementation team is involved at the early stage of evaluation, to identify any barriers to adoption, 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 by

working directly with the public healthcare institutions and experienced clinical experts or experts expected to use the technology.

For funding decisions contingent on specific prices being agreed with the company through the VBP process, public healthcare institutions will be instructed to purchase the medical technology through the national public healthcare supply chain agency and adhere to the maximum selling price (cost price plus stipulated margin) that was recommended by MOH MTAC. This ensures that the savings generated from price reductions offered by the company are passed onto the patients, and that selling prices are consistent across public healthcare institutions.

13.3. Evaluation of implemented medical technology utilisation and/or outcomes

ACE conducts utilisation reviews and/or outcomes evaluations on selected medical technologies, to assess the impact of funding implementation on use, patient outcomes and healthcare cost. ACE assesses the utilisation rate before and after funding implementation (where feasible), to understand if the intended consequences have been achieved (e.g. whether reducing the affordability barrier through subsidy has resulted in a positive utilisation trend, or how the uptake compares with predicted use or against comparators/alternative technologies). In addition, ACE monitors if use of the medical technology aligns with the guidance recommendations.

Outcomes evaluations may also be conducted for medical technologies with anticipated high impact on patient outcomes and the healthcare system (where feasible), to assess whether the intended outcomes are achieved in the local setting. Where required, educational audits will be conducted to improve adherence to the guidance recommendations for identified institutions.

13.4. Review of guidance and funding 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 if any new evidence or cost information has become available since the original evaluation, and whether it is likely to have a material effect on the funding decision or guidance recommendations.

Where there is a considerable amount of new evidence or information, the topic may be scheduled in the ACE work plan for re-evaluation as a full or expedited topic. Following MOH MTAC's consideration of the new evidence, the existing guidance may remain the same, be revised, or be superseded with new guidance, depending on MOH MTAC's recommendations.

14. Company application for updating or removal of funded medical technologies

For medical technologies evaluated by ACE that have specific versions (e.g. brands, models) listed for subsidy, companies will have an opportunity to apply to update or remove existing versions for the company's own medical technology.

Based on the application, the appropriate evaluation pathway will be assessed by ACE. In general, if the proposed update and pricing are deemed reasonable, an accelerated pathway may be considered. In contrast, a comprehensive pathway applies if an in-depth review of comparative evidence on the product's safety, clinical- and cost-effectiveness is deemed necessary. Revision of prices, as part of the submission, will be subject to similar considerations as outlined in Section 12. ACE reserves the right to decline an application.

An evaluation by ACE via an accelerated pathway will take approximately 3 to 4 months and a comprehensive pathway will take approximately 18 months. The evaluation is then submitted to MOH MTAC for funding recommendation (more details for MUP in Addendum 1). Companies will be required to sign an agreement or a variation to the existing agreement, if recommended.

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16. Addendum 1: Evaluation methods and processes for implants under consideration for inclusion in the Ministry of Health (MOH) Implant Subsidy List (ISL)

16.1. Introduction

The MOH ISL is a national list of implants that have received positive subsidy recommendations from MOH MTAC. Implants listed on the ISL have been deemed to be clinically and cost effective. The ISL was implemented in December 2023 to apply enhanced subsidy to clinically and cost-effective implants for specific clinical indications.

Implants are a subset of medical technologies defined by the Health Products (Medical Devices) Regulations 2010 as any medical device 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.

16.2. Pre-requisite for subsidy consideration

Only implants registered with the Health Sciences Authority (HSA) will be eligible for subsidy consideration. Unregistered implants, including those accessed via special access routes (e.g. GN-26/27) or exempted from HSA registration, are not eligible for subsidy consideration. Subsidy consideration of implants will apply to indications that have been approved by HSA.

16.3. Architecture of the ISL

The ISL groups implants by their biomechanical actions, implant functions, and health outcomes. This classification system was developed through extensive consultations with clinicians in public healthcare institutions, referencing overseas implant classification systems, clinical evidence and pricing analyses. The five-tier architecture includes clinical function, clinical category, product category, product group, and product listings, as shown in Figure 4. ACE reserves the right to update the nomenclature of the classification system and classification of implants as required.

Reasonable prices and clinical criteria are applied at the product group level, while subsidies are applied at the individual product listings.

Prices determined to be reasonable for each product group are an internal price guide based on the respective local prices and overseas reimbursement prices. They are subject to review from time to

time. Overseas prices are from a basket of reference jurisdictions, including but not limited to Australia, Belgium, France, New Zealand, South Korea, and Taiwan.

The clinical criteria specify the population eligible for subsidy. Although the clinical criteria for many product groups usually reflect the HSA-registered indication(s), more restrictive clinical criteria may be developed in consultation with local clinical experts for selected product groups, taking into consideration the cost of technology, potential for misuse, and clinical and economic evidence. Patients using listed implants as per the clinical criteria will be eligible for subsidy.

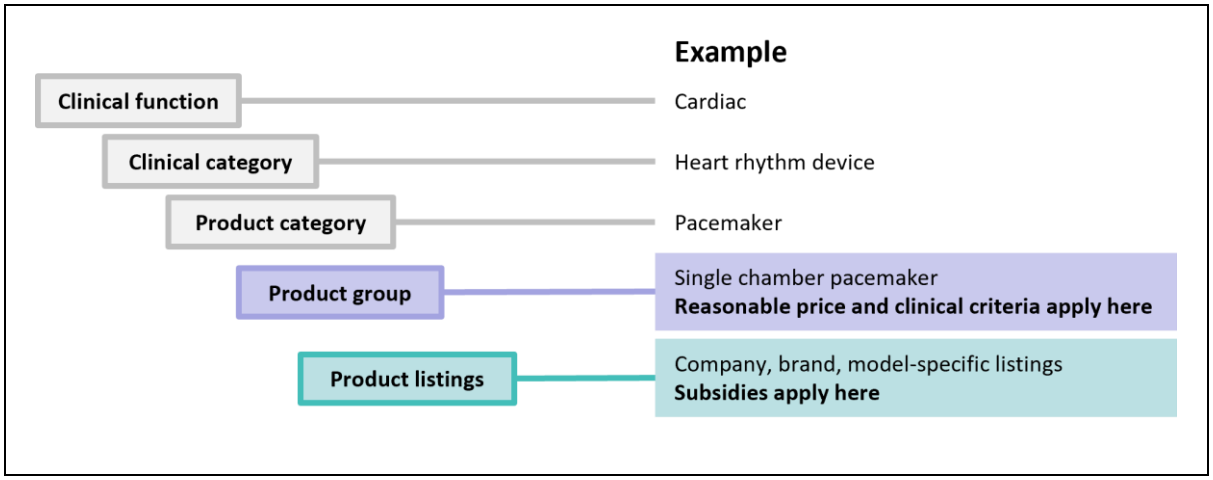


Figure 4: Five-tier classification system of the ISL

Clinical functions

Clinical functions are the primary classification based on anatomical areas and therapeutic specialties offered as clinical services in Singapore. Examples include cardiac, cardiothoracic, ophthalmic, or orthopaedics.

Clinical categories

For each clinical function, clinical categories are assigned based on the types of clinical interventions available for different conditions. For example, the cardiac clinical function includes clinical categories of heart rhythm device, heart rhythm monitoring and interventional cardiology.

Product categories

Within each clinical category, different product types are further classified into product categories that address a certain clinical condition. For example, under the heart rhythm device clinical category, product categories include pacemaker, implantable cardioverter defibrillators, cardiac resynchronisation therapy.

Product groups

Within each product category, different product groups are assigned based on similar biomechanical action, implant function and health 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 pacemaker is in a separate product group from single-chamber pacemaker.

16.4. Process for implants undergoing evaluation for inclusion on the ISL

Figure 5 shows the overall process for implants undergoing evaluation for inclusion during initial development of the ISL, and review and update of the ISL.

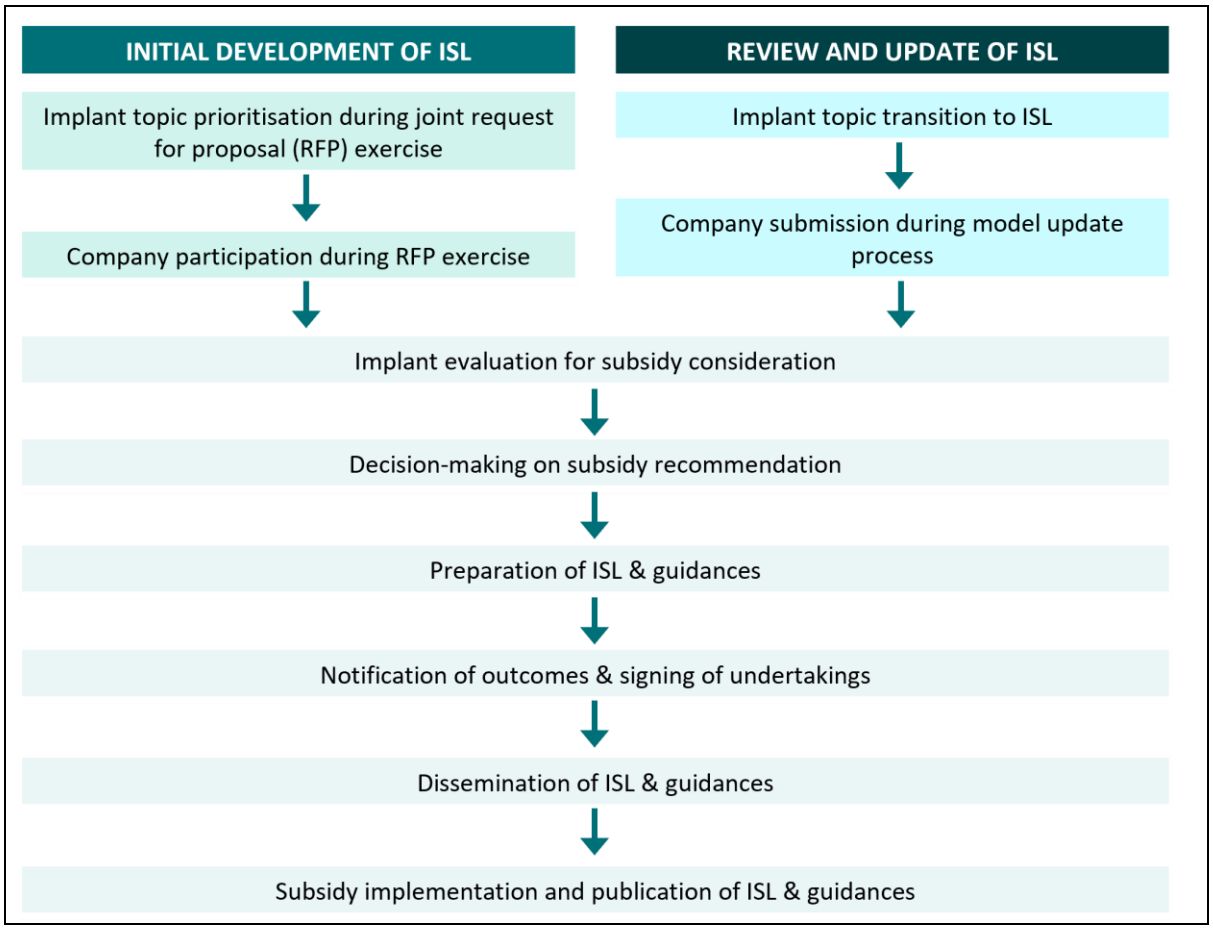


Figure 5: Overall process for implants undergoing evaluation for inclusion on the ISL

Abbreviations: ISL, Implant Subsidy List.

During initial development of the ISL, ACE works closely with the national public healthcare supply chain agency to identify and prioritise implant topics for inclusion on the ISL, based on potential budget impact, implant utilisation volume, and initial national contracting timelines and resources. For prioritised implant topics, ACE and the national public healthcare supply chain agency will conduct a joint request for proposal (RFP) exercise in line with the respective national contracting timelines. Companies that would like their relevant implant products to be considered for inclusion on the ISL should participate in the respective RFP exercise. Implant products submitted during the joint RFP exercise will be concurrently considered by the national public healthcare supply chain agency - for national procurement to supply public healthcare institutions - and by ACE for ISL subsidy consideration. Upon invitation by ACE, companies can submit evidence using the prescribed evidence form (see Annex 3). It is not mandatory for companies to submit evidence to ACE. The evaluation will

still be conducted by the ACE technical team and presented to the MOH MTAC to inform their funding recommendations, irrespective of company involvement.

For implant topics that have transited onto the ISL for subsidy implementation, the model update process (MUP) would apply. During this process, companies can apply to add, revise, or remove their implant products. More details are in Section 16.5 of this Addendum. From time to time, ACE may also initiate reviews for existing ISL items due to new evidence, or updates to reimbursement status or prices in ACE's reference jurisdictions.

Evaluation of implants for subsidy consideration

ACE's evaluation of implants for subsidy consideration includes but is not limited to, verifying and reclassifying (if necessary) product grouping of implants submitted by companies, applying HTA principles to assess their clinical- and cost-effectiveness, conducting pricing analyses, and clinician consultations. Other considerations such as supply issues or changes in local clinical practice may also be included if relevant. During the initial development of the ISL, prices for subsidy consideration are negotiated with companies through the joint RFP exercise.

Decision-making on subsidy recommendation

ACE's evaluation will be presented to MOH MTAC for subsidy recommendation of the implant. More information on MOH MTAC's decision-making criteria is in Section 12 of the main guide.

Preparation of the ISL and guidances

After MOH MTAC recommends implants for listing, MOH would include the recommended implants on the ISL. Concurrently, ACE develops relevant technology guidances for selected implants, as necessary.

Notification of Outcome and Establishment of Agreement

A Notification of Outcome (NOO) is sent to all companies that submitted proposals to advise them of MOH MTAC's recommendations, and to provide sufficient time for downstream stock supply and inventory management at the public healthcare institutions. Each company is only informed of the outcome for their product(s). Companies that receive a positive recommendation for their product(s) should not disseminate the information in the NOO in an indiscriminate manner until the date of funding implementation.

A Letter of Undertaking (LOU) is issued to companies of technologies with positive funding decisions. The LOU 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 company 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 product in line with specified clinical criteria.

Dissemination and implementation

The updated ISL and guidances are disseminated to public healthcare institutions ahead of subsidy implementation to allow adequate time to effect changes needed for implementation. Due to the volume of implants covered on the ISL, clinical, operational and financial staff at the public healthcare institutions may further curate their use list from the ISL and update their workflow and IT systems for each ISL update and implementation.

The updated ISL will be uploaded onto the MOH ISL website. The respective Technology Guidance will also be published on ACE's website.

16.5. Model Update Process (MUP) for ISL

The ISL is a dynamic list that is updated three times a year to incorporate new implant models and any updates to existing implant listings.

This section explains the general considerations and process when ACE receives company applications during a MUP cycle to add or revise ISL implants, remove ISL implants, and notify information relevant to the supply of ISL implants (Figure 6).

Implants eligible for MUP

Implant topics become eligible for MUP when they transit to the ISL and subsidy implementation has been effected. Within each topic, only implants assessed to be clinically- and cost-effective will be listed on the ISL. Implants will transit to the ISL progressively by implant topics.

Companies should only apply for ISL subsidy consideration for implants that have already obtained HSA registration.

Companies eligible for MUP

To ensure proper supply and implementation of subsidy in public healthcare institutions, implants listed on the ISL should be included in the respective national implant procurement contracts maintained by the national public healthcare supply chain agency. Companies that participate in the relevant joint RFP exercises and are identified as vendors in the prevailing national implant procurement contracts of interest would generally be eligible for MUP unless informed otherwise.

Companies that did not participate in the relevant RFP exercises or are not existing vendors in the relevant national implant procurement contract are not automatically eligible for MUP. In such cases, companies can write to ACE for advice on the next steps in ISL application by furnishing the relevant implant product information (including HSA registration status).

MUP application windows

The MUP application windows open three times a year for the first 15 days of April, August, and December. During these periods, companies can use the prescribed application form to apply for inclusion of new implants on the ISL, re-submission of price proposals for implants previously submitted for subsidy consideration, and/or revision of existing ISL implants.

Occasionally, ISL implants may also become obsolete, be withdrawn from the market, face safety or supply issues, or undergo novation due to changes in distributorship. To allow timely processing of such changes, companies can directly submit such information to ACE any time during the year at MOH_ACE_Medtech@moh.gov.sg.

ISL product grouping scheme and proposed price

In the MUP application form, companies are required to clearly indicate the product grouping scheme applicable to their submitted implant product and the proposed price. For each application, ACE will perform the necessary due diligence, which includes but is not limited to, confirming the classification of the implant, applying HTA principles to assess clinical and cost effectiveness, and conducting pricing analyses. Clinical inputs may also be sought as necessary. Companies are encouraged to include best prices to avoid rejection or delay, as ACE may not further negotiate on prices given the high volume of implants submitted in each MUP cycle.

Two pathways apply:

- **Accelerated pathway**: Where an existing ISL product grouping scheme applies and the proposed price is deemed to be reasonable, implant products will undergo the accelerated pathway. The estimated timeline from ISL MUP window to application outcome is approximately 3 to 4 months;
- **Comprehensive pathway:** Where a new product group is proposed, the implant would be subjected to an in-depth review of comparative evidence on the product's safety, clinical- and cost-effectiveness. Clinical experts will be consulted as needed. The review may take the form of an expedited or full evaluation as described in Section 3 of the main guide. The estimated timeline from ISL MUP window to application outcome is approximately 18 months.

To ensure expedient evaluations and processing of applications, companies are encouraged to provide clear information and adhere to the stipulated timelines and templates when submitting MUP application forms and/or corresponding with ACE. Failure to adhere to the instructions on the application forms can delay processing or result in rejection of the application for subsidy consideration.

Evidence submission by company

Companies proposing a new product group can submit evidence using the prescribed evidence form in the MUP application form. Companies are encouraged to adhere to the prescribed format and instructions.

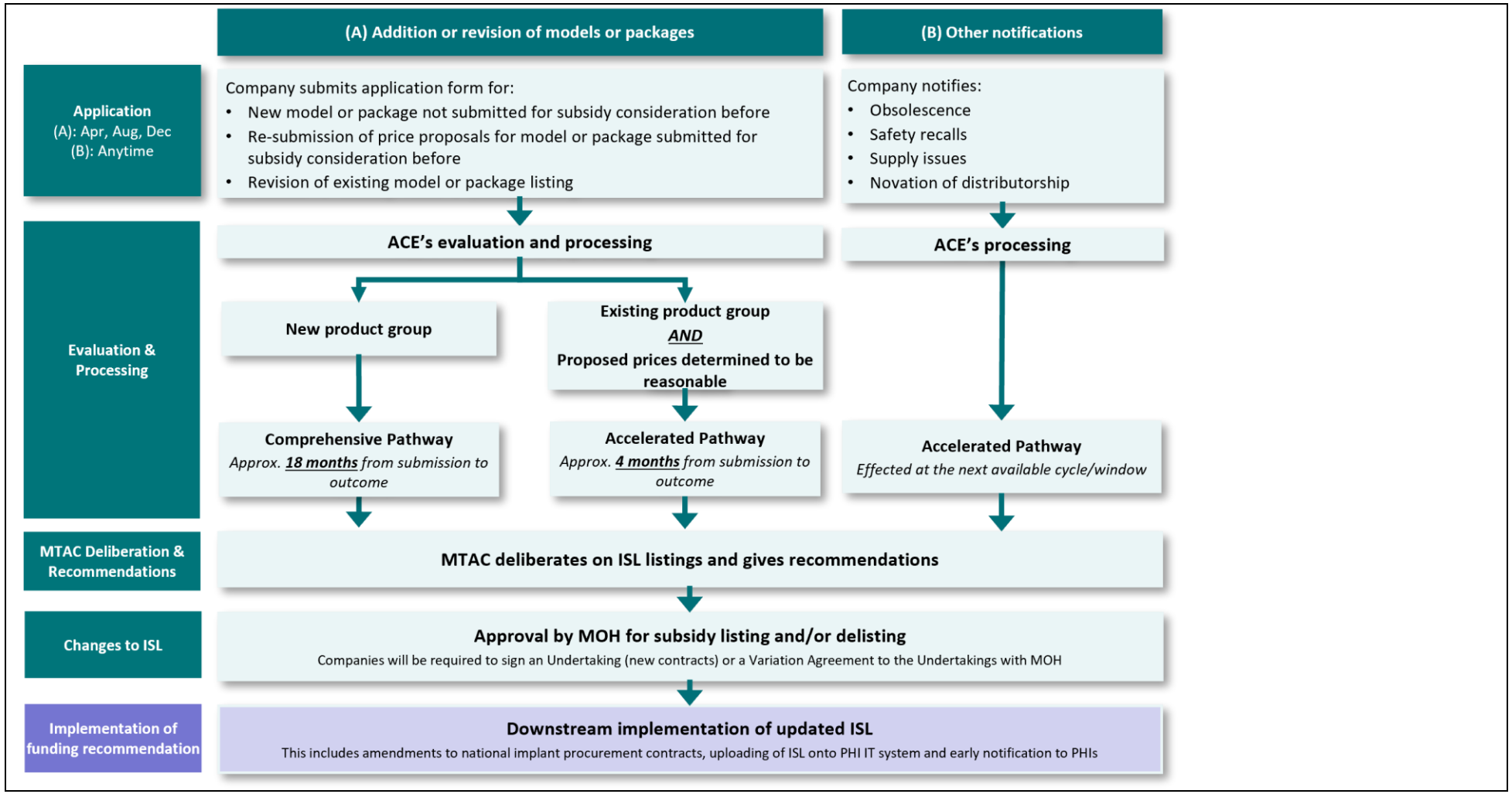


Figure 6: Inclusion process of the implants in the ISL
Abbreviations: ACE, Agency for Care Effectiveness; ISL, Implant Subsidy List; MOH, Ministry of Health; MTAC, Medical Technology Advisory Committee; PHI, public health institutions.

17. Addendum 2: Evaluation methods for investigative technologies

Investigative technologies may have 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 investigative technologies are used with concomitant treatments. Screening refers to the application of tests or procedures to detect disease early in asymptomatic people, and are not eligible for application by public healthcare institutions, patient organisations, and companies.

The evaluation of investigative technologies involves estimating patient outcomes that will result from using the technology, estimating the costs to the healthcare system (government, patient, insurer), and determining the cost-effectiveness of using the technology. Outcomes and costs typically include those arising from treatments required after the investigative technology has been used, and also cover the relevant section of the care pathway. When it is not obvious where in the care pathway the investigative technology is best placed, different options are assumed and evaluated.

Regardless of their use, evaluations of investigative technologies share similarities with evaluations of therapeutic technologies, as both are interventions aimed at improving patient quantity and quality of life. However, they also differ in several important ways. The most important difference is that the benefits of investigative technologies are typically indirect, as outcomes affecting the patient are from treatments rather than directly from the investigative procedures. Another important difference is that tests are frequently used in conjunction with other tests, and a composite series of tests is used in clinical decision-making. This makes the evaluation of investigative technologies more complex. Studies of investigative technologies rarely follow patients through treatment to final outcomes. In addition, the evaluation of investigative technologies usually requires information about their impact on clinical management decisions and their effects of treatment. If these are not known, analyses can be performed, but the validity of the results will be less certain. All these factors increase the uncertainty in the decision-making process for investigative technologies.

The accuracy of most investigative technologies is assessed by comparing the test with a reference standard at a particular point in time. This 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 period, to determine if the predicted events occur. Alternatively, linked evidence may be used, if available, in the absence of direct evidence.

Investigative technologies can affect health in several ways. The outcomes of an investigative technology are primarily information, which may affect treatment decisions and resultant outcomes. The test may also have direct side effects, for example, injury from invasive tests, reaction to contrast media, anxiety from the test results, or have direct benefits when the test provides treatment. A test result can also lead to follow-up tests, which can be invasive and have the potential for further side effects. Most benefits from investigative technologies are those arising from treating the identified disease. Unnecessary treatments 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 investigative technologies is studies that follow patients from testing, through treatment, to final outcomes ('end-to-end studies'). However, in most cases, end-to-end studies are rarely available for an investigative technology. A linked evidence approach is therefore taken which includes the following three components:

- Evidence on diagnostic accuracy;
- Evidence on impact by the investigative technology on management decisions; and
- Evidence on the effectiveness of treatment as a result of the investigative technology.

A comprehensive literature review using a pre-defined protocol for studies related to the three components mentioned above 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 investigative technologies is similar to treatment assessments. However, due to the differences highlighted previously, more extensive modelling is often required, including for initial testing, follow-up testing, treatment and monitoring. The same model is often used to estimate both clinical effectiveness (e.g. patient outcomes) and cost effectiveness.

18. Addendum 3: HTA evaluation framework for digital health technologies (DHTs)

18.1. Introduction

DHTs encompass a wide range of technologies that may promote, improve or support healthcare system functioning and delivery of health care. While there is currently no universal definition for DHT among international regulatory and HTA bodies, the HSA defines digital health as including telehealth and telemedicine, mobile health, wearable devices, health information technologies and personalised medicine.

The growing demand for healthcare innovations has seen DHTs proliferate rapidly into clinical practice, to cover diverse purposes including health-related (e.g. diagnostic, prognostic, therapeutic) and system-focused (e.g. data sharing, electronic medical records) functions. Unlike other medical technologies, DHTs often represent complex interventions with multiple interacting components across multiple levels of the healthcare system, with multiple outcomes of potential interest to decision makers and payers. The end users of DHTs can vary widely, from administrative and healthcare professionals to individual consumers.

Most DHTs have the primary goal of improving care while reducing costs. Their value claims include improving health outcomes, increasing the efficiency of health service delivery, and enhancing user experience and satisfaction compared to existing alternatives. However, despite these potential benefits, the digital nature, vast volume and rapid iteration pose challenges for regulatory bodies and HTA agencies worldwide when evaluating DHTs using existing frameworks. This has created the need for adapted frameworks to guide regulatory and reimbursement decisions for these technologies.

This HTA evaluation framework works to address these challenges by complementing existing regulatory and technical standards that apply to DHTs. It focuses on evaluating DHTs by assessing their value claims within the local healthcare system, compared to current standards of care. It also aims to balance the feasibility for DHT developers with the rigour needed to instil confidence in the DHT use within the local healthcare system.

Given the rapid evolution of DHTs, especially those with adaptive algorithms, this framework may be reviewed periodically, at appropriate time intervals, to ensure its continued relevance.

18.2. Classification of DHTs

Despite the lack of standardised reimbursement pathways for DHTs, common factors in determining the evidentiary requirements were observed across agencies with evaluation frameworks for assessing DHTs. These factors primarily relate to the DHT's intended purpose and its potential risk to end users and the healthcare system.

In terms of functions, DHTs are stratified into three risk-based tiers (Figure 7, adapted from the NICE's evidence standards framework (ESF). The NICE ESF has been designed such that most regulated medical devices and in vitro diagnostics (IVDs) fall within tier C. DHTs in tier C are intended for treating and diagnosing medical conditions, or guiding care choices, and hence pose a higher potential risk for end users than DHTs in tier A and tier B. DHTs in tier C are further subdivided into four groups based on their intended purpose, which align with the International Medical Device Regulators Forum (IMDRF) and HSA's risk classification framework for software as a medical device (SaMD). The four groups function to:

- Inform clinical management: Information provided by the DHT will not trigger an immediate or near-term action by clinical or care staff, but informs options for treating, diagnosing, preventing, or mitigating a disease or condition.
- Drive clinical management: Information provided by the DHT will be used to aid in treatment or diagnoses, to triage or identify early signs of a disease or condition, or to guide next diagnostics or next treatment interventions.
- Diagnose a condition: Information provided by the DHT will be used to take an immediate or near-term action to diagnose, screen or detect a disease or condition.
- Treat a condition: Information provided by the DHT will be used to take an immediate or near-term action to treat, prevent or mitigate by providing therapy to a patient.

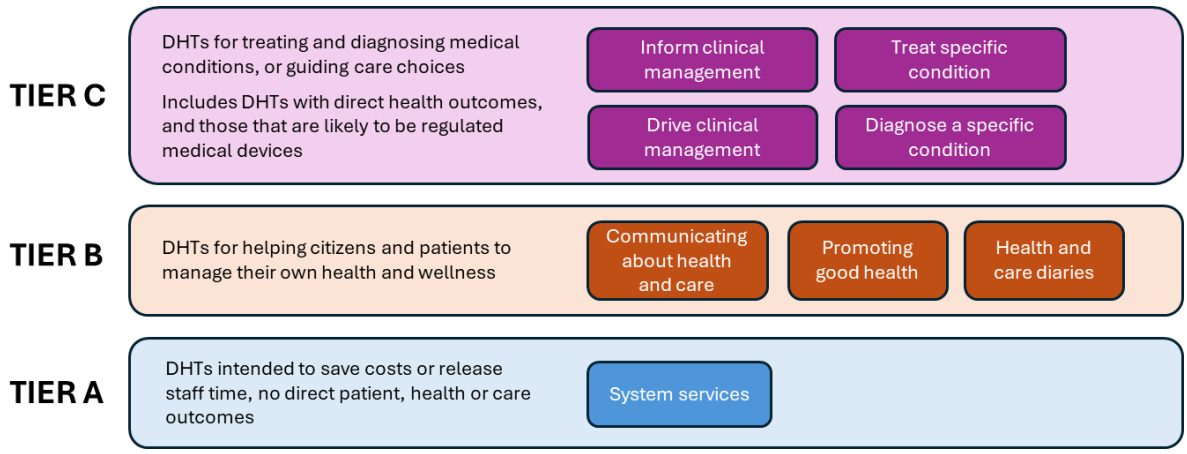


Figure 7: DHT classification by intended functions and risk tiers. Adapted from NICE ESF (2023)

For the purpose of framing HTA questions, DHTs can be classified into eight groups according to their primary health purpose (Figure 8), rather than by their functions, in the order of increasing clinical risk to an individual. This approach recognises the often-overlapping nature of DHT functions and provides value claims with a more meaningful basis for establishing evidence standards, especially for multi-purpose DHTs. Under this classification, tier C DHTs would generally include Groups 3 to 8.

DHT grouping	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8
Type of DHTs by health purpose	 Whole-of-system level for health administration	 General health and well-being	 General population-based screening	 Clinical data tracking (primarily consumer-facing)	 Predictive or prognostic tool	 Clinical monitoring (primarily healthcare professional-facing)	 Diagnosis	 Therapeutics
Description	Non-health system software, health system operational software, health system clinic software	Wearable personal fitness trackers, mobile apps purchased by consumers	Artificial intelligence for image reading for breast or lung cancer screening	DHTs that support patient self-management	DHTs that are used to estimate the future health trajectory of a person	DHTs that are used to measure progression or recurrence of disease	DHTs that are used to confirm, characterize, or measure the features of a specific health condition	DHTs that are intended to directly improve health outcomes

Figure 8: DHT classification by primary health purpose

18.3. Scope of the HTA evaluation framework for DHTs

The primary objectives of this HTA evaluation framework for DHTs are:

- To guide the evaluation approach to support MOH mainstream subsidy decisions; and
- To serve as a reference on the standards required for DHT evidence for PHIs, healthcare professionals (HCPs), consumers and the industry.

This framework primarily targets DHT evaluators, decision-makers, and DHT developers. At this stage, the scope encompasses DHTs which meet all the following criteria:

1. HSA-registered DHTs, primarily SaMDs, including mobile apps, standalone software or online tools. (Note: Class A DHTs, which are exempted from HSA registration, fall outside the scope of this framework);
2. DHTs with higher clinical risks, as illustrated by Groups 4 to 8 in Figure 8;
3. Patient-focused DHT solutions; **and**
4. DHTs with high cost per patient and/or high budget impact.

In line with international practice and ACE's evaluation scope of medical technology (Section 2.2), the following DHTs are typically outside the scope of this framework:

- Software in medical device (SiMD). These are software that is integral to, or embedded in, a medical device. SiMD is evaluated as part of the hardware medical device, where a conventional HTA approach applies.
- DHTs used purely for improving system efficiency, training, research or general population-based screening.

18.4. Topic selection for DHTs

Topic selection shortlists DHTs that align with the framework's objectives and MOH's health priorities for HTA evaluation.

The process will start with a call for expression of interest (EOI) from the PHIs, to identify DHT topics for which they intend to seek mainstream subsidy. ACE will assess the eligibility of identified topics and consider them against the prioritisation criteria listed in Table 5 to select those suitable for evaluation.

Table 5. Prioritisation criteria for DHT

Criteria	Considerations
Eligibility	The primary health purpose of the DHT is within the scope of the framework (refer to Section 18.3
Disease burden and unmet need	The DHT addresses: • A national health priority in Singapore • The top disease and economic burden in Singapore • A local clinical care gap
Patient benefits and clinical risks	Potential impact of the DHT on the target population: • The size of the target population • Degree of improved patient outcomes or experience • The potential risk of negative impacts (e.g. inferior safety or effectiveness) or "low-value care"
System benefits and feasibility of adoption	• Potential impact of the DHT on the system (e.g. infrastructure, workforce, care pathway) • Feasibility to implement the required system changes to realise the benefits of the DHT
Evidence availability	Availability of sufficient evidence (e.g. quantity, quality) to support decision making
Budget impact	• Availability of key costing information associated with the DHT and its comparator(s), including costs related to acquisition, setup, operations and maintenance • Whether the implementation of the DHT is likely to result in cost saving, cost neutrality or additional cost to MOH

Changes to a DHT previously assessed by HSA that are considered to have affected the safety and effectiveness of the DHT may trigger a reassessment by ACE. DHT developers will be required to notify ACE when such a change has occurred. Reassessment can also be triggered by requests from other key stakeholders (including MOH divisions), PHIs, notifications of serious adverse events, or consumer complaint reports to regulatory bodies.

18.5. Evaluation domains for DHTs

The HTA evaluation domains for DHTs can be categorised into (i) technology design, (ii) clinical evidence, (iii) budget impact analysis (BIA), (iv) economic evaluation, (v) performance

monitoring, and (vi) organisational feasibility and other considerations (Figure 9)Figure 9. The rationale of their inclusion is found in the subsequent sections below.

Of note, the clinical evidence section covers the clinical evidence standards required to demonstrate the benefit of a DHT. Additionally, the guiding questions in technology design, (performance monitoring, and organisational feasibility and other considerations, are important for evaluating whether the respective domains are adequately addressed. While not all questions will be relevant in every context, each should be carefully considered to ensure a comprehensive assessment.

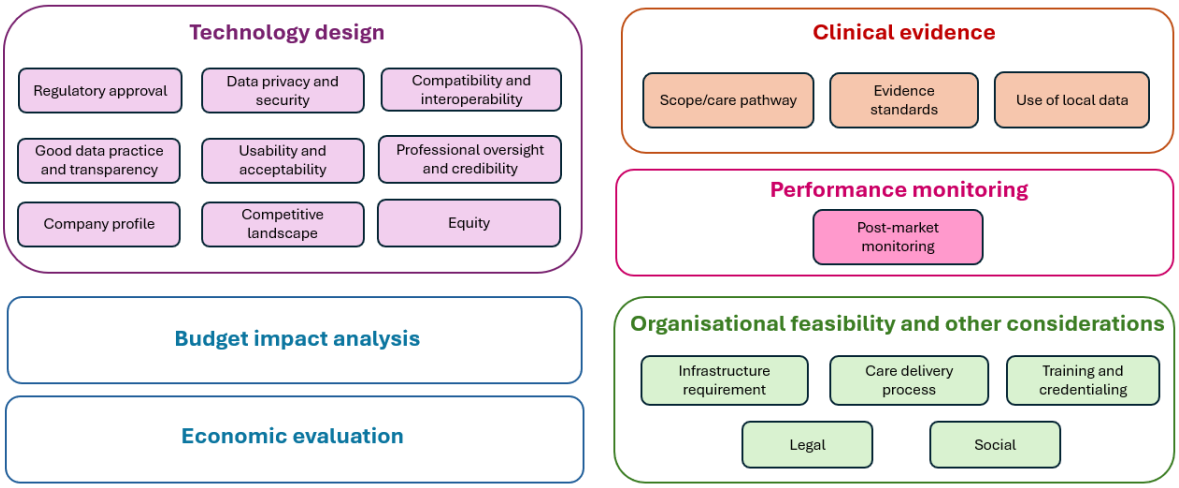


Figure 9: Overview of evaluation domains of DHTs

18.5.1. Technology design

It is important that DHTs have the appropriate technical standards for safety and reliability when used in the local context. HSA-registered DHTs have generally been assessed for various technical domains, including cybersecurity, compatibility and interoperability, and good data practice and transparency. DHTs should also meet prevailing good practices specified in other relevant MOH guidelines (e.g. MOH Artificial Intelligence in Healthcare Guidelines). Additionally, DHTs used in the MOH Holdings Entities must also comply with relevant MOH policies (e.g. HealthTech Instruction Manual).

Guiding questions to assess the technical domains of DHTs are summarised in

Table 6. It is anticipated that not all questions will apply to all DHTs. DHT developers/users should address all questions that are relevant to a particular DHT, with justification when a question is not relevant or cannot be addressed.

Table 6. Domains for technology design factors

Technology design factors	Guiding questions
Regulatory approval	• Has the DHT obtained approval from HSA?
Data privacy and security[1]	• Does the DHT comply with local data protection legislation and standards? • Do end users have control on how their personal health information is stored and shared? • What are the mechanisms in place to avoid unauthorised access to personal data and unauthorised use of health information? • Is there evidence that platform updates, operating system patches, service continuity, backup, and recovery are well managed? • Is the DHT regularly audited for actual data transmissions to third parties? • How does the developer intend to prevent, detect, respond and where possible, recover from security risks? • Are changes to privacy policies communicated to users in a timely way?
Compatibility and interoperability	• Is the DHT compatible with multiple relevant operating systems (e.g. iOS, Android, Windows, UNIX etc) and multiple operating platforms (e.g. smartphone, tablet, computer)? • Can the DHT be integrated with multiple IT systems (e.g. electronic health record) for care and service delivery, using relevant patient identifiers and standard terminologies?

Good data practice and transparency	• What datasets were used for training, validating and testing the DHT, and what are the relevant attributes of the datasets?
	  ○ Title, source and version of datasets
	  ○ Size of training, validation and testing datasets
	  ○ Labelling of data
	  ○ Use of any synthetic training, validation or testing data
	• Are the datasets representative of the intended target population for the DHT (e.g. demographics, clinically relevant subgroups)?
	• Has data quality been validated prior to developing and training the DHT?
	• Is there adequate disclosure of the algorithm characteristics to understand the association between inputs and outputs for clinical decision-making?
	• For the DHT with adaptive algorithms, what processes are in place to ensure the continuous learning process does not compromise the pre-specified safety and performance of the DHT?
	• What are the metrics against which the DHT performance is measured?
	• Have the end users been consulted to ensure that the explainability and limitations of the algorithms meet their expectations?

[1] Examples of relevant standards and guidelines are Personal Data Protection Act, Health Information Bill, Healthcare Cybersecurity Essential Guidelines and Cybersecurity Labelling Scheme.

Technology design factors	Guiding questions
	• If the DHT is enabled by artificial intelligence (AI), are the end users informed that they are interacting with an AI medical device?
Usability and acceptability	• What roles did the intended user groups (e.g. patient, healthcare professionals and other service users) play in the design, development and testing of the DHT? • How were user acceptability and experience appraised before and after deployment? • Does the DHT use an appropriate user interface, including level of complexity, means of information display, and language tailored to its intended user groups? • Does the DHT create additional burdens on the users, which may affect uptake or adherence?
Professional oversight and credibility	• What is the level of human intervention in the care and service delivery process associated with the DHT (e.g. human-in-the-loop)? • What is the user's susceptibility to "automation bias" (i.e. accepting the DHT output as the best course of action without seeking additional confirmation), and how might this be affected by time-critical applications? • What is the process in place to ensure the DHT's decision outputs align with current clinical practices (e.g. expert review and sign-off, locally recognised clinical guidelines, periodic review)? • What is the monitoring process in place to document and analyse the occasions where the DHT's decision outputs are overridden by healthcare professionals?
Company profile	• What is the company's history in terms of longevity and senior leadership? • How is the company currently funded (e.g. innovation grant, venture capital, other funding)? • How well is the company's track record for driving adoption of DHTs by health systems and securing funding from payers?
Competitive landscape	• What are the current and upcoming companies and products that are likely to compete in the same space? • What are the key differences in the value propositions between the company products and the competitor products?
Equity	• Does the DHT have limitations in terms of languages and network connectivity? • How does the DHT overcome access barriers for users, including those with poor digital literacy, disabilities, or lack of financial resources? • Are there actions taken in the design of DHT to mitigate against algorithmic bias that could lead to unequal impacts between different groups of people or service users?

18.5.2. Developing the scope

The ACE technical team will develop the scope of evaluation based on the PICO framework, and in consultation with local clinical experts and other stakeholders (e.g. industry) where necessary (Section 4). For DHTs, key areas of consideration during the scoping process are summarised below.

Intended use

The intended use of the DHT, as registered with HSA, should be clearly defined and include key information such as:

- Primary health purpose of the DHT (e.g. prognosis, diagnosis, therapeutics);
- Value claim of the DHT (e.g. improve health outcomes, increase efficiency of health service delivery);
- Setting of use (e.g. primary care, inpatient setting).

In addition, specific conditions or circumstances under which the DHT should not be used should be explicitly stated.

Target population

The target population of the DHT should be clearly defined according to the specific health condition as per its intended use registered with the HSA.

In addition, the size of the target population and the expected uptake of the DHT within the target population should be specified, taking into consideration potential variations arising from subgroups with different expected uptake rates due to digital literacy, internet connectivity and access to the DHT.

Proposed clinical pathway

Based on its intended use and target population, the details of the proposed care pathway incorporating the DHT should be provided, including the key elements below:

- The place of the DHT in current clinical pathway;
- Whether the DHT would replace or serve as an add-on to current standard of care;
- Whether the proposed pathway would change where care is delivered (e.g. specialist to primary care settings) or who delivers it (e.g. tasks shifting from doctors to nurses); and
- Whether there are any significant changes needed to effectively implement, operate and maintain the pathway using the DHT, particularly with regard to workforce.

18.5.3. Clinical evidence standards required to demonstrate benefits

As the landscape of DHTs continues to evolve, it is imperative to establish a robust, yet practical, evidence base to support their evaluation.

The level of evidence required to demonstrate the claimed benefits of DHTs is commensurate with their primary health purpose and clinical risk (Figure 8). For DHTs with multiple health purposes, the primary health purpose is determined based on the purpose associated with the highest clinical risk.

As a guide, Table 7 below lists the evidence standards for DHTs belonging to Groups 4 to 8 that are within the scope of the framework. While the evidence standards serve as a general guide, the evidence base should be proportional to the potential impact on patients, the nature of clinical decisions being supported, and the context in which the DHT is being used. Adherence to the preferred evidence standards is especially important for DHTs that address a serious or critical condition, as inaccurate information or ineffective use may result in significant negative consequences. As some DHTs primarily improve health system efficiency (e.g. improved throughput, reduced resource utilisation) without compromising patient outcomes, health system outcomes would be important endpoints to capture under these circumstances.

Table 7. Evidence standards based on DHT classification

Primary health purpose	Evidence standards[a]

DHTs for therapeutic purposes ***(Group 8 DHTs)***	• High-quality RCTs (preferred) or comparative real-world studies to demonstrate impact of the DHT on:
	  ○ Patient or clinically relevant outcomes
	  ○ Health system outcomes
	• The intervention should be compared to the comparator that is most likely to be replaced in the local clinical practice and is typically the current standard of care for the health condition being reviewed.

DHTs for diagnostic purposes ***(Group 7 DHTs)***	• Observational studies to demonstrate:
	  ○ Diagnostic-related outcomes (e.g. test accuracy against a valid reference standard, or concordance with standard practice)
	  ○ Impact of the DHT (e.g. time to diagnosis, resource utilisation)
	• Linked evidence preferred, demonstrating the linkage between test accuracy and subsequent patient or clinically relevant outcomes

DHTs for predictive or prognostic purposes ***(Group 5 DHTs)***	• Prospective observational (preferred) or retrospective follow-up studies to demonstrate the ability of the DHT to provide predictive or prognostic information over time
DHTs for clinical data tracking or clinical monitoring ***(Groups 4 or 6 DHTs)***	• Observational or real-world evidence to demonstrate the impact of the DHT on: ○ Changes in behavioural or relevant clinical or system outcomes • For DHTs which may directly impact therapeutic or diagnostic decisions, the respective evidence standards highlighted above may apply

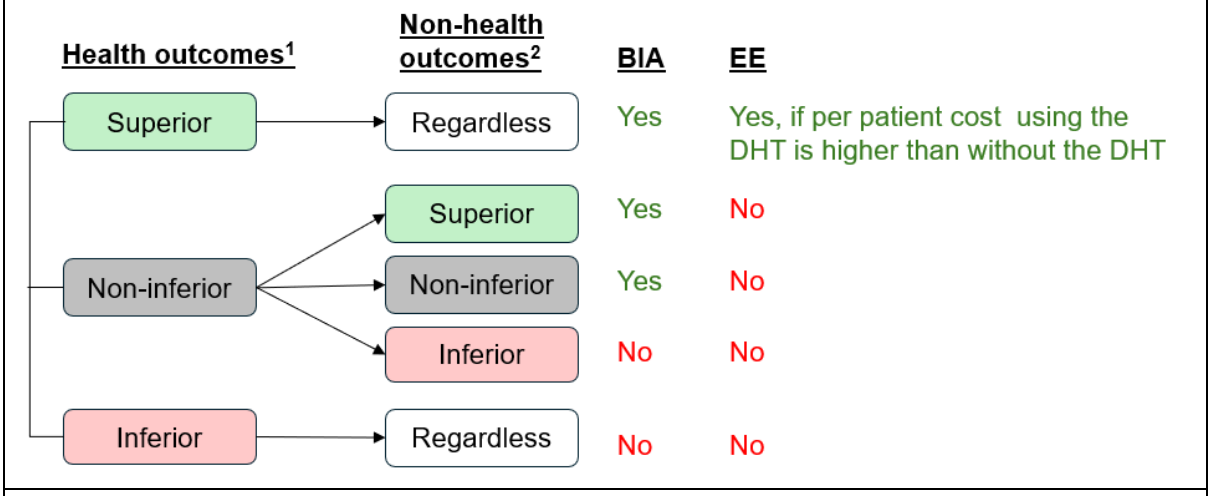
Note:

a. DHTs that address a serious or critical condition (where accurate and/or timely diagnosis or treatment is critical) carry a risk of significant negative consequences arising from inaccurate information or ineffective use. For such DHTs, adherence to the preferred evidence standards is especially important.

18.5.4. Budget impact analysis

Most DHTs are perceived to produce improved patient health outcomes and/or are related to superior non-health outcomes (e.g. health service efficiency), at lower costs than the

alternatives. Therefore, unlike many other medical technologies, their "value for money" assessment places a greater emphasis on budget impact analysis (BIA). Figure 10 illustrates when an economic evaluation may be useful to supplement BIA.



Abbreviations: BIA, budget impact analysis; DHT, digital health technology; EE, economic evaluation

Notes:

1. Health outcomes include patient or clinically relevant outcomes.
2. Non-health outcomes include mainly health system outcomes (e.g. change in workflow, care pathway, manpower allocation or resource utilisation).

Figure 10: When an economic evaluation is needed to supplement budget impact analysis

A BIA specific to the DHT's implementation setting should be conducted. The BIA should present the utilisation and net financial impact of implementing the DHT from the healthcare system perspective. A shorter time horizon (i.e. 1 to 3 years) is considered due to the evolving nature of DHTs, with scenario analysis considered over longer time horizons if deemed necessary.

The BIA should be based on the proposed care pathway using the DHT in local clinical practice and should reflect whether the DHT would replace or add to current care. The BIA should include details such as:

- size of target population and estimates of expected uptake, noting potential variations in uptake rates among different subgroups (e.g. level of digital literacy) or change over time;
- all direct costs associated with the DHT, including the cost of the technology;
- all direct costs associated with the comparator(s).

If there is a strong indication that DHT implementation will result in significant cost offsets over time, downstream costs may be included in the BIA. The timeframe for estimating downstream costs should be commensurate with the timing of the claimed offsets.

All data sources and assumptions for BIA inputs should be clearly stated and justified. Uncertainties in the BIA estimates should also be further explored using sensitivity and/or scenario analysis.

18.5.5. Economic evaluation

For DHTs with evidence of superior health outcomes at a higher average cost per patient than without the use of the DHT, an economic evaluation may be performed to supplement the BIA. Some contributing factors may include:

- The use of DHT on a large scale (e.g. national basis);
- Extensive change required within organisation due to the use of DHT (e.g. changes to IT system, staffing or care pathways); and/or
- High implementation cost.

For such DHTs, an economic evaluation in the form of a CEA, CUA or CCA should be performed. A CEA may be considered if the outcomes map cleanly to a single natural outcome measure (such as avoidance of a particular adverse event), where incremental cost-effectiveness can be expressed as the cost per event avoided. A CUA may be considered if the DHT directly improves health outcomes and the incremental health benefits lie mainly in survival or quality of life, producing additional quality-adjusted life years. A CCA may be considered if the overall benefits of a DHT are multi-dimensional and cannot be adequately captured by a single outcome measure. A CCA provides a breakdown of costs and effects in a disaggregated manner, allowing decision makers to choose the combination of costs and effects of DHTs that are most relevant to the local context, and apply their own weighting to the effects. More information on conducting a CCA for DHTs can be found in the guidance set out by the UK Office for Health Improvement and Disparities.

Sensitivity and scenario analyses should be conducted to explore parameter and structural uncertainties within the economic model. Further details on CEA are described in Section 6.

For DHTs with evidence of:

- Superior health outcomes that are cost-neutral or cost-saving;
- Non-inferior health outcomes; or
- Superior non-health outcomes (e.g. health service efficiency) that are conditional on non-inferior health outcomes;

and with a lower average cost per patient as compared to care without the use of the DHT, a targeted review of existing economic literature, together with the BIA will generally suffice. Further modelling is not required.

For DHTs demonstrating inferior health outcomes after review of clinical evidence, economic evaluation will not be conducted regardless of the value claim for non-health outcomes.

18.5.6. Performance monitoring

The DHT developer should provide a feasible plan to measure the DHT's performance and garner support from key stakeholders, including PHIs, HCPs and consumers, to ensure the

provision of high-quality data post-implementation. This is particularly important for DHTs in which performance is expected to change over time, such as those using adaptive algorithms or with subsequent updates. The monitoring plan should be agreed by key stakeholders and may include the domains in Table 8. Post-market data should be shared as and when required.

Table 8. Domains for post-market monitoring

Domain	Guiding questions
Post-market monitoring	What are the processes for measuring performance (e.g. including user feedback, complaints, and adverse events, real-world data, etc.) over time, to detect any impacts of planned changes or other factors that may impact performance?
	What are the processes to report changes in performance (e.g. when and to whom)?
	Are AI or machine learning algorithms expected to regularly retrain, reverse or change functionality?
	What are the sources of retraining data? How will the quality of the data be assessed?
	Are there plans for updating the DHT? If software, what type of change is it? ● Adaptive (e.g. maintaining software with dynamic environment) ● Perfective (e.g. recoding to improve performance) ● Corrective (e.g. correct problems) ● Preventive (e.g. correct latent faults before problems occur)
	Is there an independent overview process for reviewing changes in performance of the DHT?
	How could the post-market data be used to enable or disable new DHT functionalities (e.g. addition or removal of functionalities stated in the original submission, etc.)?

18.5.7. Organisational feasibility and other considerations

To ensure successful implementation of the DHTs and to fully realise the claimed benefits, the DHT developer should clearly describe the requirements for DHT deployment. These should include important contextual barriers and enablers for DHT uptake, which may cover:

- Infrastructure required for deploying the DHT e.g. data requirements, compatibility with the existing IT systems, scalability to show that the DHT can perform at the scale needed;
- Changes to the care pathway or process of care delivery; and
- Clinical endorsement and training to allow end users of the DHT to understand DHT's outputs and their interpretation to support uptake.

Other important considerations (e.g. legal or societal) related to the use of the DHT should also be highlighted. The relevant guiding questions are summarised in Table 9.

Table 9. Domains for organisational feasibility and other considerations

Domain	Guiding questions
Organisational feasibility	
Infrastructure requirement	What are the requirements for data such as specific formats, data standardisation (e.g. Digital Imaging and Communications in Medicine (DICOM)), completeness or quality?
	What are the key infrastructure (e.g. the current operating environment) and service-level changes to existing pathways and associated systems to implement, operate and maintain the new pathway?
	Is a data flow map for deployment of the DHT provided to allow efficient implementation?
	Is the process for load testing described? How does this relate to the expected uptake for the DHT (e.g. having servers that can scale to manage the expected number of service users)?
Care delivery process	Has the developer provided details on the proposed new care pathway(s) incorporating the DHT for the relevant population and setting? Please provide a flowchart clearly listing the steps of the new pathway(s).
	What changes are required to staff workflow, staff communication and interactions, electronic communications and information/reporting systems?
	If implementing the DHT removes the constraints of distance and shares patient data, how does this impact staff workflow and interactions between medical staff, patients, and their carers?
Training and credentialing	Is there adequate description on the outputs and their interpretation, benefits and limitations of the DHT to allow informed decision on incorporating the DHT in a person's care?
	What are the plans for training end users of the DHT to allow the benefits of the DHT to be realised in practice?
	Is accreditation required for professionals (i.e. medical practitioners, allied health workers, technicians) to prescribe and/or use the DHT?
Other considerations	

Domain	Guiding questions
Legal	Which party owns the data related to the DHT (i.e. patient, developer, third party, medical practitioner)?
	Which party is responsible for monitoring and reviewing the patient data entered into the DHT?
	How would insurance(s) (i.e. professional indemnity, life, health, income) for all stakeholders (i.e. patients, medical professionals, developers) be affected through use or recommendation of the DHT?
	How would professional registrations be affected through the use or recommendation of the DHT?
	Which party (e.g. manufacturer, medical practitioner who prescribed it) is responsible for the medical advice provided by the DHT?
Social	How would the use of the DHT affect the users' relationships with medical professionals, family, friends, and other relevant social relations?
	How would the DHT impact patient autonomy?
	Does the DHT address a health inequality in the Singapore healthcare system, or improve access to care among vulnerable populations?

19. Annex 1: Prioritisation criteria

Checklist for prioritisation of medical technologies

Note: The prioritisation criteria and checklist format in this annex may be revised from time to time. Users should verify they are using the most current version. Please check with the MTAC Secretariat [MOH_MTAC_Secretariat@moh.gov.sg] for the latest version.

Name of the technology	Manufacturer	Medical device class	Registration number	Registration date	HSA-registered indication

Proposed indication	
Purpose of use (for investigative technologies only)	

Population	
Intervention	
Comparator	

Elimination criteria		
Registration status of the technology for the indication(s) requested	If required, has the proposed medical technology been registered with relevant regulatory bodies (e.g. HSA) for the indications requested?	**No** (stop the checklist) **Yes** (proceed to the following)
Recently evaluated by ACE (e.g. last two years)	Is the topic identical or similar to a topic recently evaluated by ACE with no material change in evidence or local clinical management?	**No** (proceed with the following) **Yes** (stop the checklist)
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?	**No** (stop the checklist) **Yes** (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	Need score
NEED		
1. **Disease burden and unmet clinical need**		
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 proposed medical technology. This is often a *subgroup* of the affected population with greater clinical benefit from the proposed medical technology.	0 = Unknown 1 = <100 people 2 = 101 - 1,000 people 3 = 1,001 - 5,000 people 4 = 5,001 - 10,000 people 5 = >10,000 people Score =
Disease severity		0 = Unknown

Prioritisation criteria	Details	Need score
	Severity of the disease treated with the proposed medical technology with respect to mortality, morbidity, disability, function, impact on quality of life, etc.	1-2 = Low combined mortality, morbidity and/or quality of life 3-4 = Moderate combined mortality, morbidity and/or quality of life 5 = High combined mortality, morbidity and/or quality of life Score =
Unmet needs	Are there any alternative technologies currently in use for the condition? If so, are there major limitations with the current technologies?	0 = Unknown/no clinical needs 1 = Low clinical needs 2-3 = Moderate clinical needs 4-5 = Many and serious unmet needs Score =
2. Claimed benefits (based on literature scan)		
(Comparative) Safety	Potential of the proposed medical technology to produce a reduction in intervention-related adverse effects (consider their clinical significance) compared to alternatives.	-2 = Additional significant harms -1 = Additional mild to moderate harms 0 = Unknown/no reduced harm 1 = Minimally reduced harms 2-3 = Moderately reduced harms 4-5 = Significantly reduced harm Score =
(Comparative) Clinical benefits for patients	Potential of the proposed medical 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.	-2 = Significantly reduced benefit -1 = Mild to moderate reduced benefit 0 = Unknown/no additional benefit 1 = Small additional benefit 2-3 = Moderate additional benefit 4-5 = Significant additional benefit Score =
Cost-effectiveness (from published literature)	Dominance or incremental cost-effectiveness of the proposed medical technology compared to alternatives.	-2 = Mostly favouring comparator(s) -1 = Some favouring comparator(s) 0 = Mixed with no clear direction, or unknown 1 = Some favouring intervention 2 = Mostly favouring intervention Score =
(Comparative) Healthcare system benefits	Potential of the proposed medical technology to reduce resource use, e.g. to facilitate outpatient treatment, or to require fewer staff, or to reduce hospital stay.	-2 = Significantly reduced system benefit -1 = Mild to moderate reduced system benefit 0 = Unknown/no system benefit 1 = Small system benefit 2-3 = Moderate system benefit 4-5 = Significant system benefit Score =

Prioritisation criteria	Details	Need score
3. Organisational consideration		
Organisational feasibility	The potential impact on changes in the organisation of care, workforce, facility, and training/credentialing requirement when adopting the proposed medical technology.	0 = Unknown 1 = Substantial impact (with many system interruptions) 2-3 = Moderate impact 4 = Small impact 5 = No impact (minimal system interruptions)
		Score =
4. Overseas reimbursement/recommendation status		
Reimbursement status in reference countries (see attachment 1)	Whether the proposed medical technology has been recommended for reimbursement in ACE reference countries/ regions	-1 = Negative recommendation 0 = No recommendation / conflicting recommendation 1 = Positive recommendation
		Score =
		Total need score =
POTENTIAL BUDGET IMPACT		
Direct cost of the technology	Costs related to set-up the service offering the proposed medical technology (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.	
ADDITIONAL CONSIDERATIONS		
Impact of the HTA	Indicate whether a recommendation based on the HTA is likely to influence funding decision, taking into account other factors not limited to ethical, political or policy considerations.	
Medical service provision	Has Health Regulatory Group (e.g. RPL, RCE) and/or Health Services Group (e.g. HSD) within MOH given approval for the service to be provided in the PHIs?	
Additional clinician input, if needed (typically for topics from horizon scanning efforts)	Consult with at least one clinical expert and indicate the following as needed: • Is there a clinical need (e.g. gap in local patient care, current technology)? • Would this proposed medical technology meet this need or fill the gap? • Which clinical specialty is likely to use this proposed medical technology? • Are PHIs currently using this? If not, is this being procured for future use? When is the estimated start date of use? • (Optional) Cost of proposed medical technology, if available.	

Attachment 1: Recommendation/Conclusion/Reimbursement status of proposed medical technology in reference agencies

CADTH	HQO	MSAC	NICE

Attachment 2: Summary table of studies identified during scoping search

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

20. Annex 2: 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. alternate allocation 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: ▪ Non-randomised experimental trial ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised experimental trial ▪ Cohort study ▪ Case-control study

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening intervention
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single-arm studies ▪ Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single-arm studies
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

21. Annex 3: Company evidence submission template to support evaluation by ACE

COMPANY EVIDENCE SUBMISSION FOR SUBSIDY CONSIDERATION

Instructions for submission

This is the template for submission of evidence to the Agency for Care Effectiveness (ACE). The evidence provided in this submission will be taken into consideration by the ACE technical team if the submitted evidence follows the prescribed format and instructions in this form, and may be presented to the MOH Medical Technology Advisory Committee (MTAC) to inform the subsidy decision.

Companies should endeavour to only submit good quality, ideally comparative evidence with appropriate comparators. Companies should carefully consider the evidence they wish to submit and are strongly advised against a data dump to avoid any protraction or delay in the evaluation of their product(s). Submissions that do not follow the prescribed format or instructions in the respective sections can be excluded from consideration.

MOH and MOH MTAC are not obligated to accept any evidence submitted by companies in its subsidy decisions.

SECTION A - APPLICANT INFORMATION

Name of company:	
Name of product manufacturer (if different from applicant company):	
Point of contact:	
Designation:	
Contact number:	
Email address:	
Date of submission:	

PLEASE INDICATE SUBMISSION CLASSIFICATION	
Please tick (✓) one of the following on confidentiality of submitted information:	
This submission contains **NO** information provided in confidence.	
This submission contains **SOME** confidential information clearly marked as **CONFIDENTIAL**.	

1. Clinical need

<State clearly the indication(s) applied for consideration. Define the proposed population and any relevant sub-populations. Please estimate the number of patients who would benefit from this product. Describe the expected place of the proposed product in the local treatment pathway for the indication(s) applied. Explain how the proposed product may change the existing pathway if it is subsidised. For a proposed product with multiple indications applied for consideration, present the pathways separately as necessary.>

2. Summary of clinical effectiveness and safety evidence	
Fields with an asterisk (*) are compulsory. Please do not exceed 2,000 words (excluding references) for this section. Please provide the references (including relevant PDFs) and word count appropriately.	
Comparator*	<By default, all applications must identify at least one comparator unless there a strong basis for not doing so. This may be a product or the current treatment or therapy that is most likely to be replaced by the product in the application.>
Summary of clinical effectiveness and safety evidence*	<Provide a brief overview of the key trials which demonstrate the clinical effectiveness of the model for the relevant HSA-registered indication for this submission. Include a summary of any adverse reactions and safety evidence.> <A brief summary of key results from non-randomised comparative evidence sources (including real world data), registry data that provide additional evidence to supplement randomised trials can be included. Evidence from animal studies or cadaveric studies are out of scope.> <If there is a total of more than 10 studies identified for clinical effectiveness and safety per product group, please summarise and submit the top 10 studies with best quality and most appropriate study design. Preference should be given to good quality, comparative evidence that clearly demonstrates superiority in relevant patient outcomes. If non-comparative evidence is included, please distinguish them clearly in a separate paragraph in the summary write-up.> <Where possible, please distinguish studies containing the product(s) under submission from other studies of mixed or other brands >
Summary of cost-effectiveness evidence (including costs)*	<ACE prefers cost-effectiveness evidence expressed in incremental cost-effectiveness ratios using cost per quality-adjusted life year gained unless there are compelling arguments to use another outcome variable. Please provide details of measurable evidence of cost savings (due to improved patient outcomes, e.g. reduction in hospital stay) to the Singapore public healthcare system achieved through the use of the model. Where applicable, please include the estimated charge of the procedures involved in the use of product(s).>
Details of any ongoing studies	<Provide details of all ongoing studies from which additional clinical effectiveness evidence is likely to be available in the next 12 months for the indication being evaluated. Details include estimated completion date, estimated publication date and preliminary findings from these ongoing studies.>

2. Summary of clinical effectiveness and safety evidence	
Fields with an asterisk (*) are compulsory. Please do not exceed 2,000 words (excluding references) for this section. Please provide the references (including relevant PDFs) and word count appropriately.	
Concluding remarks (if any)	<The submitting party can include brief concluding remarks at the end of the evidence submission.>

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

Medical Technology Evaluation Team
Agency for Care Effectiveness
Email: ACE_HTA@moh.gov.sg