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Themed Section: Drug Policies in Asia

Health Technology Assessment and Its Use in Drug Policies: Singapore

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ABSTRACT

Introduction: Singapore has a robust health care system that is well known for delivering good health outcomes. In the public health care sector, subsidies and financial assistance are provided for drugs listed on the Standard Drug List and Medication Assistance Fund. Additional financing mechanisms are also available to provide further support for patients in need.

With new technologies entering the market at high costs, health technology assessment (HTA) is playing an increasingly important role to inform their relative value and determine how best to allocate finite health care resources to ensure long-term sustainability of the health care system. **Role of HTA:** National HTA efforts are currently focused on informing subsidy decision making and improving patient access to cost-effective drugs. The Agency for Care Effectiveness (ACE) was established in 2015 to support the Ministry of Health Drug Advisory Committee make evidence-based recommendations for the public funding of drugs. Standardized HTA methods and processes

have been developed in line with international best practice to ensure that ACE's evaluations are conducted in a consistent and robust manner. Since ACE's establishment, subsidies are now provided earlier within a drug's life cycle, and value-based pricing has led to more cost-effective prices being negotiated with companies to improve affordability for patients and the public health care system. **Conclusion:** To achieve greater impact, Singapore needs to expand its HTA capacity beyond subsidy decision making and drive appropriate care in a sustainable manner for future generations.

Keywords: decision making, drug, HTA, policy, reimbursement, Singapore, subsidy.

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Introduction

The Republic of Singapore is an island country with a total population of 5.6 million (approx. 4 million residents) and gross domestic product (GDP) per capita of S\$73,167 [1]. It is reported to be the healthiest country in Asia, with an average life expectancy of 83 years and an infant mortality rate of 2.4 deaths per 1,000 live births, which is among one of the lowest in the world [1]. Its health care system was ranked second in the world by the Bloomberg Healthcare Efficiency Index in 2016 [2]. It also ranks second globally for best health care outcomes [3], achieved at a total government health care spend of S\$8,610 million (2015), equivalent to 2% of GDP [4].

In Singapore, everyone has access to health care. Public health care services are situated across the island within three integrated clusters: National University Health System, National Healthcare Group, and Singapore Health Services. Each of the three clusters includes general hospitals, at least one community hospital, several polyclinics, and a medical school to offer a comprehensive range of

services, encompassing acute hospital care, primary care, and community care [5]. The public sector delivers 80% of acute care and 20% of primary care, with the rest delivered by private sector providers [6]. Patients can choose their providers at all levels of care.

The government's health care philosophy is built on five fundamental principles: (1) to nurture a healthy nation by promoting good health; (2) to promote personal responsibility for one's health and avoid over-reliance on state welfare or medical insurance; (3) to provide good and affordable basic medical services to all Singaporeans; (4) to rely on competition and market force to improve service and raise efficiency; (5) to intervene directly in the health care sector, when necessary, where the market fails to keep health care costs down [7].

In line with these principles, the health care financing system is built on a shared responsibility among individuals and families, insurers, and the government. The current system is a combination of government subsidies, compulsory individual health care savings accounts (Medisave), risk-pooling via both voluntary private and

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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<https://doi.org/10.1016/j.vhri.2018.03.007>

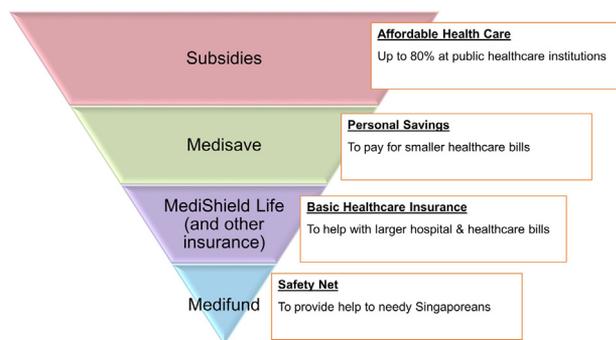


Fig. 1 – Health care financing in Singapore (“S+ 3Ms”).

mandatory government health insurance plans (MediShield Life), out-of-pocket contributions from patients, and a government endowment fund that acts as a safety net for the needy (Medifund) (Fig. 1) [8]. In the context of pharmaceuticals, government subsidies help ensure access to affordable and effective treatments for common medical conditions for subsidized (public) patients, while the national health insurance scheme (MediShield Life) reduces the cost burden of treatments for inpatients and selected expensive outpatient treatments, such as chemotherapy for cancer and immunosuppressants for transplant recipients.

Despite a successful health care system that is well known for its efficiency and quality, Singapore faces similar global fiscal challenges driven by an aging population, an increasing burden of chronic diseases, and growing demands from citizens for expanded health care services, leading to rising health care costs. At the same time, advancements in medical technology have seen new and more expensive treatments entering the market, in part, also contributing to the growing health care costs.

Between 2013 and 2016, drug spending in the public sector alone increased by 25% in Singapore from US\$296 million to US\$370 million. Overall, the pharmaceutical market in Singapore across both the public and private sectors is forecasted to increase to US \$1.2 billion in 2021 [9]. As the Singapore government evolves and transforms its health care system to meet the changing needs of its population, it is mindful of ensuring long-term financial sustainability. There is an impetus to move beyond quality to value for the patient, and to clearly demonstrate value in health care spending. To this end, health technology assessment (HTA) is a useful tool to inform the relative value of new health technologies, compared to existing standards of care, and in turn determine how best to allocate finite health care resources. This article focuses on the role of HTA to inform national drug subsidy decisions in Singapore.

Reimbursement and Pricing in Singapore

Marketing Authorization

Drugs are regulated by the Health Sciences Authority (HSA) to ensure that they meet specific efficacy, safety, and quality standards before they are marketed in Singapore. The process to review and grant marketing authorization of drugs takes approximately 9 months [10]. There are no price controls on drugs at the point of marketing authorization. Any patients who can afford to pay for a drug have access as soon as it is made commercially available by the company.

Reimbursement: Subsidies and Financial Assistance Schemes for Drugs

In the public health care sector, subsidies and financial assistance are provided to eligible patients for drugs included in the Standard Drug

List (SDL) and Medication Assistance Fund (MAF). The SDL was established in 1979 and modeled after the World Health Organization’s Model List of Essential Medicines, with adaptations to suit local disease profiles and practices. As of February 2018, a total of 568 drugs were included on the SDL, representing therapies essential for the management of common diseases affecting the majority of patients. Drugs on the SDL are subsidized at 50% for all Singapore citizens who are patients in a public health care institution. Patients from lower to middle income households can receive a higher subsidy of up to 75% [11]. The list is reviewed periodically to take into account changes in clinical practice and advances in medical science.

The MAF is a financial assistance scheme to help eligible Singaporeans pay for high-cost drugs that are not on the SDL but have been assessed to be clinically efficacious and cost effective. Drugs are listed on the MAF with specific clinical criteria to ensure appropriate use. Eligible patients can receive up to 75% assistance for MAF drugs if they are from lower to middle income households based on means testing [12]. As of February 2018, there were 47 drugs listed on the MAF.

Other government initiatives are also in place to supplement the existing subsidies for drugs, further improving affordability of treatments for patients. These include the Pioneer Generation package for patients aged 65 years and older through which seniors are eligible for additional drug subsidies [13]; Medisave, which can be used for outpatient treatment of chronic conditions such as diabetes and stroke, at public health care institutions and participating private general practitioners under the Community Health Assist Scheme (CHAS) [14]; and MediShield Life, which provides coverage for all Singaporeans for ward charges and medical costs associated with inpatient treatment, and for specific costly outpatient treatments such as dialysis and oncology drugs [15]. Finally, Medifund assistance is available for low-income Singaporeans who require further financial support to pay their medical bills [16].

Role of HTA in Drug Policies

Organizations Involved in HTA

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

HTA is not new to Singapore. In 1995, the Ministry of Health (MOH) began conducting HTAs, evaluating the benefits, risks, and clinical effectiveness of select health technologies to inform policy-making for the management and planning of health services in Singapore [17]. Subsequently, in 2001, the Pharmacoeconomic and Drug Utilisation Unit (PEDU) was set up to support the MOH Drug Advisory Committee (DAC) make evidence-based drug subsidy recommendations. To ensure long-term sustainability of the Singapore health care system, MOH established the Agency for Care Effectiveness (ACE) in August 2015, as the national HTA agency to consolidate and further expand HTA capacity to drive better decision making about clinically efficacious and cost-effective patient care [18]. The function of PEDU was consequently devolved to ACE, and new evaluation and decision-making frameworks were established to support drug subsidy deliberations. Table 1 summarizes the key characteristics of HTA to inform drug subsidy policy considerations in Singapore.

In addition to the HTA capacity within ACE and MOH, the integrated health care clusters also have health services research units with hospital-based HTA capacity [19,20]. Such units assist Pharmacy and Therapeutics (P&T) Committees within each hospital in incorporating HTA principles to manage drug formularies [21].

Table 1 – Key characteristics of national health technology assessment of drugs in Singapore.

Principle	Information requirement	Singapore
Purpose	Centralized decision-making body? Is HTA used to inform resource allocation decision?	Drug Advisory Committee (DAC) within Ministry of Health. The DAC appraises the clinical and economic evidence, and makes a recommendation to the MOH on whether or not the drug should be listed on the SDL or MAF.
Independence and transparency	Who conducts the HTA? Are details of the conclusions, procedures and practices, decisions made publicly available?	The ACE technical team conducts the evaluations. Drug companies are invited to submit supporting evidence (optional). Yes, drug guidances are published on ACE's website (www.ace-hta.gov.sg) and outline: <ul style="list-style-type: none"> • Conditions of subsidy • Clinical need and a summary of the clinical and cost-effectiveness evidence which informed the Committee's deliberations • Estimated annual cost of the technology and the number of patients likely to benefit from treatment.
Selecting topics	What are the selection priorities?	Topics are prioritized annually based on specific criteria including population size, disease severity, claimed therapeutic benefit over alternative treatments, budget impact and value that ACE could add in conducting a technology evaluation. Topics are more likely to be prioritized for evaluation if the drug represents a therapeutic gap that is expected to be of significant benefit to patients in terms of clinical efficacy or improved side-effect profile, and there is sufficient evidence to support an evaluation.
Methods for assessing costs and benefits	Are there published methods or guidance? Does the analysis include economic evaluation or cost-effectiveness?	Yes, ACE's <i>Drug Evaluation Methods and Process Guide</i> is published on ACE's website (version 1 published February 2018). Yes. In-house economic evaluations are conducted for full evaluations. Expedited evaluations rely on published economic evidence generalized to the local context where relevant.
Perspective	Is the full societal perspective considered in HTA to optimize societal resources?	No, ACE considers only the health care payer's perspective in economic evaluations (which covers QALYs and benefits gained by patients). Budget impact of treatments from the patient's perspective is included in evaluations to inform DAC's deliberations regarding affordability of treatments for patients.
Timing	How long does the assessment of a technology take?	3 to 9 months depending on the complexity of the topic and the number of drugs included (single vs. multiple technologies).
Audience	Who are the decision-makers?	Subsidy recommendations and clinical criteria governing use of drugs are made by the DAC.
Link between HTA and decision-making	Is there a clear distinction between the assessment and the decision? Are the results widely published?	Yes. HTA is conducted by ACE. Subsidy decisions and guidance recommendations are made by DAC. Yes, guidance documents containing the Committee's recommendations and rationale for their decisions are published on ACE's website. Select topics are also published in international journals.
	Are there published criteria for assessing effectiveness e.g. is there a base case?	Yes. ACE has a defined Reference Case which its follows for all full evaluations to ensure consistency, and improve comparability between technology evaluations. The reference case is outlined in ACE's <i>Drug Evaluation Methods and Process Guide</i> .
	Is there a threshold of cost-effectiveness?	No defined threshold. Cost-effectiveness is one of several factors which are considered to inform subsidy decisions. Upper and lower limits of base-case ICER point estimate (from sensitivity analyses) are considered when determining cost-effectiveness.

ACE, Agency for Care Effectiveness; DAC, Drug Advisory Committee; HTA, health technology assessment; ICER, cost-effectiveness ratio; MAF, Medication Assistance Fund; MOH, Ministry of Health; QALY, quality-adjusted life-year; SDL, Standard Drug List.

HTA to Inform Drug Subsidy

ACE has developed core processes and methods underpinning topic selection and evaluation of the clinical efficacy and cost-effectiveness of drugs, by drawing on methodologies from

overseas HTA agencies, and contextualizing them to the Singapore setting. Potential drug topics for technology evaluation are identified predominantly through annual applications by public health care professionals (such as clinicians or pharmacists). Each topic is prioritized for evaluation by considering a range

of factors including clinical need for the new treatment, its therapeutic benefit over current standard of care, disease severity, population size, and estimated budget impact to the government.

Once a topic is selected, an expedited or full evaluation is conducted, depending on the estimated budget impact and uncertainty around the clinical and cost parameters for each drug. Full evaluations are conducted for drugs that are expected to have high budget impact or high impact on population health owing to superior outcomes relative to current standards of care. They typically take 6 to 9 months to complete (Fig. 2), in line with a defined reference case, and include a systematic review of clinical evidence and the development of economic models to derive local cost-effectiveness and budget impact estimates. The majority of evaluations, however, follow the expedited process (Fig. 3), which usually takes 3 to 4 months, involving a review of published clinical and economic literature, including work completed by other HTA agencies, with considerations of generalizability to the local context.

All evaluations are conducted internally by the technical team in ACE; however, stakeholder involvement is an integral component throughout the evaluation process to capture and improve the real-world value and applicability of ACE's work. Local clinicians are consulted to ensure all evaluations reflect local clinical practice and are relevant to clinicians' and patients' needs. In addition, value-based pricing is conducted in parallel with drug evaluations to ensure that the price of drugs recommended for subsidy represents a cost-effective use of health care resources and is commensurate with the drugs' value in Singapore's context. Under this process, manufacturers are invited to submit key clinical information and their best cost prices for their drugs, which then inform ACE's clinical and cost-effectiveness analyses and budget impact assessments.

For complex topics, independent academic centers from overseas that have experience in conducting and appraising HTAs may also be consulted to review and critique ACE's work to strengthen the methodological rigor of the evaluation.

National drug subsidy recommendations are made by the MOH Drug Advisory Committee (DAC) and are informed by ACE's technical evaluations. The DAC comprises senior health care professionals and is responsible for ensuring that public funding of drugs is made in an evidence-based, equitable, efficient, and sustainable manner. Their recommendations are made in line with a specific decision-making framework that considers four core criteria on the basis of the available evidence: (1) clinical need of patients and nature of the condition; (2) clinical effectiveness and safety of the drug; (3) cost-effectiveness -i.e. the incremental benefit and cost of the technology compared to existing alternatives; and (iv) estimated annual cost of the drug and the number of patients likely to benefit from the technology. Specific factors and judgments that should be deliberated when considering each criterion are also described within the framework (Table 2). When determining the cost-effectiveness of a drug, the DAC does not use a maximum acceptable incremental cost-effectiveness ratio (ICER) threshold, as ICERs are not precise values and are associated with a degree of uncertainty. Instead, upper and lower limits of the base-case ICER (from sensitivity analyses) are considered when determining uncertainty surrounding the cost effectiveness point estimate, and whether a drug represents good value for money.

Although quantitative estimates from an evaluation may appear to provide objective evidence to inform optimal subsidy decisions, assumptions used in economic models are often based on individual value judgments or preferences. The deliberative process in committee meetings is therefore fundamental to provide the necessary flexibility in the process to discuss the appropriateness of value judgments that underpin the

evaluation. It also provides an opportunity for the DAC members to express their views and develop consensus decisions. In instances where discrepancies in opinion arise among committee members, the chair has the deciding vote.

Subsidy recommendations, the DAC's rationale for their decision, and a brief summary of the key clinical and economic evidence are documented in guidance and published on ACE's website. This serves to increase the level of transparency of decision making, and guide appropriate prescribing behaviors. The maximum selling price at which a drug is considered cost-effective is also communicated by MOH to all public health care institutions to facilitate harmonization of prices for patients. Guidance documents are considered for review when any new clinical evidence or cost information is published that is likely to have a material effect on the subsidy recommendations.

Impact of HTA

ACE's HTA work informs MOH's subsidy decisions and serves to target funding to cost-effective drugs to optimize health benefits within finite resources. Before ACE, subsidy decisions were largely informed by clinical efficacy and safety data. This was in part due to the fact that historically, drugs were typically considered for subsidy at least 5 years after marketing authorization in Singapore, often once the drug was off-patent (generic), to allow clinicians time to become familiar with the drug and justify the clinical need for its subsidy for patients. The lack of urgency for subsidy also reflected the relatively affordable cost of most treatments at that time. However, with rising drug costs and increasing pressure to adopt new technologies early to ensure faster access to innovations, ACE's drug evaluation processes and methods need to continually evolve to enable treatments to be considered for subsidy earlier in their life cycle and to improve affordability for patients.

The ability to subsidize drugs earlier is in part driven by new process steps in which better prices can now be achieved through value-based pricing (VBP) negotiations conducted with pharmaceutical companies during the HTA evaluation. In its first year, ACE's VBP process led to price reductions for patented drugs of up to 55% from existing cost prices (i.e., prices at which public health care institutions procure the drug). By enforcing maximum selling prices to patients for drugs with VBP arrangements, the lower prices translated into improved affordability for all public patients, including those not eligible for subsidy.

Over the next few years, a number of high-cost biologics will lose patent exclusivity worldwide, allowing market penetration of almost 50 biosimilars that are currently in development [22]. Increased competition among the biologics has the potential to deliver significant cost savings through increased uptake of the best value product. ACE's work will be pivotal to inform subsidy decisions for biosimilars, while efforts will be made to encourage appropriate treatment choices and raise clinicians' and patients' awareness, willingness, and receptiveness to use biosimilars.

As part of HTA implementation, it is mandatory that all public health care institutions make the drugs recommended by the DAC available for their patients. ACE is currently establishing tools to support clinicians in adopting guidance recommendations and advancing the use of cost-effective drugs in their practice. They include developing Appropriate Care Guides that provide evidence-based recommendations on care practices and pathways to guide specific areas of clinical practice, incorporating reminder "flags" in the IT clinical decision support system in each public health care institution, to influence practice at the point of prescription and alert prescribers of the existence of ACE guidance for particular treatments, and conducting continuing medical education activities for health care and industry professionals when relevant. Drug utilization reviews and audits

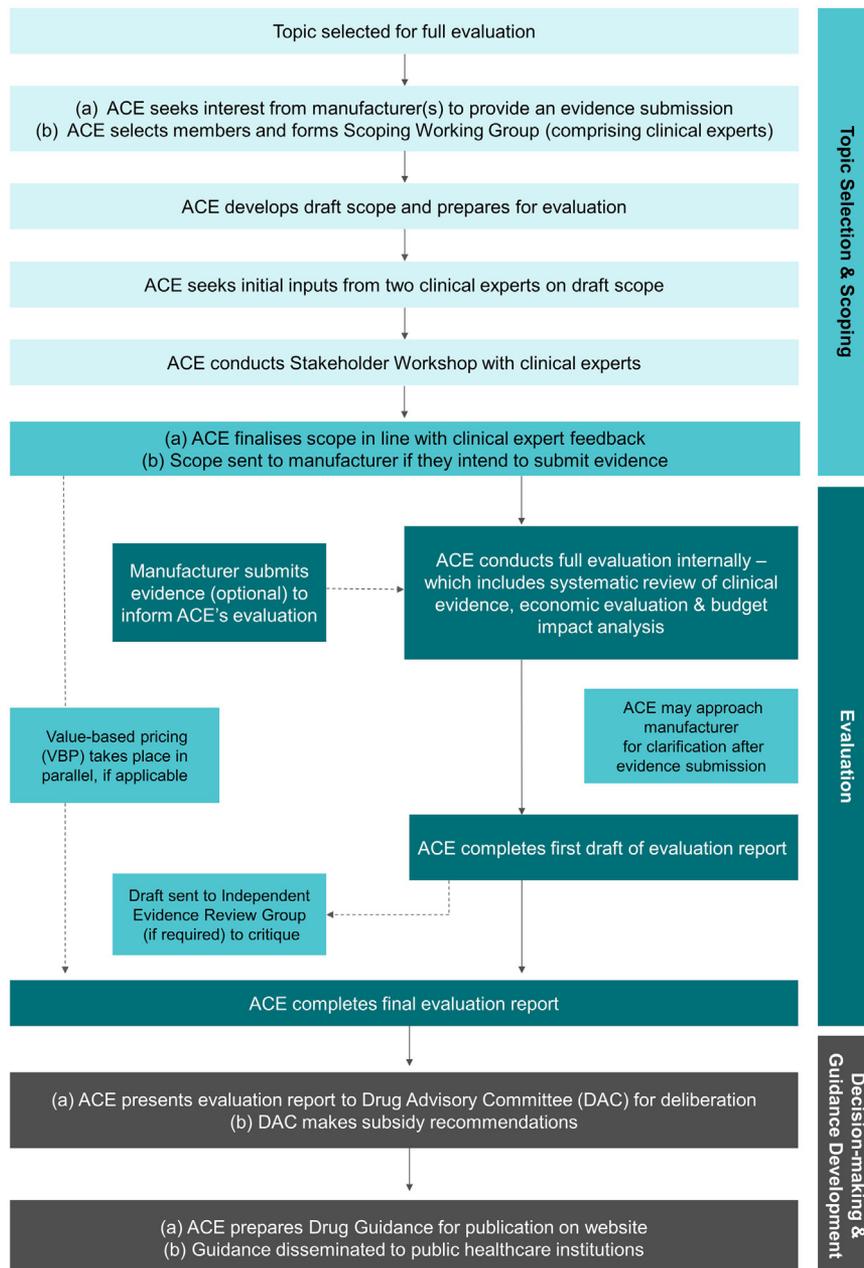


Fig. 2 – ACE's drug evaluation process for full evaluations.

to track changes in drug dispensing patterns and appropriate use are also being carried out by MOH, to streamline hospital formularies, drive appropriate drug utilization, and monitor the impact of ACE guidance on prescriber behavior.

Challenges

Advancement of Medical Technologies

The arrival of novel medical treatments such as immunotherapy [23] and gene therapy [24] has profoundly changed the clinical landscape and raised new challenges in HTA. As these treatments are used in targeted populations often defined by stringent eligibility criteria, it is usually difficult to determine where they fit in existing treatment algorithms, and hence their value

proposition can be uncertain. HTA methods will need to evolve continually to address these challenges and ensure that evaluations are relevant to decision makers and reflect local clinical practice and patient need. A shift toward incorporating real-world evidence into HTA to supplement clinical trial end points is likely, to improve the generalizability of trial outcomes to the local context and provide more assurance of longer-term health outcomes to payers, to justify the premium price tags and significant opportunity costs associated with subsidizing these novel therapies [25].

Local HTA Capacity and Capability Building

Conducting HTA requires specialized skills. In Singapore, there are currently few who are formally trained in HTA methods to robustly assess the clinical and cost-effectiveness of treatments.

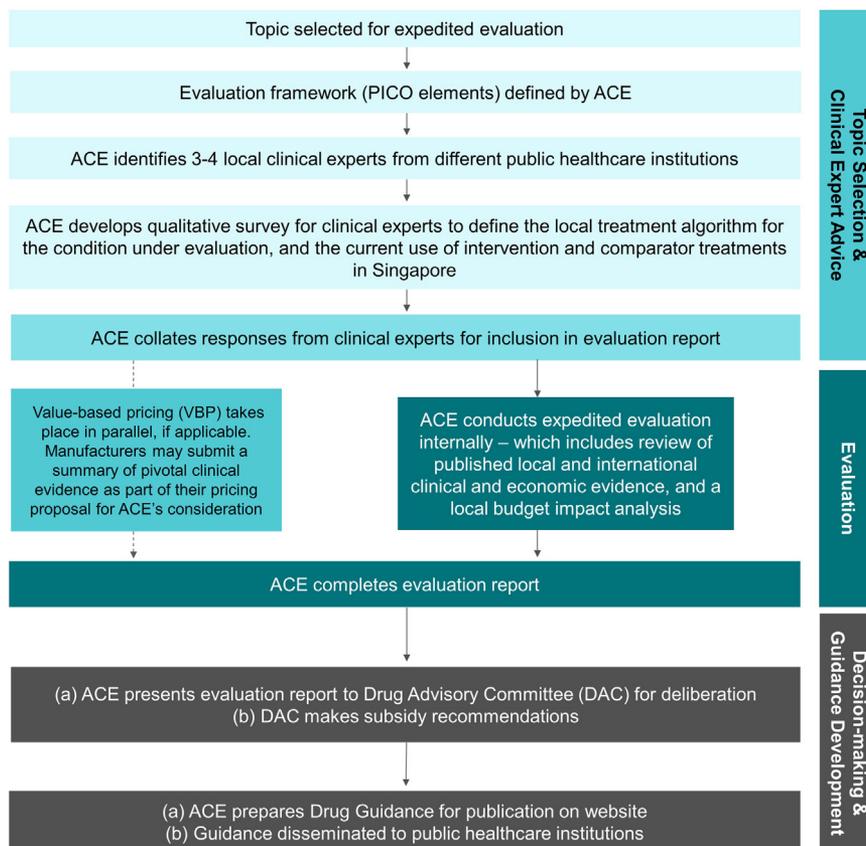


Fig. 3 – ACE’s drug evaluation process for expedited evaluations.

Table 2 – MOH Drug Advisory Committee decision-making framework.

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

To address this knowledge gap and build local capabilities, local universities are incorporating HTA methods into their curriculum to raise awareness and knowledge of HTA and evidence-based medicine among current and future health care professionals. In addition, overseas training of ACE staff and hospital HTA researchers in specific technical competencies such as network meta-analysis and advanced economic modeling methods has helped to strengthen local capabilities. Coupled with these efforts, ACE leverages on the knowledge and expertise of renowned HTA specialists from Australia, Canada, and the United Kingdom, through the appointment of an International Advisory Panel, who review Singapore's HTA processes and methods and ensure that they are aligned with international best practice. ACE is also a member of HTAsiaLink [26] and the International Network of Agencies for HTA (INATHA) [27], which foster collaborations and exchange of information among HTA agencies worldwide. Staff from ACE and hospitals' HTA groups also participate in regional and international HTA conferences, and publish their work in peer-reviewed journals to share their results and increase the visibility of Singapore's HTA capabilities. ACE also shares its HTA methods and processes on its website, and through targeted educational forums, to facilitate learning through exchange of experience.

Monitoring the Impact of HTA on Prescriber and Patient Behaviors

While HTA to inform evidence-based decision making in Singapore has achieved considerable progress, monitoring the impact of policy decisions resulting from ACE's evaluations and changes in prescribing behaviors of clinicians, is challenging and requires considerable efforts. Improvements are needed in the way data on local drug use and disease burdens are captured, supported by a centralized IT infrastructure system to aggregate and share information in a timely manner across the public sector. To truly see how HTA drives changes in practice, two key enablers are needed: (1) optimizing data analytics—conduct data linkages and analyses using various data sources such as prescribing data, national clinical audits and reports, and disease registries [28] and (2) driving behavioral changes through targeted educational efforts among physicians and patients. Comprehensive program evaluation capabilities to measure HTA impact and patient outcomes need to be established and are currently being considered as part of ACE's expanding remit.

Conclusion

National HTA efforts are currently focused on informing subsidy decision making and improving access to drugs of good value in the health care system. HTA will continue to play an important role, as the MOH strives to move beyond quality to value for the patient, to ensure that patients receive care, with the same, or better outcomes, more cost effectively. To achieve greater impact, Singapore needs to expand its HTA capacity beyond subsidy decision-making in the future and drive appropriate care more meaningfully and in a sustainable manner for future generations. To do this, there are ongoing efforts to further harmonise HTA methods and processes, improve data integration, increase awareness and understanding of HTA in the local clinical community, and measure the impact of guidance recommendations and other HTA products on shaping prescriber and patient behaviors.

Acknowledgments

The information described is a result of work supported by the Agency for Care Effectiveness. No funding was received.

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