

# HTAi Asia Policy Forum 2018 Background Paper

**Improving access to high-cost technologies in the Asia region**

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## Executive summary

The aim of the 2018 Asia Policy Forum is to try to understand what the term “high-cost technologies” means to countries in the Asia region and to explore the types, and experience to date, of mechanisms that are available to increase access to these technologies.

One of the greatest challenges facing policy-makers in the Asia region when moving towards universal health care is defining the right balance of health care technologies in benefit packages, whether they are pharmaceuticals, devices, diagnostics or procedures, in benefit packages. Although the financial demands on the health system are great, with the shift in the burden of disease to non-communicable disease and a large ageing population, investment in innovative high-cost healthcare technologies may, in the long-term, deliver a return-on-investment.

From the results of the surveys conducted, it is unsurprising that the meaning of the term “high-cost technology” differs markedly across the region given the diverse nature of the populations and economies. The challenges that payers face in accessing these technologies include a lack of good quality data, including real-world data, patient affordability and, ultimately, the budgetary impact of high-cost technologies. Managed entry schemes (MES) have been identified as a means of accessing these technologies either earlier in the regulatory timeline or at reduced costs to the system. Most of countries surveyed had, at some time, introduced a new health technology using an MES, primarily to allow early access to pharmaceuticals rather than devices or diagnostics. The most common reasons given by payers and industry for implementing an MES were that the technology would have significant budgetary impact, there was high clinical demand for the technology and that there was uncertainty around economic analysis or cost-effectiveness of technology. Most countries were interested in patient outcome data such as reductions in morbidity or mortality, in addition to data on reduced health system costs. Most industry active in the region had experience with financial-based schemes, most of which involved discounts or rebates, with few having experience with outcome-based or evidence generation schemes. Most of the alternative funding arrangements between industry and payers were put in place to increase access to pharmaceuticals, with only one device funded under an access with evidence agreement.

It is clear that alternative access schemes have an important role to play in the region, however, it is early days in the implementation of these schemes. The 2018 HTAi Asia Policy Forum (APF) aims to share the experience of both payers and industry across the region, in identifying mechanisms that allow early access to, whilst mitigating risk and reaping the benefits of, innovative technologies.

## Introduction

In 2017, the HTAi APF discussed universal health care (UHC) in the Asia region, and the potential role and importance of real-world evidence. From discussions in 2017, it was evident that there was a disconnect between data accessible by health departments and that accessible by industry.<sup>2</sup> All members attending the 2017 HTAi APF agreed that access to, and the sharing of data was of utmost importance.

The theme of the 2018 HTAi APF follows on from those discussions, and will discuss, with practical examples, the challenges and pitfalls of different post-regulatory mechanisms that may improve or enable access to high-cost technologies in the Asia region.<sup>a</sup>

Countries in the Asian region are diverse, including some of the world's least and most developed nations, with populations ranging in size from thousands to hundreds of millions.<sup>4</sup> This diversity is reflected not only in the political, administrative and economic systems of the region, but importantly, in healthcare systems that address the needs of over 4.2 billion people.<sup>5</sup> In 2015, healthcare expenditure in the region ranged from US\$32 per capita (2.6% of GDP<sup>b</sup>) in Bangladesh, to US\$3,733 per capita (10.9% of GDP) in Japan ([Appendix 1](#)).<sup>6</sup> On average, Asian economies spend just over US\$600 (4.5% of GDP) per person per year on health, with around 57 per cent of total health expenditure being on the provision of public health care.<sup>4</sup>

Health policy makers in the region grapple daily with balancing health budgets and reducing health inequalities whilst at the same time wanting to enable patients to access innovative healthcare technologies. Prioritisation of the move towards UHC is an integral part of getting this balance right, by managing the expectations of the population with the provision of essential health care. When companies develop a new pharmaceutical or device, the focus is on obtaining the evidence required to achieve regulatory clearance in order to bring the product to market. However, payers may require different types of evidence to determine if the innovation is clinically necessary and beneficial for patients in routine healthcare settings. Rapidly increasing health expenditure means that the decisions that need to be made on whether to add a new medicine or device to a healthcare package are not binary, and must consider not only the magnitude of the health benefit, but affordability and whether the technology represents a return on investment or value for money.<sup>7</sup> Similarly, industry faces the challenge of finding appropriate mechanisms to enable health systems in the region to access innovative, clinically beneficial devices and medicines at an affordable price. The shared commitment from all key stakeholders to improve the health of people in the region and to the principles of UHC, ensuring equitable access to health care for all patients, lays the foundation for regional collaboration in health, and to learn from the experiences of others, especially around the issue of access to high-cost technologies.

Technology has long been acknowledged as one of the key drivers of increasing health care costs through the development of new treatments medicines, devices, procedures and diagnostics. However, healthcare technologies can also deliver enormous benefits, not only to patients but to the healthcare system. With access to innovative healthcare, the patient journey is enhanced, with better treatments resulting in fewer side-effects, an improved quality of life and, ultimately, a longer life. For the payer, investment in new technologies may result in better patient outcomes, better patient flow through the healthcare system and reduced overall costs. However, of concern is the potential for lack of equity and unequal access to the benefits that innovative technologies may bring for patients in the public sector compared to those in the private sector.<sup>8</sup> It is envisaged that this inequity may increase in the absence of policy change with the development of high-cost technologies such as gene therapy

*a. It should be noted that in 2010 the HTAi Global Policy Forum discussed the principals that should govern managed entry schemes (Klemp et al 2011)*

*b. GDP = gross domestic product*

and regenerative medicines. Across the region there is no consistent nor agreed upon definition of “high-cost”; a technology that is considered “affordable” in one country may be viewed as high-cost in another. Some technologies may have a relatively low acquisition cost; however, the burden of disease may make them unaffordable in terms of the overall payer’s budget.

A good example of affordability would be the overall budget impact of funding hypertensive medication in China, where the medication is low-cost but the estimated number of adults affected by hypertension is high at 325 million.<sup>9</sup> This may be contrasted with the funding of an orphan drug, which in isolation would be considered expensive but is used to treat a condition with few affected patients. For example, haemophilia has an estimated prevalence of between 2.9 and 3.6 per 100,000 in China, with haemophilia B representing approximately 16 per cent of this population. Based on the current population of 1.4 billion this would equate to an estimated 2,240 affected individuals.<sup>10</sup> In 2016, the FDA approved Albutrepenonacog alfa (Idelvion®, CSL Behring), a long-acting haemophilia B drug that combines albumin with factor IX to reduce injection frequency at a cost of US\$500,000 per year.<sup>11</sup> Based on these very rough estimates, in China it would cost between US\$1.8 to 18 billion<sup>c</sup> to treat all patients with hypertensive medications (eg thiazide diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, and beta blockers, ranging from 0.5 to 5.0 standard doses per person per year)<sup>9</sup> compared to US\$1.12 billion to treat all patients with haemophilia B.

Decision-makers need tools to enable them to prioritise, first and foremost, which technologies to invest in and add to the benefits package. Technologies and interventions that may work well in high-income countries may not work as well in lower and middle-income countries due to many reasons including differences in population, socioeconomic characteristics, service delivery, infrastructure and care pathways. It has been acknowledged that decision-making and priority-setting can be informed and assisted by health departments in the region investing and building capacity in health technology assessment (HTA).<sup>8</sup> Not only can HTA inform on the clinical safety and effectiveness of a new technology, but modelling of population data, treatment pathways and costs can better target conditions that would result in an acceptable return on investment for fiscally challenged health departments. A good example of this is the economic modelling conducted of a hypertension treatment program in Bangladesh, which perhaps was not initially identified as a health care priority in that country. As in so many countries in the region, the burden of disease in Bangladesh is shifting from acute and infectious to non-communicable conditions such as cardiovascular disease. Modelling has projected that investing in a proactive hypertension management program (that provides blood-pressure lowering drugs to up to 60 per cent of hypertensive adults), would result in an annual return on investment of almost 13:1 and 9:1, if implemented by 2021 and 2030, respectively. Economic modelling can be used to demonstrate that not only does an investment such as this prevent premature death in thousands of people but also enables the country to accrue a substantial net economic benefit from life-years saved.<sup>12</sup>

Although priority-setting for the investment of new healthcare technologies is important, consideration must also be given to the disinvestment or reassessment of technologies already funded and added to healthcare benefit packages that have since proven to be not be as effective or as safe as initially expected when used clinically, leading poorer health outcomes and wasted resources. A good example of this is the addition of trastuzumab, or Herceptin, to the publicly funded Indonesia National Health Insurance (INHI) formulary in 2010 for the treatment of HER-2 positive breast cancer patients. The recommended treatment regimen is 16 cycles over a 12-month period; however, the INHI only funded eight cycles over six months, with patients having to pay out-of-pocket to complete the 12-month course. Treatment with trastuzumab costs US\$12,000 for six months, and to extend

*c. Cost of hypertensive medications ranged from 11.40 to 62.50 international dollars per patient per year, depending on standard dose. To convert to US dollars, multiply the international dollar figure by the PPP exchange rate*

the treatment to the full recommended 12-months would cost an additional US\$20,000. It should be noted that many patients could not afford the out-of-pocket payments for the additional six months of treatment, with only one third of HER2-positive breast cancer patients receiving trastuzumab for the full 12 months. Interestingly a comparison of outcomes found that trastuzumab therapy for 12 months reduced the recurrence rate in post-operative HER-2 positive breast cancer women but did not significantly reduce mortality compared to women treated for only six months.<sup>13</sup> With the introduction of UHC into Indonesia in 2014, the health system was faced with supplying and financing a wide-range of healthcare interventions.<sup>14</sup> Drugs such as trastuzumab represent a huge expense to the UHC system and thought is now being given to ways in which to disinvest ineffective and inefficient technologies from the benefits package.

A full ranging debate of the many issues and challenges around the funding of technologies would include a more robust and in-depth discussion of these issues that have just been touched on: affordability and budget impact, acquisition costs versus net costs, return on investment and disinvestment. However, the focus of the 2018 APF is a high-level discussion with practical examples, highlighting the challenges and pitfalls of alternative funding mechanisms/managed entry schemes that enable access to high-cost healthcare technologies.

## Access to high-cost technologies

There is a paucity of literature describing the region's experience of access to high-cost technologies. Countries in the Asia region have expressed a great deal of interest in this topic, demonstrated by the recent conference held in Taiwan in August 2018, hosted by Taiwan's National Health Insurance Administration in conjunction with the Center for Drug Evaluation. The aim of the conference was to discuss mechanisms to manage access to, and reimbursement of, high-cost pharmaceuticals, with examples and presentations from NICE in the United Kingdom, Australia and South Korea.

Whilst the term 'high-cost' is cited often in the literature and policy discussions, few countries in the world, let alone in the Asia region, use a standard definition of what constitutes high-cost. Broadly speaking, high-cost implies new, novel and innovative technologies, with attention focussed on pharmaceuticals in the early stages of their lifecycle, such as biological therapies and targeted therapies for the treatment of cancer and rare conditions.<sup>15</sup> Based on a recent survey, only Malaysia and China define "high-cost". The Malaysian Ministry of Health defines high-cost as technologies that cost more than RM 200,000 (approximately US\$50,000). China has recently developed a policy around access to healthcare technologies, with the China Food and Drug Administration regulating market access, and the Ministry of Health (MOH) overseeing and developing policy around the allocation, management and assessment of healthcare technologies. High-cost devices are separated into two categories:

- Type A – very high-cost devices such as proton and heavy ion radiation therapy, PET/MR and other high technological radiation therapies that cost more than 30 million RMB (approximately US\$5 million). Investments in these technologies are overseen by the MOH; and
- Type B – devices such as PET/CT, MRI and surgical robots that cost between five to 30 million RMB (approximately US\$1 to 5 million). Investments in these technologies are overseen by provincial health bureaus. Recently HTAs have been conducted on some high-cost technologies such as the Da Vinci surgical robot, with results translated to the national allocation plan (personal communication).

Few countries in the region have an explicit policy regarding access to high-cost healthcare technologies, with most countries making investment decisions on a case-by-case basis. Malaysia has an explicit policy in place, which can be found in full in [Appendix 2](#) (guidelines available upon request). In short, the Malaysian Health Technology Assessment Section (MaHTAS), Medical Development Division, Ministry of Health (MOH) has a mandate to conduct a HTA on new health technologies. Assessments, including an economic analysis, are conducted when there are obvious safety, clinical

effectiveness or ethical/legal issues; however, an emphasis is given to high-cost health technologies that cost more than RM 200,000 (approximately US\$50,000) that may have economic implications or affect national policy. A positive recommendation does not automatically result in the inclusion of that health technology in the benefit package, but it allows internal advocates to make a request for funding using the usual budgetary request mechanisms. Funding may be partial, in which case implicit or explicit rationing mechanisms would be required, as the demand for such technologies exceed the supply.

Although Thailand, South Korea, and Taiwan do not have an explicit policy for the investment in high-cost technologies, they do require proof of value-for-money before approving coverage of (mainly pharmaceutical) healthcare technologies.<sup>7</sup> In addition, it should be noted that Thailand grants a two-year temporary market authorisation of new pharmaceuticals as a means of monitoring outcomes before granting full authorisation.<sup>16</sup> Although Vietnam does not have an explicit policy regarding high-cost technologies, a review of evidence on high-cost medicines reimbursed by health insurance was recently conducted, focusing on the use of these medicines from a provider perspective.

### Alternative funding mechanisms/managed entry schemes

The challenge of investing in high-cost technologies in healthcare systems operating under significant budgetary pressure has led to the increasing use of managed entry schemes (MES) by decision-makers. The reimbursement of new and innovative technologies may be associated with significant risk because of uncertainty around the clinical evidence, cost-effectiveness, budget impact, price or the eligible patient population. With conventional reimbursement decisions, the risk associated with the uncertainty around the true value of a technology is transferred from the manufacturer to the healthcare payer. However, when MES are used, by reducing the total budget impact or by creating an opportunity for the development of additional information to inform future reviews of the funding decision, the risk to the payer is reduced.<sup>17</sup> In addition, the risk of paying for technologies that may represent poor value for money for health care payers is reduced.<sup>18</sup> MES are appealing to manufacturers as products are able to gain market access that otherwise might have been rejected. Therefore, decision-makers in countries such as Australia and the United Kingdom are increasingly linking reimbursement strategies to the degree of uncertainty in the evidence base and, as a result, reimbursement for innovative technologies is then linked to some form of patient access or risk-sharing scheme.<sup>19</sup>

A wide range of funding mechanisms have been used to mitigate this risk or uncertainty and limit the budget impact on payers, including coverage or access with evidence development, managed entry, pay-for-performance and risk sharing agreements with industry in order to introduce new and innovative technologies into health systems. MES may also offer an alternative “disinvestment” strategy, in that they offer the opportunity to reassess the clinical effectiveness and cost-effectiveness before a commitment is made to add them to a benefits package for reimbursement.<sup>20</sup> A recent survey of 16 eastern and central European countries that had implemented managed entry agreements for pharmaceuticals found that the majority entered into these agreements due to finite health system resources (n=10), or to enable patient access to new drugs (n=6) or to deal with the uncertainty around cost-effectiveness and use in real-life (n=6).<sup>15</sup> The need for feasibility and value of an MES should be carefully considered by all stakeholders, including patient representatives and clinicians, in addition to sponsors and payers.<sup>21</sup> An MES can be challenging to implement, especially where they are reliant on data collection, and may themselves be costly to implement and administer. Other challenges around the implementation of an MES include the potential for lengthy negotiations, unclear success measures, the complexity of the agreements and, ultimately, how to use the new evidence to inform coverage decisions.<sup>15</sup>

Broadly speaking MES can be categorised into performance-based (outcomes or evidence generation schemes) or financially-based schemes ([Figure 1](#)). MES may be implemented after regulatory approval

but before HTA, or after HTA where gaps in the evidence have been identified (Figure 2). In addition, an MES may be initiated by the payer or by the sponsor/manufacturer, as demonstrated by a recent Australian study where four out of 11 pharmaceuticals considered for an MES were proposed by the payer.<sup>21</sup>

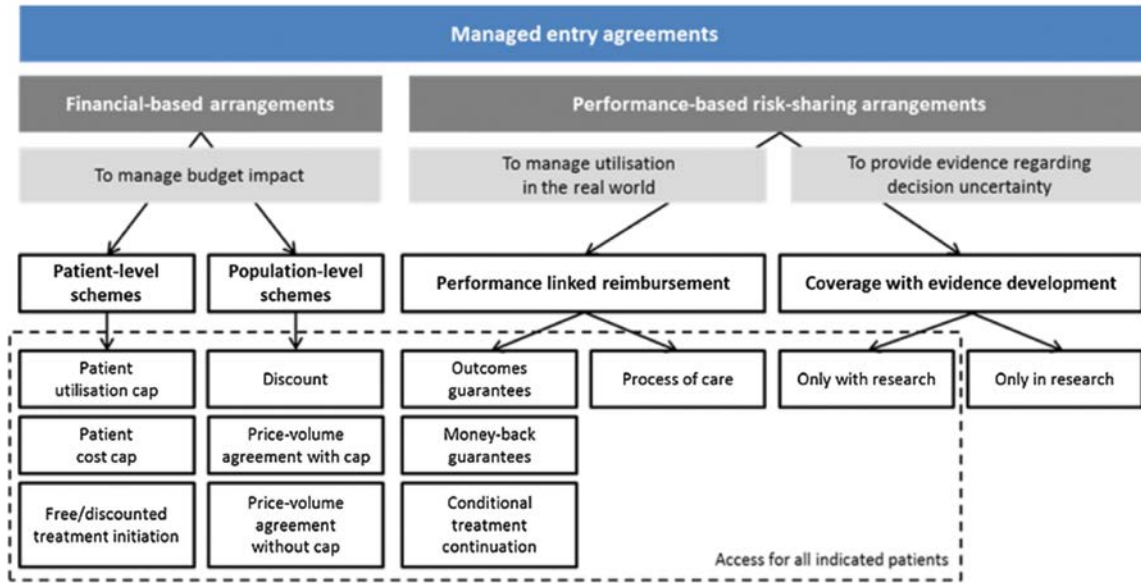


Figure 1 Taxonomy of managed entry agreements (printed with permission)<sup>22</sup>

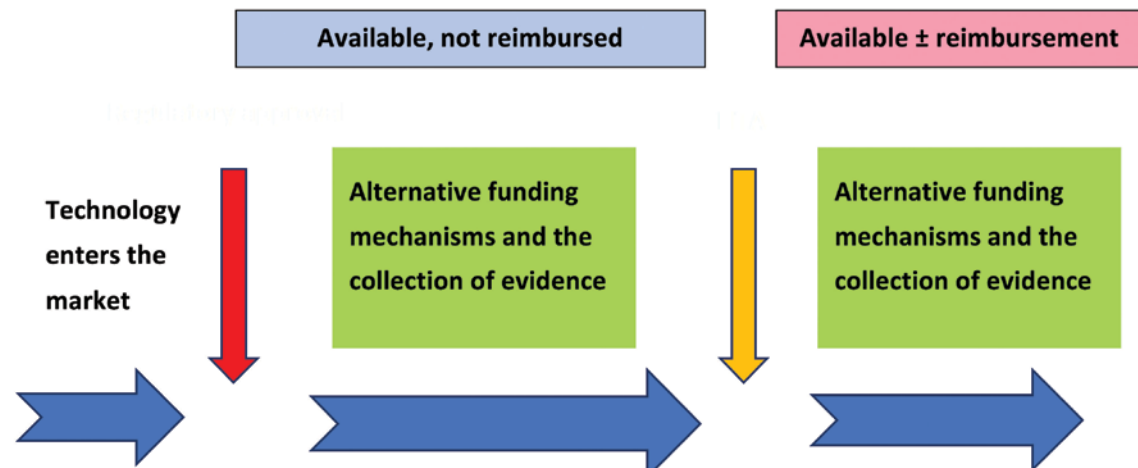


Figure 2 Schematic demonstrating the movement of a technology into the health system

*A performance-based risk-sharing arrangement is an arrangement between a payer and a pharmaceutical, device, or diagnostic manufacturer where the price level and/or nature of reimbursement is related to the actual future performance of the product in either the research or 'real world' environment.<sup>1</sup>*

## Definitions:

**Outcome-based schemes** are those in which the price, level, or nature of reimbursement are tied to clinical or intermediate endpoints measured in the future and ultimately related to patients' quality or quantity of life.<sup>7</sup> For example, performance-based reimbursement schemes (also known as patient access schemes) where an arrangement between manufacturers and payers results in the performance of the product being tracked in a defined patient population over a specified period of time, and the level of reimbursement is tied by a formula to pre-specified outcomes.<sup>23</sup> The benefit to the payer is that they can provide access to innovative technologies to patients at a discounted net price, decreasing the financial exposure for potentially under-performing products, and the benefit to manufacturers is access to the market at or near launch.<sup>1</sup> These would also include risk sharing agreements which are agreements between a payer (in this case we would consider the publicly funded health system) and a manufacturer where the price level and/or revenue received is related to the future performance of the product in a real-world environment.<sup>24</sup>

A good example of a performance-based reimbursement scheme is that of crizotinib proposed by the sponsor, Pfizer Inc, to the Australian pharmaceutical benefits advisory committee (PBAC) in 2013. Crizotinib was intended to treat patients with anaplastic lymphoma kinase-positive advanced non-small cell lung carcinoma (NSCLC). Although the sponsor offered a price reduction, this was rejected by the PBAC, who suggested a price reduction of at least 30 percent was required to achieve an acceptable ICER<sup>d</sup>. Uncertainty related to the magnitude of overall survival of patients treated with crizotinib compared to the comparator pemetrexed was the main area of concern for the PBAC. Under the MES agreement, the initial price of crizotinib could either be maintained or reduced depending on the outcome of the MES, but there was no option of a higher price. The sponsor was required to collect outcome data, specifically 12-month survival data for the first 50 crizotinib-naïve patients to receive treatment. Price reduction penalties were in place if data was not reported in the stipulated two-year time frame, in addition to financial penalties if the claimed 12-month survival benefit (threshold survival rate of 68.9%) was not realised. In 2017, data collected over the term of the MES demonstrated a 12-month survival rate of 70 per cent. Having fulfilled the requirements of the MES agreement, crizotinib was subsequently listed for publicly funded reimbursement at the initial MES entry price.<sup>21</sup>

In addition, conditional treatment continuation schemes would also be included in this outcomes-based category of MES. These schemes allow individual patients to access continued coverage of a technology (usually a pharmaceutical) based upon short-term treatment goals being reached, ensuring that only patients who benefit remain on treatment and inappropriate patient populations are not treated. The benefit to the payer in these situations is that their long-term cost exposure is minimised and replaces the need to limit patient access via authorisation, and manufacturers benefit from market access.<sup>1</sup> Patients, however, need to be aware that treatment, often subsidised, will cease if the criteria defining a satisfactory response are not reached at a pre-specified follow-up time.<sup>25</sup> Although not as common as other MES, conditional treatment continuation (CTC) schemes have been introduced in several countries for the same drug. Italy, Canada and Australia all introduced CTCs for patients with Alzheimer's being treated with galantamine, donepezil or rivastigmine, with patients required to demonstrate an improvement in cognitive function at a pre-specified follow-up time.<sup>25,26</sup>

**Evidence generation schemes** in which a positive coverage decision is conditioned upon the collection of additional evidence through clinical studies, which might result in continued, expanded or withdrawn coverage.<sup>7</sup> For example, coverage with evidence development (CED) or access with evidence development (previously called conditional coverage) where the coverage of a treatment or technology is conditional on data being gathered through a clinical trial or registry to determine its effectiveness.<sup>27,28</sup> The benefit to the payer of CED is that they can provide access to innovative

*d. ICER = incremental cost-effectiveness ratio*



products while additional population level evidence is generated that may support future coverage decisions, and the benefit to the manufacturer is that they receive market access that otherwise would be denied due to insufficient evidence at time of product launch.<sup>1</sup> An early example of CED was the funding of risperidone (Johnson and Johnson) to treat schizophrenia in France and Sweden in 2003 and 2004, respectively. The French Ministry of Health agreed to cover risperidone at the market asking price only if studies were conducted by the company in order to evaluate whether risperidone assisted patients to remain compliant with their medications. If the reverse was true, the company agreed to reimburse the French government a portion of its expenditure on the drug. In Sweden, policy-makers required additional data on quality of life and hospitalisations of patients from use in real-world clinical practice.<sup>26</sup> Many other examples of CEDs exist including Oncotype Dx in the USA, an expensive 21-gene panel designed to determine whether women with early-stage breast cancer would benefit from chemotherapy. In 2007, the insurer United HealthCare agreed to the temporary coverage of Oncotype Dx at a price of US\$3,460 while data on the number of women diverted away from expensive chemotherapy was collected. If substantial numbers of women for whom the test showed no benefit still received chemotherapy, United HealthCare reserved the right to lower the price paid for the test.<sup>28</sup> <sup>29</sup> The United States Centers for Medicare & Medicaid Services has an extensive listing of procedures, diagnostics and devices that are currently the subject of a CED agreement including TAVI<sup>e</sup>, allogeneic hematopoietic stem cell transplantation for myelofibrosis, myelodysplastic syndromes and sickle cell disease, autologous platelet-rich plasma for patients who have chronic non-healing diabetic pressure wounds, and Cochlear implantation.<sup>30</sup>

**Financially-based schemes** negotiate company contributions to the cost of a product (e.g., discounts or rebates price-volume agreements, utilisation caps) for a particular patient or population without linking reimbursement to health outcomes.<sup>7</sup> These include managed entry agreements (MEA) where an arrangement is made between a manufacturer and payer or provider to reduce the risk incurred by health services, enabling coverage or reimbursement of a health technology subject to specific conditions: usually (1) that the price of the technology be reduced through a range of different financial schemes and/or (2) that further data on usage of the technology will be collected.<sup>31,32</sup> In countries where cost-effectiveness thresholds exist (explicit or implicit), these financial-based risk-sharing schemes may be viewed as agreements that bring the price down to within the willingness-to-pay threshold.<sup>15</sup> A good example of financially-based schemes are those implemented in South Korea for groups of drugs for the treatment of migraine, hyperlipidaemia and hypertension. Of the 1,226 hypertension drugs listed by the National Health Insurer, price reductions were put in place for 285 following a reassessment of clinical usefulness and price. In addition, drugs were delisted if they failed to show a level of clinical usefulness or if their prices were higher than the 80 percentile of the highest price among drugs containing the same ingredients.<sup>7</sup> Similarly in Thailand, an economic and budget impact analysis on the introduction of the human papilloma virus vaccine (HPV) was conducted. In 2009, the price of US\$450 per course did not represent good value for money and it was recommended that it would have to be reduced by 60 per cent in order for the vaccine to become cost-effective. The manufacturers agreed to reduce the price to US\$200 per course, and although the Thai government still did not add the vaccine to the benefit package due to high budget impact, patients in the private sector who could afford the vaccine out-of-pocket benefited from the significant price reduction.<sup>33</sup>

The advantages and disadvantages of MES are summarised in [Table 1](#).

e. TAVI = transcatheter aortic valve implantation

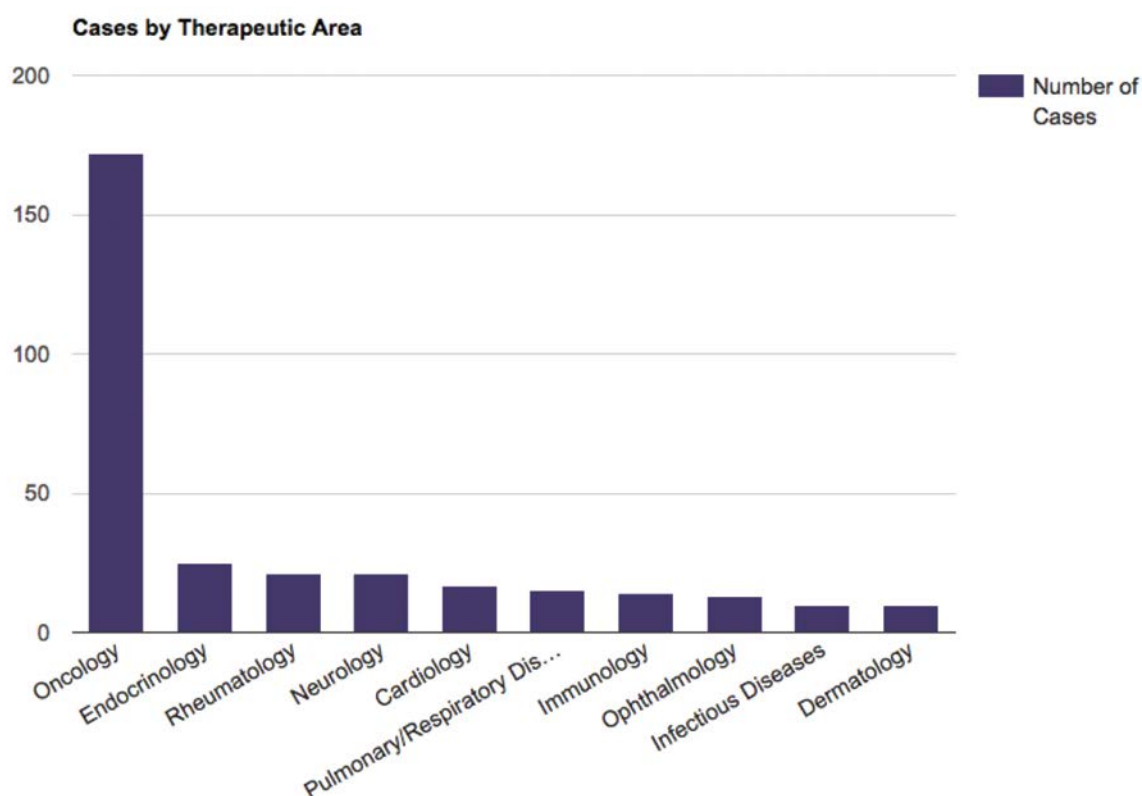
**Table 1** The advantages and disadvantages of managed entry schemes<sup>34</sup>

Perspective	Advantages	Disadvantages
Patients/society	<ul style="list-style-type: none"> <li>• Access to innovative health care technologies</li> <li>• More treatment options and potential health improvements</li> <li>• Promotion of investment for innovation</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of technology not being beneficial</li> <li>• Risk of discontinued access to technology at end of agreement</li> <li>• Potential of issues relating to data protection</li> </ul>
Providers	<ul style="list-style-type: none"> <li>• Greater knowledge and improved disease management</li> <li>• Access to innovative health care technologies</li> <li>• Limiting budgetary impact</li> <li>• Reduction of uncertainty concerning effectiveness</li> </ul>	<ul style="list-style-type: none"> <li>• Costs/bureaucracy of implementation and monitoring of agreements</li> <li>• Complexity of data collection and patient follow-up</li> <li>• Complexity of managing multiple agreements</li> </ul>
Payers	<ul style="list-style-type: none"> <li>• Collection of additional evidence to support decision-making</li> <li>• Management of uncertainty (effectiveness and budget)</li> <li>• Therapy directed at patients with potential to benefit most, avoiding risk in patients who would not benefit</li> </ul>	<ul style="list-style-type: none"> <li>• Difficulty in defining appropriate and measurable performance indicators</li> <li>• Lack of integrated information systems for data collection at the local and national level</li> <li>• Intensive allocation of resources in data collection and analysis/monitoring of agreements</li> </ul>
Industry	<ul style="list-style-type: none"> <li>• Access of innovative technologies to the market</li> <li>• Improved performance of technology</li> <li>• Innovation rewarded. Research and development stimulated</li> <li>• Confidentiality of terms of agreement</li> </ul>	<ul style="list-style-type: none"> <li>• Costs/bureaucracy of implementation and monitoring of agreements</li> <li>• Risk of not demonstrating proposed effectiveness</li> <li>• Financial unpredictability, depending on the type of agreement</li> <li>• Biased selection of patients with worse prognosis</li> </ul>

Much of the literature describes the experience of MES in Western Europe, Australia, the United States and Canada.<sup>25, 28, 32, 35-41</sup> Although literature does exist describing various mechanisms of access in low-to-middle income countries, these tend to be countries other than the Asia region such as those in Central-Eastern Europe, the Middle East and North Africa.<sup>15, 42, 43</sup> A review of world-wide, publicly listed performance-based risk-sharing schemes revealed that Australia, Italy, Sweden, the United States, and the United Kingdom are the top five countries that are implementing these schemes<sup>44</sup>, which may be a reflection of a superior negotiating power and a greater experience in HTA, as well as the regulatory and policy structures in place around healthcare.<sup>7</sup> Carlson et al (2017) also reported that in the past few years coverage with evidence development (CED) schemes have declined in use world-wide but remain popular; however, in the majority of cases performance-linked reimbursement was the scheme of choice. Of the 437 schemes identified world-wide, the majority were for pharmaceuticals, of which most were for oncology (41%) (Figure 3). There were only 24 (5.5%) cases of devices and 13 (3.0%) diagnostics, the majority of which occurred in the United States (22 and 11, respectively).<sup>44</sup> This is slightly at odds with a 2013 abstract presented at ISPOR<sup>f</sup>, reporting that Canada, the United Kingdom and the United States had the most experience with CED applied to devices, and that Germany and the Netherlands had introduced new policies for CED for devices and procedures. The types of devices that had undergone CED in these jurisdictions included ICD<sup>g</sup>s, stents, TAVI, laparoscopic surgery and spinal cord stimulators.<sup>45</sup>

f. ISPOR = International Society for Pharmacoeconomics and Outcomes Research

g. ICD = implantable cardioverter-defibrillator



**Figure 3** Number of MES by therapeutic area (printed with permission)<sup>1</sup>

The recent review by Lu et al (2015) was conducted to identify and characterise alternative market access agreements (between healthcare payers and manufacturers) in the Asia-Pacific region. Although the search strategy identified 106 MES, the majority occurred in Australia (n=98, 92.5%), with five in New Zealand and three in South Korea. The majority of these schemes were for pharmaceuticals, with only three for medical devices. The agreements in place in Australia and New Zealand all targeted established technologies likely to have a high budget impact due to either the high cost per patient of the pharmaceutical itself (predominantly to treat cancer or inflammatory conditions), or a large burden of disease. However, the three agreements in place in South Korea were all financially-based schemes that targeted entire classes of established medicines, such as hyperlipidaemia and hypertensive medications, with large patient groups that would have a great impact on the health budget.<sup>7</sup>

## High-cost technologies in the Asia region: Case study

### Expedited access to regenerative medicine in Japan

Japan is faced with a large, ageing population, which was estimated to be 30 million people aged 65 years or over in 2013. Longevity of the Japanese population has led to the increase of conditions associated with ageing such as arthritis, cardiovascular disease and Alzheimer's dementia. In response to the future challenges of providing health care to this large, ageing population, in 1999, the Japanese government initiated the Millennium Project, primarily to conduct tissue engineering research, in the hope that investment in innovative tissue and cell-based medicines would hold the solution for the unmet medical needs of this ageing population.<sup>46</sup>

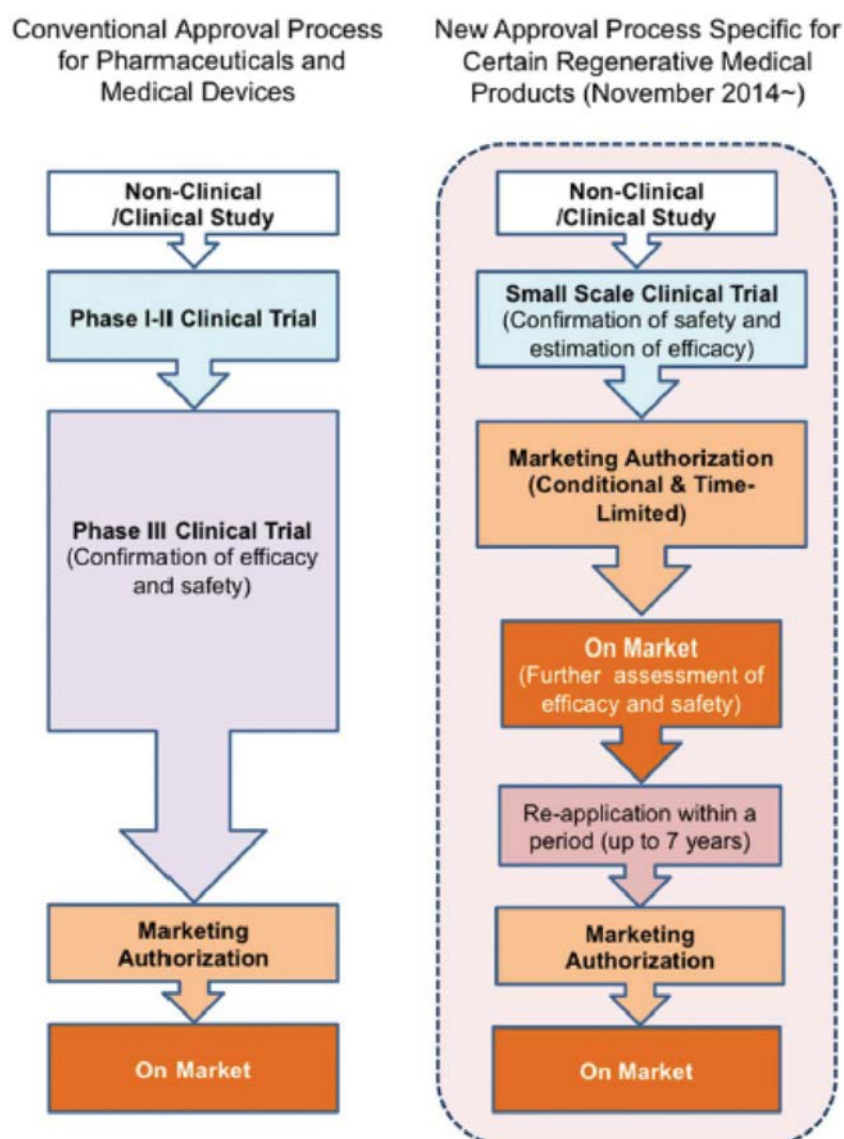
In Japan, regenerative medicines are defined as "processed human cells for medical use to reconstruct, restore, or form structure or function of the human body and to treat or prevent human diseases as well as gene therapy products"<sup>47</sup> and are categorised as a distinct product, separate from pharmaceutical and medical devices. Regenerative medicines are classified into three categories according to their potential risk level:

- Class I: high risk for human health and includes induced pluripotent and embryonic stem cells, transgenic cells and allogenic cells;
- Class II: medium risk for human health, including autologous somatic stem cells cultured in vitro and those for non-homologous use; and
- Class III: low risk to human health, including autologous somatic stem cells for homologous use, and processed somatic cells.<sup>48</sup>

Despite some investment in the sector, the regulatory approval pathway for these products were unclear and regulations governing the administration of stem cells therapies to patients was complex. In 2013, in response to a patient death from a pulmonary embolism after receiving stem cell therapy which was prepared overseas, there were calls from the regenerative medicine sector for the government to construct an appropriate regulatory framework.<sup>49</sup> The new legal framework, the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act) was developed and came into effect in November 2014. Under the PMD Act, there are two pathways that cell- and tissue-based therapies can use to obtain regulatory marketing approval (Figure 4). The first is the conventional authorisation pathway that is used for pharmaceuticals and medical devices, where regenerative medicines must demonstrate their safety and efficacy through early Phase I and II, and finally late Phase III clinical trials. This approach has been considered difficult due to the biological heterogeneity of cell- and tissue-based therapies.<sup>48</sup> Under the PMD, sponsors can seek market approval for up to seven years using the expedited regulatory pathway for cell- and tissue-based therapies that are not homogeneous<sup>h</sup>, which requires only data from small, early phase trials that demonstrate safety and are "likely to predict efficacy".<sup>47, 48, 50</sup>

Unlike other expedited regulatory pathways in the US and Europe, the Japanese expedited-approval system does not specify the severity of the target disease or patient population, or require comparisons with existing treatment conditions.<sup>47</sup> Conditionally approved products will be eligible for reimbursement in Japan's co-payment-based UHC insurance system, whereby payers and patients seeking treatment typically split costs 70:30.<sup>50</sup> It is hoped that this pathway will accelerate access to innovative products for patients with unmet medical needs. Once the conditional period of approval has expired, a new application using safety and efficacy data collected during the trial period is required before permanent approval can be granted,<sup>48</sup> in so doing, shifting the evidentiary burden from pre-market clinical trials towards post-hoc efficacy testing.<sup>50</sup>

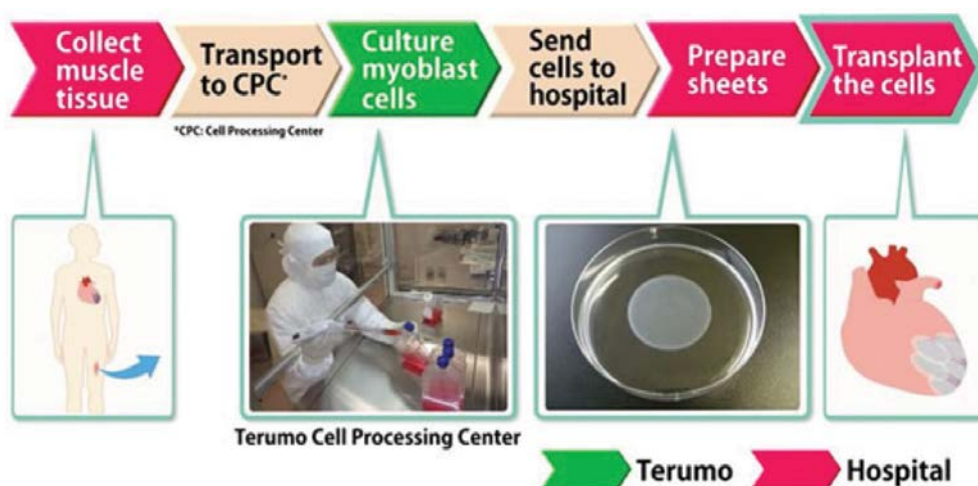
*h. Note: There is no definition of 'homogeneous' in the legislation (Jokura, et al 2018)*



**Figure 4 Comparing the new regulatory approval pathway for regenerative medicines (R) compared to the conventional regulatory approval pathway (L) (printed with permission)<sup>48</sup>**

In September 2015, HeartSheet® (Terumo Corporation), which is intended to treat patients suffering from severe heart failure caused by chronic ischemic heart disease, became the first product to be approved using the new, expedited regulatory pathway.<sup>47,51</sup> Autologous skeletal myoblasts taken from muscle tissue in the patient's thigh are cultured and then sheets of the cells are transplanted onto the surface of the patient's heart (Figure 5).<sup>52</sup> Regulatory approval granted authorisation for HeartSheet® to only be used in patients with a left ventricular ejection fraction (LVEF) less than 35 per cent and a New York Heart Association functional classification of III or IV. Interestingly, only a five-year, rather than the seven-year, conditional approval period was granted, during which time the product must demonstrate efficacy in 60 cases treated with the product and that the product yields a greater clinical benefit than that achieved by 120 control cases treated with the current standard of care. Terumo estimates that a total of 123 patients will be treated with HeartSheet® during the five-year conditional period.<sup>51,53</sup> The reimbursement price of HeartSheet® was set by the Central Social Insurance Medical Council (Chuikyo) at ¥14.76 million (approximately US\$132,401<sup>1</sup>) for a standard treatment course (one culture kit and five patches for transplantation), which was well below the ¥18.89 million (US\$169,422) requested by the company who indicated that the lower price was "problematic from a business perspective".<sup>53</sup>

i. September 2018 exchange rate



**Figure 5** The process of treatment using HeartSheet (printed with permission)<sup>52</sup>

Of concern to critics of the implementation of the expedited pathway, is the level of evidence provided to support the conditional market approval of the HeartSheet® product. Approval was granted on the basis of a single, small scale study of seven patients, who demonstrated no statistical improvement in the study's primary endpoint, with five patients having no change in LVEF and two experiencing a deterioration in LVEF 26 weeks post-HeartSheet® transplantation.<sup>53</sup> The expedited approval process may be interpreted as a means of companies being able to subsidise late-stage clinical testing through publicly paid reimbursements, with the public insurance payers entering into partnerships with a private-sector entities during the most costly stage of product development.<sup>50</sup> In addition, concerns have been raised regarding the expedited approval and funding of an expensive regenerative medicine that targets a growing epidemic of disease such as chronic heart failure, which has been estimated to peak at 1.3 million people by 2035, rather than a technology that targets rare disease. Critics maintain that the reimbursement price indicates to the market that the Japanese government has high willingness-to-pay threshold for innovation that only promises rather than demonstrates health gain and that it is insensitive to risk or uncertainty in its assessment of the value of new technologies. This may make it difficult for the payer to then justify paying less for future technologies that have evidence of equal or greater health benefit. In addition, it may also signal to developers that a low level of evidence is sufficient to achieve market access.<sup>53</sup>

A second product, TEMCELL HS Injection® (JCR Pharmaceuticals Co. Ltd.) was approved under the new regulatory framework in late 2015. TEMCELL®, a mesenchymal stem cell product, is considered an orphan drug intended to treat acute graft-versus host disease that may occur after an allogeneic bone marrow. Unlike HeartSheet®, approval for TEMCELL® was conditional on all data on all cases treated with the product being collected as post-marketing surveillance.<sup>47</sup> In 2015, it was announced that the Japanese Government's National Health Insurance body had set the reimbursement price for TEMCELL® at ¥868,680<sup>j</sup> (US\$7,079) per bag of 72 million cells, with the average adult patient in Japan expected to require 16 to 24 bags of 72 million cells. Based on this usage, a treatment course of TEMCELL® in an adult Japanese patient will cost between ¥13.9 million (US\$113,000) to ¥20.8 million (US\$170,000).<sup>54</sup>

*j. 2016 prices*

## Summary of the results from the agency and industry surveys

As previously mentioned, one of the greatest challenges facing policy-makers in the Asia region when moving towards UHC is defining the right balance in benefit packages. A shift in the burden of disease from predominantly infectious diseases to non-communicable ones such as cardiovascular and diabetes, added pressures from an ageing population and a demand for medical technology all increase the financial demands on the health system. The aim of the 2018 HTAi APF, is to try to understand what the term “high-cost technologies” means to countries in the Asia region and to explore the types, and experience to date, of mechanisms that are available to increase access to these technologies.

As such, a short survey of both payers and industry representatives participating in the 2018 APF was undertaken to capture their experience of alternative access mechanisms and the types of mechanisms, and to elucidate some of the challenges and barriers in the implementation of these schemes. A copy of the questions asked in both the industry and agency (payer) surveys can be found in [Appendix 3](#).

### Agency survey results

A total of nine public sector agency participants responded to the survey, representing Indonesia, India, Korea, Malaysia, the Philippines, Singapore, Taiwan, Thailand and Vietnam. The main results of the agency survey are summarised in [Table 2](#).

### High-cost technologies

One of the issues identified by preliminary discussions was the difficulty of defining exactly what is meant by “high-cost technologies”. As previously noted, most countries do not have an explicit policy in this regard and answers given in the survey are estimates based on experience within the health sector. When agencies were asked to think about the cost of a technology’s overall annual budgetary impact, three agencies (India, Taiwan and Thailand) defined a high-cost pharmaceutical as 2.5 times the health expenditure per capita of their country, and three defined it as greater than 10 times (Indonesia, Malaysia and the Philippines<sup>k</sup>). The same countries used the same definition and values for what they considered a high-cost device, with the exception of India, where it was considered to be five times the health expenditure per capita. Some countries, such as Vietnam, are interested in developing an explicit threshold, which could then be used for decisions on coverage and price negotiation for selected high-cost medicines. In South Korea, the cost of the new technology should be considered relative to the existing technology. In addition, factors such as the nature of the disorder should always be considered, such as the cases previously discussed, where the prevalence of the condition being treated is low; so although the technology is expensive, the impact on the total health budget may be minimised. Although only a guide and not an explicit value, in South Korea treatment costs exceeding one times GDP per capita would be considered a high-cost medication.

### Challenges faced in accessing high-cost technologies

The challenges faced by countries in the provision of access to high-cost technologies are as varied as the region’s populations, economies and health systems. Challenges include those related to legislative, regulatory and budgetary constraints, the lack of evidence supporting the use of these new technologies, patient affordability and even socio-cultural barriers. Four of the nine countries surveyed reported data as the biggest issue faced, whether it was a lack of quantitative data (safety, effectiveness and especially cost-effectiveness data) or poor-quality data, or uncertainty around how to collect data, especially on an individual patient level. One of the flow-on effects of this lack of data,

*k. In the Philippines when any health care technology (pharmaceutical, device or procedure) exceeds \$2,000 or 15x our per capita health expenditure, it is considered very expensive and would cause ‘catastrophic health expenditure’ to households.*

is that there is a degree of uncertainty around the value for money of these high-cost technologies in the local setting. This uncertainty was cited as the major reason that the Philippines has not prioritised access to high-cost technologies; rather, it is concentrating on the provision of basic health services to the entire population. The need for real-world data was again reiterated by several respondents, and it was acknowledged that the collection of appropriate data may be hindered by limited resources. A lack of qualitative evidence to inform decision-making, especially around the acceptability of new technologies, was also identified as an issue, particularly when considering that many of the countries in the region have large, heterogeneous populations with a range of socio-cultural characteristics. One interesting point raised by Thailand was the advent of co-dependent technologies, which may result in a lack of access when one side of the co-dependent equation is missing. For example, when access to a high-cost drug depends on the patient being positive for a particular genetic mutation, but the mutational analysis isn't available.

### Experience with managed entry schemes

When asked if their countries have an explicit, written policy in regard to implementing MES in place, four countries indicated that policies were in place but only for certain conditions or technologies. Of the five countries without such a policy, three intend to develop one within the next one to two years; development was not on the immediate horizon for one country, but there was interest in the concept, and one country had no plans to develop a policy at all. Whilst the Philippines has no single explicit policy document in place, it does have different Medicines Access Programs in place in selected public facilities. Each MAP<sup>1</sup> has its own policy for all technologies, not just high-cost ones, which can utilise financial-based schemes. Similarly, Taiwan does not have an explicit policy in place, but has a price-volume agreement for some high budgetary impact pharmaceuticals. In addition, in April 2018 Taiwan drafted the "General rules of reimbursement submission for high-cost drugs", for drugs that cost more than 500 million NTD per year (US\$16.6 million). This agreement requires an approved indication for which it has been reimbursed in one of the reference countries (Canada, Australia or the United Kingdom), clear and measurable efficacy endpoints and evaluation methods and lists of all serious adverse events, as well as an estimate of the cost of managing adverse events.

The majority of countries included in the survey (88.9%) have at some time introduced a new health technology using an MES, with only one country reporting no experience with MES. Overwhelmingly, an MES was set in place to allow access to pharmaceuticals, with only three countries using an MES to fund access to devices and one to a diagnostic. The types of agreements and technologies approved varied greatly from country-to-country and this may offer an opportunity for collaboration and exchange of information or learnings across the region. In Vietnam, alternative market access agreements have been applied for some high-cost cancer pharmaceuticals such as Tarceva (erlotinib) and Nexavar (sorafenib) where the manufacturer has supported 50 per cent of the costs for a limited time period (e.g., three months for Nexavar). Similarly, a 50 per cent discount allows patients access to robotic surgery in Vietnam. In Malaysia, alternative access schemes have been used to fund access to imatinib for chronic myeloid leukaemia and brentuximab vedotin for certain types of Hodgkin's Lymphoma and systemic anaplastic large cell lymphoma. Thailand has used an MES to enable access to imiglucerase for the treatment of Gaucher type I disease. Although in the Philippines, the MAPs were not created solely for high-cost technologies, the majority of the drugs funded via a MAP are considered to be high-cost. Examples of these are drugs for paediatric cancer, breast cancer (trastuzumab and letrozole), insulin and intravenous immunoglobulin to treat Kawasaki disease.

South Korea is one of the most active countries in the region in implementing managed entry schemes, with numerous high-cost technologies, including pharmaceuticals, devices and diagnostics, funded and reimbursed. The Conditional Approval System of Health Technology, where data is required to be collected for three years, has been in use since 2014 for Class-II-b technologies. Recent

1. <https://pharmadiv.doh.gov.ph/our-programs?id=5#types-of-medicines-access-program>



examples include autologous platelet rich plasma, irreversible electroporation for pancreatic cancer, intravitreal autologous platelet concentrate injections for the treatment of macular holes, and autologous peripheral blood stem cells for the treatment of myocardial infarction. In addition, the Temporary Exemption of nHTA scheme allows a one-year temporary regulatory exemption period, during which time evidence must be generated in order for the technology to undergo HTA. The use of rhBMP-2 mixed autogenous tooth derived bone grafts has a current exemption, due to end mid-2019. There are currently three high-cost technologies funded under an evidence-generating program, all of which require an 80 per cent co-payment. TAVI for severe aortic stenosis is due for evaluation in late 2018, and the percutaneous left atrial appendage closure device for stroke prevention, WATCHMAN™, is due for evaluation in late 2020 as is the next generation sequencing Oncogene panel. The most prolific agreements in place are risk-sharing arrangements to fund access to orphan drugs and anticancer drugs where no other alternatives to treat life-threatening conditions exist. This scheme was introduced in South Korea in 2013, and as of July 2018, a total of 32<sup>m</sup> drugs are funded by a variety of mechanisms including coverage with evidence development, expenditure caps or refunds. Since 2013, only the one risk-sharing agreement for lenalidomide, used to treat multiple myeloma, has been terminated.

The proportion of new healthcare technologies that were funded or reimbursed in the public health system using alternative funding approaches was unknown or low in most countries, with the exception of South Korea, which has funded 13 of 34 (38%) new anti-cancer and orphan drugs under the National Health Insurance scheme using risk-sharing arrangements.

All countries gave multiple reasons as to why an alternative market access approach was considered. Unsurprisingly, the most common criteria (75%) was that the technology in question would have a significant budgetary impact. Following on from this, most countries (62.5%) were concerned with the uncertainty around the economic analysis or cost-effectiveness of the technology. The Philippines noted, however, that their limited capacity to assess the uncertainty around economic analyses prohibited its use as a criterion for implementing an alternative funding scheme. What was surprising was that clinical demand was a common reason (75%) and that, in some cases, public demand was considered (25%). Interestingly, Malaysia nominated patent protection and a single source manufacturer as other reasons for entering into such agreements. In South Korea, it was recognised that for some technologies with limited safety and effectiveness data there is a clinical need, especially for the treatment of rare diseases or disorders where there are no other treatment alternatives. In cases such as these, it is incumbent on the government to create a support system that enables technologies with potential, especially for those where there is little incentive for development due to patent or ownership rights.

## Evaluating outcomes

When it came to evaluating the outcomes of the alternative access schemes, most countries (6/8, 75%) relied on a single entity to collect data for analysis; however, the agency responsible varied with an even spread between the public payer, third party (e.g., academic institution) or the manufacturer. Two countries used a range of agencies to collect data. A similar spread of results was reported for the payment of data collection.

The majority of countries (7/8, 87.5%) were interested in collecting data on patient outcomes such as reductions in morbidity or mortality and reduced health system costs (4/8, 50%). Most countries collected data on multiple outcomes; however, three countries only collected single outcomes, two of which were interested in patient outcomes, with one country interested in reduced health system costs. Interestingly, few countries collected data on patient satisfaction, including quality of life, and only one country collected data on a demonstrated disinvestment from other technologies.

*m. clofarabine, cetuximab, enzalutamide, crizotinib, eculizumab, regorafenib, pomalidomide, pertuzumab, trastuzumab, pembrolizumab, nivolumab, pembrolizumab, palbociclib, osimertinib, carfilzomib, ramucirumab, sapropterin, vemurafenib, ibrutinib, olaparib, trametinib, olmutinib, alectinib, dabrafenib, ponatinib, defibrotide, galsulfase, elosulfase, blinatumomab, siltuximab, atezolizumab, olaratumab, vandetanib*

**Table 2 Survey results from payer agencies**

<b>A high-cost pharmaceutical would be considered</b>		
2.5 times the health expenditure per capita for your country		3/9 (33.3%)
5 times the health expenditure per capita for your country		0/9 (0%)
>10 times the health expenditure per capita for your country		3/9 (33.3%)
<b>A high-cost device would be considered</b>		
2.5 times the health expenditure per capita for your country		2/9 (22.2%)
5 times the health expenditure per capita for your country		1/9 (11.1%)
>10 times the health expenditure per capita for your country		3/9 (33.3%)
<b>Challenges faced in accessing high-cost technologies</b>		
Data – lack of, poor quality etc		4/9 (44.4%)
HTA and the use of, and access to, real-world data		3/9 (33.3%)
Budget impact		4/9 (44.4%)
Patient affordability/out-of-pocket expenses		2/9 (22.2%)
Access		1/9 (11.1%)
Disinvestment of “old” technologies		1/9 (11.1%)
Lack of streamlined processes		1/9 (11.1%)
Regulatory/legislative		1/9 (11.1%)
Patient expectations		1/9 (11.1%)
<b>Does your country have an explicit, written policy that addresses managed entry schemes (MES)?</b>	Yes	4/9 (44.4%)
	No	5/9 (55.5%)
<b>Of those countries without a MES policy, is there an intention to develop one?</b>	No	1/5 (20%)
	Not yet but interested	1/5 (20%)
	Yes, in next 1-2 years	3/5 (60%)
<b>Has your country ever introduced a new health technology using one an MES?</b>	Yes	8/9 (88.9%)
	No	1/9 (11.1%)
<b>If yes, what was the MES used to provide access to?</b>	Pharmaceutical	8/8 (100%)
	Device	3/8 (37.5%)
	Diagnostic	1/8 (12.5%)
<b>Number of new healthcare technologies entering your publicly funded health system using an MES?</b>	Unknown	4/8 (50%)
	One	1/8 (12.5%)
	Small number	2/8 (25%)
	>10	1/8 (12.5%)
<b>What were the most common decision-making criteria for the MES?</b>		
Technology would have significant budgetary impact		6/8 (75%)
Insufficient clinical (safety/effectiveness) evidence to support widespread introduction and reimbursement of technology		3/8 (37.5%)
Uncertainty around economic analysis/cost-effectiveness of technology		5/8 (62.5%)
High public demand for technology		2/8 (25%)
High clinical demand for the technology		6/8 (75%)

**What outcome data would usually be required to be collected?**

Patient outcomes (reductions in morbidity/mortality)	7/8 (87.5%)
Reduced health system costs	4/8 (50%)
Demonstrated disinvestment from other technologies	1/8 (12.5%)
Change in patient management	1/8 (12.5%)
Clinician satisfaction	0%
Patient satisfaction – quality of life	3/8 (37.5%)
Other – Adverse events	1/8 (12.5%)

**Who had responsibility for data collection?**

a) Public payer	2/8 (25%)
b) Non-payer government agency	0
c) Manufacturer	1/8 (12.5%)
d) Third party (eg academic institution)	3/8 (37.5%)
Combination a, c, d	1/8 (12.5%)
Combination a, b, c, d	1/8 (12.5%)

**Who paid for the data collection?**

a) Public payer	3/8 (37.5%)
b) Non-payer government agency	1/8 (12.5%)
c) Manufacturer	1/8 (12.5%)
d) Third party (eg academic institution)	0
Combination a, c, d	1/8 (12.5%)
Combination b, c,	1/8 (12.5%)
Combination a, b, c, d	1/8 (12.5%)

**Industry participants survey**

A total of 10 industry representatives responded from six different companies, with only one company reporting no experience in alternative market access schemes, and one company, Merck, describing their experience in five different countries in the region<sup>n</sup>. The main results of the industry survey are summarised in [Table 3](#).

**Experience with managed entry schemes**

As expected, of the five companies active in the region, most had experience with financial-based schemes (88%), of which most involved discounts or rebates (86%). Only one company, Biomarin, had experience with all three types of MES, and few had experience with outcome-based or evidence generation schemes. The majority of schemes were put in place to increase access to pharmaceuticals, most of which were not in the public domain, with the exception of KEYTRUDA® (pembrolizumab), an anti-PD-1 immunotherapy for non-small cell lung carcinoma, discounted by Merck for use in South Korea. The one device, the WATCHMAN left atrial appendage closure device, was funded under an access with evidence agreement with Boston Scientific in South Korea. Three companies had agreements in place in South Korea and Taiwan, with one company having agreements in Thailand, Hong Kong and India.

*n. Hong Kong, Malaysia, South Korea, India and Thailand. Note that Merck reported no alternative funding agreements in Malaysia. One survey from Merck described results of alternative funding mechanisms in Australia. This was not included in the analysis.*

Most companies cited multiple reasons as to why an MES was implemented, with only Pfizer citing a single reason, that the technology would have significant budgetary impact, for the funding of the pharmaceutical in question (not in the public domain). Reassuringly, the decision-making criteria for the implantation of an MES cited by industry representatives were similar to those cited by the agencies, with significant budgetary impact, uncertainty around cost-effectiveness and high clinical demand being the most frequent.

### Evaluating outcomes

When it came to data collection, three companies reported that they did not have an active role, two of which were involved in financial-based (discount/rebate) schemes; therefore, it was unlikely that data collection was a pre-requisite. One company only agreed to collect data, whilst four others collected data and provided data analysis, one through an independent third party. One of these companies also sponsored a clinical trial for the pharmaceutical in Thailand, with data generated to inform a cost-effectiveness analysis, whilst another provided a post-approval registry. Of the five participants actively involved in data collection and analysis, all five were interested in patient outcomes such as morbidity and mortality, with two interested in patient satisfaction and quality of life. Others were particularly interested in the clinical usefulness of the technology and change in patient management, as well as cost-effectiveness data, reduced health system costs and disinvestment opportunities.

When asked if any of the technologies had been added to the benefit package in the country where the MES was implemented, the majority of the agreements are still in an active phase and are yet to be completed (62.5%). However, one of these was for a technology that has been added to benefit packages in other countries in the region. The drug, KEYTRUDA® has successfully been added to the benefit package in South Korea after the completion of the financial-based scheme. When asked what proportion of the company's technologies have utilised an alternative funding approach in the Asian region, most respondents found it difficult to estimate, with the majority stating it was a small number. One estimate was less than five per cent, one less than 10 per cent and one (Biomarin) estimated that between 20 to 40 per cent of the company's technologies would be subject to a MES.

**Table 3** Survey results from industry participants

<b>What types of MES has your company had experience in the region with?</b>	
<b>Outcome-based scheme</b>	<b>3/9 (33.3%)</b>
Performance-based reimbursement scheme	2/3 (66.7%)
Risk-sharing agreement	1/3 (33.3%)
<b>Evidence generation scheme</b>	<b>2/8 (25%)</b>
Coverage with evidence development	1/2 (50%)
Access with evidence development	2/2 (100%)
<b>Financially-based scheme</b>	<b>7/8 (87.5%)</b>
Managed entry agreements	2/7 (28.6%)
Discounts and/or rebates	6/7 (85.7%)
<b>What were the technologies funded?</b>	
Pharmaceutical	6/8 (75%)
Device	1/8 (12.5%)
Diagnostic	1/8 (12.5%)
<b>In which country/countries was the MES implemented?</b>	
South Korea	3/8 (37.5%)
Taiwan	3/8 (37.5%)
Hong Kong	1/8 (12.5%)
India	1/8 (12.5%)
Thailand	1/8 (12.5%)

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**What was the decision-making criteria stated by policy-makers for the MES?**

Technology would have significant budgetary impact	7/8 (87.5%)
Insufficient clinical (safety/effectiveness) evidence to support widespread introduction and reimbursement of technology	3/8 (37.5%)
Uncertainty around economic analysis/cost-effectiveness of technology	6/8 (75%)
High public demand for technology	2/8 (25%)
High clinical demand for the technology	4/8 (50%)
Other High burden of disease	1/8 (12.5%)
Low treatment compliance	1/8 (12.5%)

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**Was your company actively involved in developing the evidence for this technology during this alternative access funding (post-regulatory) period by**

Sponsoring a clinical trial	1/8 (12.5%)
Provision of technology and consumables (free) for an initial trial period	0
Collecting data	5/8 (62.5%)
Providing data analysis	4/8 (50%)
Not involved	3/8 (37.5%)
Other (please specify) Post-approval registry	1/8 (12.5%)
Generating CE evidence	1/8 (12.5%)

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**What outcome data was required to be collected?**

Patient outcomes (reductions in morbidity/mortality)	5/5 (100%)
Reduced health system costs	1/5 (20%)
Demonstrated disinvestment from other technologies	1/5 (20%)
Change in patient management	1/5 (20%)
Clinician satisfaction	0
Patient satisfaction – quality of life	2/5 (40%)
Other (please specify) Cost-effectiveness	2/5 (40%)

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**Have any of the technologies been added to the benefit package in at least one country in the Asia region via the usual coverage processes after the MES?**

MES period not completed	5/8 (62.5%)
Only a price volume agreement	1/8 (12.5%)
Yes	1/8 (12.5%)

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**The final question in the agency survey was:**

*“Are there are issues you would like to raise or discuss during the Forum, especially the breakout sessions, in relation to the challenges of using these alternative funding mechanisms. These could be issues that you have experienced or ones that you envisage happening”.*

**In the survey completed by industry, participants were asked**

*“If you have experienced this approach in the Asia region and in other countries, in your opinion are there any factors that required special consideration when using an alternative access market approach in the Asia region compared with countries elsewhere?”*

The responses to these questions are listed here as potential talking points for discussions during the 2018 HTAi APF.

**Agency**

- The issue of governance/regulation for these alternative funding mechanisms
- Many low and middle-income countries have very weak regulatory framework and implementation to follow-up on these technologies after they are introduced. To complicate the issue, it is extremely difficult to withdraw a technology once it has been introduced as people get used to it.
- Is it ethical and safe to even consider such alternate market access mechanisms for fast tracking/introducing a new technology in countries with weak regulatory implementation capacities?
- Cost-sharing rationale and mechanisms
- How to discuss or bargain with industry for “irrational price”. For example, the price of human insulin is more expensive in Indonesia than in Thailand, while the price of analog insulin is lower in Indonesia than that in Thailand; as a result, analog insulin is used in Indonesia (99%).
- Patent issues on medical devices
- Coverage with evidence development
- The use of alternative funding mechanisms for high-cost non-pharmaceutical health technologies such as devices/diagnostics/procedures.
- The difficulty in sustaining disease registries and the possibility of collaboration in this area.
- How to decide the appropriate patient outcomes? Should overall survival or progression-free survival be used? Should QoL be considered?
- How to deal with uncertainty and incomplete information? Clinical trials developed for regulatory purpose may be insufficient to resolve payer uncertainty.
- When using managed entry agreements for new health technologies, what level of clinical

safety/effectiveness evidence is considered sufficient to support the widespread introduction and reimbursement of technology?

- The use of real-world evidence for economic evaluation to inform policy decision making
- Should a general threshold be applied in the case of high-cost medicines/devices or should there be a specific threshold?

### **Industry**

- Issues are data collection, organising ethics approval and compiling data from multiple sites
- Acceptance of international evidence rather than having to wait three to five years for the local real-world data
- The importance of landscape analysis for effective two-way dialogue between industry and payers to not only effectively predict new technologies that will impact healthcare budgets, but to also understand the size and scale of that impact, given the clinical needs of the population.
- Ability of the health IT infrastructure to effectively capture and analyse relevant data
- Meaningful data capture
- Consider the issues of cost effectiveness/health system value of a technology separately from the budget impact to the payer, otherwise there is a risk of undervaluing new technologies
- HTA methodologies have been evolving rapidly across Asia and it is essential for industry and HTA practitioners to engage robustly to develop sound approaches that accurately assess value
- Eliminating waste and low value care
- There are few true payers in Asia, and most have yet to develop the internal capability to execute such alternative market approaches

## Appendix 1 Health expenditure by country<sup>6</sup>

Country	Health expenditure per capita (US\$)		Health expenditure as a share of GDP (%)		Health expenditure per capita based on PPP*	
	2001	2015	2001	2015	2001	2015
Bangladesh	8	32		2.6%	29	88
Bhutan	33	91		3.5%	122	287
Cambodia	32**	70		6.0%	78	210
China	45	426	4.4%	5.3%	139	762
India	20	63	4.3%	3.9%	90	238
Indonesia	17	112		3.3%	108	369
Japan	2,876**	3,733	7.4%	10.9%	2,013	4,405
Laos	15	53	4.9%**	2.8%	119**	166
Malaysia	113	386	3.0%**	4.0%	374	1,064
Myanmar	3	59	1.9%**	4.9%	24	267
Nepal	11	44	4.4%	6.1%	57	151
Pakistan	14	38		2.7%		134
Philippines	28	127	2.7%***	4.5%	102	323
Singapore	707	2,280	3.2%	4.3%	1,322	3,681
South Korea	506	2,013	4.5%	7.4%	862	2,556
Sri Lanka	34	118	4.1%	3.0%	179	353
Taiwan†	60	227			241	600
Thailand	57	217		3.8%	231	610
Vietnam	23	117		5.7%	113	334

\* PPP= Purchasing power parity in international dollars, \*\* year = 2004, \*\*\* year = 2002

† <https://www.indexmundi.com/facts/thailand/health-expenditure-per-capita>, 2014



## Appendix 2 Policy and procedures on access to high-cost health technologies in Malaysia

### Malaysian Health System

The Malaysian health system is a 'mixed' system with public and private financing and health service provision and distinct governance, organisation, financing and payment arrangements for each sector. The public sector is based on a 'National Health System' model of government-organised health care financed through general revenues, with historical line-item budgets and a salaried staff made up of civil servants. On the private side, a mix of healthcare providers operate under a light regulatory regime, earning revenues primarily through fee-for-service, out-of-pocket payments by patients, and increasingly also through private insurance. Hence, access to health technologies can occur either through the public sector or the private sector.

### HTA in Malaysia

The Malaysian Health Technology Assessment Section (MaHTAS), Medical Development Division, Ministry of Health (MOH) was given the mandate to conduct HTA especially on new health technologies that have never been introduced in the MOH facilities that may have implications on national programme and policy, and existing health technologies where there are concerns about safety, efficacy or effectiveness, and economic implications. The scope of the health technologies includes drugs, medical devices, diagnostics, procedures and the organisational and support system. This is stipulated in a circular signed by the Director General of Health in 2000. Emphasis is given to high-cost health technologies. The HTA work process is illustrated in Figure 8.

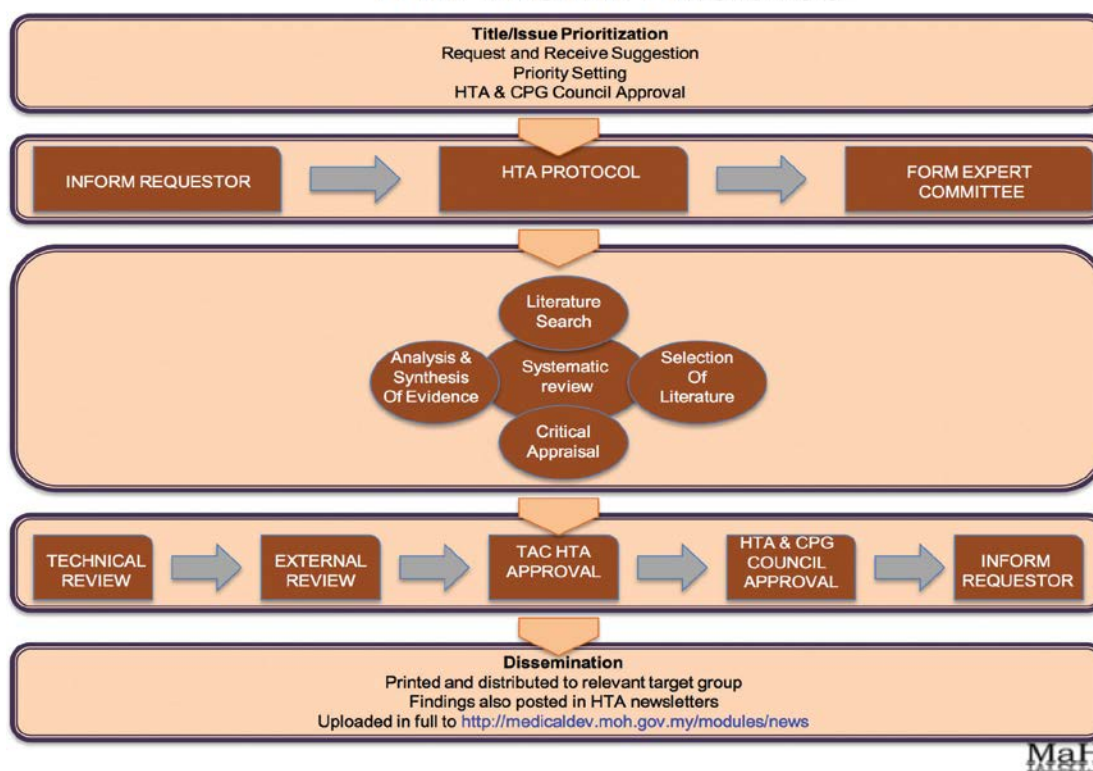
### Introduction of high-cost health technologies in Ministry of Health (MOH), Malaysia

The introduction of new health technologies especially for medical devices, procedures and programmes are increasingly informed (but not determined) by HTAs conducted by MaHTAS. This mechanism, which includes economic analysis, will result in a recommendation on the use, including conditionality or non-use of the technology. If a negative recommendation is provided, this generally means that the health technology will be excluded from use in MOH and by implication.

However, even though cost-effectiveness has been considered in the assessment, a positive recommendation does not automatically result in the inclusion of that health technology in the benefits package. Rather, it allows internal advocates to make a request for funding using the usual budgetary request mechanisms. If this is something 'new' (i.e., an addition to the historical line item budget), the request is referred to as a 'dasar baru' or new policy, and may even require approval by the cabinet (the highest body of the executive branch of the government). Funding may be partial, in which case implicit or explicit rationing mechanisms would be required, as the demand for such technologies exceed the supply. Importantly for the poor, a special fund called the medical assistance fund would use HTAs to determine if funding should be provided for the relevant health technology.

Benefits can also be removed by means of this HTA mechanism, as assessments can be conducted on older technologies with the view to review the current suitability and cost-effectiveness of such technologies, thus allowing for substitution by newer health technologies.

## HTA WORK PROCESS



MaHTAS

Figure 8 MaHTAS HTA work process

### Pharmaceuticals

The MOH has an existing formulary, commonly referred to as the 'blue book', which specifies which drugs can be purchased for and used at MOH facilities. The formulary defines the clinical indications whereby each drug may be used and the category of health personnel who may prescribe the drug. For example, 'A' category drugs, can only be prescribed by consultants and specialists, while 'B' drugs can also be prescribed by medical officers, and 'C' drugs can also be prescribed by paramedical staff (including a specific category for midwives).

Decisions to include or exclude drugs into the formulary are the remit of the Pharmaceutical Services Division of MOH. These are based on drug evaluations conducted by the division itself (not MaHTAS) three times a year, based on technical dossiers from the pharmaceutical industry. These decisions can also be informed, on an advisory basis, by the HTAs conducted by MaHTAS, especially on questions of cost-effectiveness, although the final decisions rest with the Pharmaceutical Services Division. If the drug in question has not been assessed, this division, like other government agencies, may make a request for a HTA assessment to MaHTAS. Inclusion of a drug within the MOH formulary does not necessarily mean that the drug would be fully funded nor, henceforth, available and available in adequate quantities in all MOH facilities and, hence, implicit and explicit rationing mechanism would also apply.

A huge amount of financial resources became a major hurdle in providing access to patients in need. These case studies provide examples of the mechanisms for the introduction of high-cost health technologies in MOH, Malaysia.

## Appendix 3 Surveys

### Industry survey

When there is a significant degree of uncertainty at the time of making coverage decisions around the clinical evidence, cost-effectiveness, budget impact, price or the eligible patient population for a particular technology, health policy-makers may enter into alternative market access agreements with manufacturers in order to introduce/fast track new or innovative technologies into health systems. These approaches are often used to introduce high-cost technologies with uncertain clinical evidence, potentially high spending, or to limit budget impact on payers. These alternative access mechanisms include:

1. **Outcome-based schemes** in which the price, level, or nature of reimbursement are tied to clinical or intermediate endpoints measured in the future and ultimately related to patients' quality or quantity of life.<sup>1</sup> For example, **Performance-based reimbursement schemes** where an arrangement between manufacturers and payers results in the performance of the product being tracked in a defined patient population over a specified period of time, and the level of reimbursement is tied by a formula to the outcome.<sup>2</sup> Or **Risk sharing agreements**: agreements between a payer and a manufacturer where the price level and/or revenue received is related to the future performance of the product in a real-world environment.<sup>3</sup>
2. **Evidence generation schemes** in which a positive coverage decision is conditioned upon the collection of additional evidence through clinical studies, which might result in continued, expanded, or withdrawn coverage.<sup>1</sup> For example: **Coverage with evidence development (CED)** or **Access with evidence development** (previously called conditional coverage) where the coverage of a treatment or technology is conditional on data being gathered through a clinical trial or registry to determine its effectiveness.<sup>4,5</sup>
3. **Financially-based schemes** negotiate company contributions to the cost of a product (e.g. price-volume agreements, utilisation caps) for a particular patient or population without linking reimbursement to health outcomes.<sup>1</sup> These include **Managed entry agreements (MEA)** where an arrangement is made between a manufacturer and payer or provider to reduce the risk incurred by health services, enabling coverage or reimbursement of a health technology subject to specific conditions: usually that (1) that the price of the technology be reduced through a range of different financial schemes and/or (2) that further data on usage of the technology will be collected.<sup>6,7</sup>

**Please double click the check boxes to make your selection, selecting all that apply.**

1. **Has your company ever had experience with alternative market access agreements in order to introduce a new healthcare technology into the publicly funded health system of a country in the Asia region?**
  - Yes
  - No

Only answer the following questions if your answer was YES and only thinking about some of your company's most recent healthcare technologies funded this way in the Asia region

**2. Were these alternative funding arrangements typically (tick all that apply):**

- Outcome-based scheme
  - Performance-based reimbursement scheme
  - Risk-sharing agreement
- Evidence generation scheme
  - Coverage with evidence development
  - Access with evidence development
- Financially-based scheme
  - Managed entry agreements
  - Discounts and/or rebates

**3. Were the technologies (tick all that apply):**

- Pharmaceuticals
- Devices
- Diagnostic tests

If this information is in the public domain, please name the technology.

**4. In which country/countries was this approach implemented? Check all that apply**

- |                                     |                                      |                                      |
|-------------------------------------|--------------------------------------|--------------------------------------|
| <input type="checkbox"/> Bangladesh | <input type="checkbox"/> Laos        | <input type="checkbox"/> South Korea |
| <input type="checkbox"/> Bhutan     | <input type="checkbox"/> Malaysia    | <input type="checkbox"/> Sri Lanka   |
| <input type="checkbox"/> Cambodia   | <input type="checkbox"/> Myanmar     | <input type="checkbox"/> Taiwan      |
| <input type="checkbox"/> China      | <input type="checkbox"/> Nepal       | <input type="checkbox"/> Thailand    |
| <input type="checkbox"/> India      | <input type="checkbox"/> Pakistan    | <input type="checkbox"/> Vietnam     |
| <input type="checkbox"/> Indonesia  | <input type="checkbox"/> Philippines |                                      |
| <input type="checkbox"/> Japan      | <input type="checkbox"/> Singapore   |                                      |

**5. What was/were the decision-making criteria stated by policy-makers for this funding approach (choose all that apply)**

- Technology would have significant budgetary impact
- Insufficient clinical (safety/effectiveness) evidence to support widespread introduction and reimbursement of technology
- Uncertainty around economic analysis/cost-effectiveness of technology
- High public demand for technology
- High clinical demand for the technology
- Other (please state)

6. **Was your company actively involved in developing the evidence for this technology during this alternative access funding (post-regulatory) period by**
- Sponsoring a clinical trial
  - Provision of technology and consumables (free) for an initial trial period
  - Collecting data
  - Providing data analysis
  - Other (please specify)
7. **What outcome data was required to be collected?**
- Patient outcomes (reductions in morbidity/mortality)
  - Reduced health system costs
  - Demonstrated disinvestment from other technologies
  - Change in patient management
  - Clinician satisfaction
  - Patient satisfaction – quality of life
  - Other (please specify)
8. **Have any of the technologies been added to the benefit package in at least one country in the Asia region via the usual coverage processes after the alternative access funding period?**
- Yes
  - No
9. **If any technologies weren't added to the benefit package after the alternative access funding period, what were the reasons for this? Please specify.**
10. **If you have experienced this approach in the Asia region and in other countries, in your opinion are there any factors that required special consideration when using an alternative access market approach in the Asia region compared with countries elsewhere?**
11. **What proportion of your company's technologies would you estimate have utilised one of these alternative funding approaches in the Asian region?**

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## Agency survey

When there is a significant degree of uncertainty at the time of making coverage decisions around the clinical evidence, cost-effectiveness, budget impact, price or the eligible patient population for a particular technology, health policy-makers may enter into alternative market access agreements with manufacturers in order to introduce/fast track new or innovative technologies into health systems. These approaches are often used to introduce high-cost technologies with uncertain clinical evidence, potentially high spending, or to limit budget impact on payers. These alternative access mechanisms include:

1. **Outcome-based schemes** in which the price, level, or nature of reimbursement are tied to clinical or intermediate endpoints measured in the future and ultimately related to patients' quality or quantity of life.<sup>1</sup> For example, **Performance-based reimbursement schemes** where an arrangement between manufacturers and payers results in the performance of the product being tracked in a defined patient population over a specified period of time, and the level of reimbursement is tied by a formula to the outcome.<sup>2</sup> Or **Risk sharing agreements**: agreements between a payer and a manufacturer where the price level and/or revenue received is related to the future performance of the product in a real-world environment.<sup>3</sup>
2. **Evidence generation schemes** in which a positive coverage decision is conditioned upon the collection of additional evidence through clinical studies, which might result in continued, expanded, or withdrawn coverage.<sup>1</sup> For example: **Coverage with evidence development (CED)** or **Access with evidence development** (previously called conditional coverage) where the coverage of a treatment or technology is conditional on data being gathered through a clinical trial or registry to determine its effectiveness.<sup>4,5</sup>
3. **Financially-based schemes** negotiate company contributions to the cost of a product (e.g. price-volume agreements, utilisation caps) for a particular patient or population without linking reimbursement to health outcomes.<sup>1</sup> These include **Managed entry agreements (MEA)** where an arrangement is made between a manufacturer and payer or provider to reduce the risk incurred by health services, enabling coverage or reimbursement of a health technology subject to specific conditions: usually that (1) that the price of the technology be reduced through a range of different financial schemes and/or (2) that further data on usage of the technology will be collected.<sup>6,7</sup>

**Please double click the check boxes to make your selection**

### 1. Which country does your agency represent?

- |                                    |                                      |                                   |
|------------------------------------|--------------------------------------|-----------------------------------|
| <input type="checkbox"/> Cambodia  | <input type="checkbox"/> Laos        | <input type="checkbox"/> Taiwan   |
| <input type="checkbox"/> China     | <input type="checkbox"/> Malaysia    | <input type="checkbox"/> Thailand |
| <input type="checkbox"/> India     | <input type="checkbox"/> Philippines | <input type="checkbox"/> Vietnam  |
| <input type="checkbox"/> Indonesia | <input type="checkbox"/> Singapore   |                                   |
| <input type="checkbox"/> Japan     | <input type="checkbox"/> South Korea |                                   |

Please double click the check boxes to make your selection, selecting all that apply.

2. When thinking about the cost of a technology (per device/procedure/patient) and overall annual budgetary impact of technology implementation, what would your country consider to be a high-cost technology AND would this definition differ depending if the technology was a pharmaceutical or device (see Appendix for guide on health expenditure per capita for your country).

**Pharmaceutical**

- 2.5 times the health expenditure per capita for your country
- 5 times the health expenditure per capita for your country
- >10 times the health expenditure per capita for your country

**Device**

- 2.5 times the health expenditure per capita for your country
- 5 times the health expenditure per capita for your country
- >10 times the health expenditure per capita for your country

**Other** (please specify) Note – see appendix for rates of health expenditure as a share of GDP (%) and as per capita based on PPP (purchasing power parity in international dollars)

3. Can you briefly describe the challenges that your country faces in providing access to high-cost technologies? Please include any discussion points you think relevant for the Forum.
4. Does your country have an explicit, written policy that addresses alternative market access agreements such as those defined above? (note, if Yes, can you please provide this to the Secretariat)
- Yes (for all conditions/technologies)
  - Yes (for certain conditions/technologies)
  - No
5. If No, is this something that your country is interested in developing?
- Yes in the next 1-2 years
  - Yes in the next 3+ years
6. Has your country ever introduced a new health technology using one of these alternative market access agreements?
- Yes
  - No

If you answered Yes to Q6, please answer the following questions, considering the most recent technologies that have been funded in this way (in the last 3 years).

**7. Are the most recent examples a (check all that apply)**

- Pharmaceutical
- Device
- Diagnostic test

If this information is in the public domain, please name the technologies and conditions

**8. What were the most common decision-making criteria for this alternative funding approach (choose all that apply)**

- Technology would have significant budgetary impact
- Insufficient clinical (safety/effectiveness) evidence to support widespread introduction and reimbursement of technology
- Uncertainty around economic analysis/cost-effectiveness of technology
- High public demand for technology
- High clinical demand for the technology
- Other (please state)

**9. What outcome data would usually be required to be collected?**

- Patient outcomes (reductions in morbidity/mortality)
- Reduced health system costs
- Demonstrated disinvestment from other technologies
- Change in patient management
- Clinician satisfaction
- Patient satisfaction – quality of life
- Other (please specify)

**10. Who had responsibility for data collection?**

- Public payer
- Non-payer government agency
- Manufacturer
- Third party (eg academic institution)

**11. Who paid for the data collection?**

- Public payer
- Non-payer government agency
- Manufacturer
- Third party (eg academic institution)



12. **Are there are issues you would like to raise or discuss during the Forum, especially the breakout sessions, in relation to the challenges of using these alternative funding mechanisms. These could be issues that you have experienced or ones that you envisage happening.**
  
13. **What proportion of new healthcare technologies entering your publicly funded health system would utilise one of these alternative funding approaches?**

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