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Improving Access to Orphan Drugs in Malaysia

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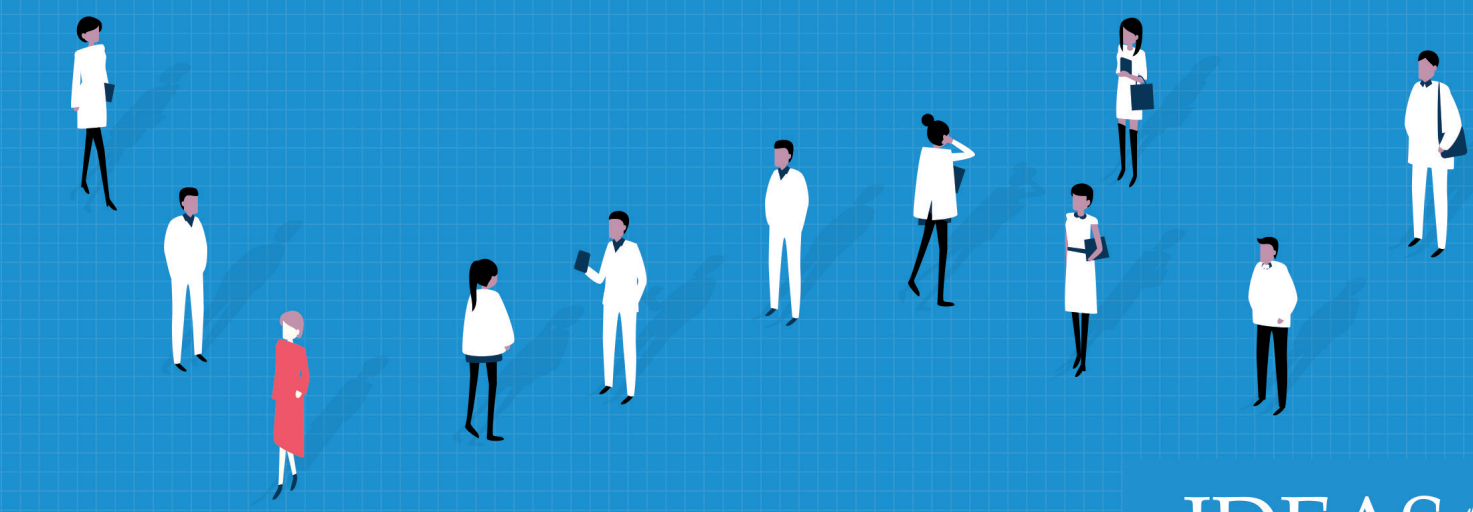

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Executive Summary

A rare disease is any disease that affects a small percentage of the population and are frequently debilitating to patients. Timely access to the right treatment is crucial for effective disease management and delayed access contributes to poorer treatment outcomes and more severe disease complications. This policy paper "Improving access to orphan drugs in Malaysia" explores the challenges associated with accessing orphan drugs in Malaysia and proposes ways in which we can improve patient access to these drugs.

We explore the current situation, which includes difficulty in receiving diagnosis and obtaining treatment in time due to the lack of expertise along with limited treatment options. Orphan drugs are harder to obtain than other conventional drugs due to lack of economic incentive for manufacturers to develop drugs which can be attributed to the small market. This leads to orphan drugs being marketed at very high prices due to an absence of economies of scale in its sale. Low prevalence of the disease within healthcare settings and population in general results in a lack of understanding among physicians. The low prevalence makes it difficult to improve knowledge on the safety and efficacy of treatments through proper studies.

The paper explores different solutions to address these problems through two broader themes: controlling the high price of drugs and increasing the budget for orphan drugs. The solutions proposed under these themes are briefly outlined below;

Controlling high prices of drugs

- Drug prices could be controlled through a more appropriate application of the Health Technology Assessment (HTA) for drug price negotiation to better reflect the unique characteristics of rare diseases. Taking into account disease severity and lack of suitable alternative treatment would yield more accurate national value assessments.

- A Management Entry Agreement could be implemented to ensure early access to drugs at a reasonable price.

- The government could also establish a regional network to boost purchasing power and achieve economies of scale to obtain lower drug prices. However, this option needs to be scrutinised more closely due to differing economic status among members of ASEAN.

- Besides that, compulsory or voluntary licensing on orphan drugs could be implemented to purchase these drugs at a cheaper price.

- In relation to advancing research for discovery of orphan drugs, Malaysia could explore pooled funding options to reduce risk associated with investment in the development of drugs.

Increasing the budget for orphan drugs

- ☑ Increase awareness surrounding rare diseases through the engagement of multiple stakeholders including politicians, policymakers, ministries, healthcare providers, families, the public and patient advocacy groups.
- ☑ Establish a co-payment system where patients within the public health system pay for part of their treatment.
- ☑ Form partnerships with private insurance companies and explore appropriate methods to reduce patient's financial burden. Specific policies could be introduced in the form of private insurance or social insurance schemes.
- ☑ Ring-fence allocations could be established for an existing fund or through the creation of a trust fund that pools resources from different organisations.
- ☑ A mortgage could be applied to orphan drugs through an agreement between healthcare payer and drug manufacturer. This would allow the cost to be spread over the period during which it would accrue the benefits of the reduced downstream costs from averted diseases.

In conclusion, there is a need to establish a separate fit-for-purpose framework to evaluate and fund rare diseases. The government should explore a new financial model to ensure rare disease patients receive the care they need as outlined in this paper. The government should also improve the access of treatment for patients of rare diseases, through various measures such as internal funding for rare diseases, which should be transparent and inclusive.

Introduction

A rare disease is any disease that affects a small percentage of the population. There are about 6,000 to 8,000 rare diseases in the world, and they are frequently debilitating to patients. While rare diseases are characterised by their rarity (less than 1:2,000 in Europe), collectively they affect 1 in 15 persons worldwide, which amounts to 400 million patients worldwide (Institute of Medicine, 2010; Kaplan et al., 2013; Song, 2012). Rare diseases are difficult to diagnose due to their heterogeneous and variable presentations as well as the lack of local population data on these conditions. In addition, the lack of medical expertise and laboratory support services often result in misdiagnosis or delayed diagnosis of rare conditions (Lee and Thong, 2013).

Timely access to the right treatment is crucial for effective disease management in modern health care. Delayed access contributes to poorer treatment outcomes, more severe disease complications, poorer quality of life and higher management cost (Weissman, 1991; Aghamohammadi et al., 2011). The vast majority of rare diseases do not have any medicinal treatment options, so patients only receive symptomatic treatment or non-therapeutic care. Appropriate treatment and support services can improve patients' quality of life and extend their life expectancy. Even if a suitable treatment for a rare disease is available in the formal care sector, the high cost of medicine could limit patients' access to treatment.

Access to treatment can be delayed for many reasons. Some of them are beyond the control of policymakers, e.g. reluctance of patients to seek treatment; some obstacles, however, can be overcome through changes in the approaches or policies within an institution or country. To facilitate the discussion, it is important to understand the structure that can affect access to drugs in a modern health care system.

There are two main stages to treatment access in health care. First, the drugs for a specific disease are developed and manufactured by the pharmaceutical industry. A drug can only be sold when it has received market authorisation by the relevant drug regulatory authority, after a review of documents on its safety, efficacy and quality. In Malaysia, the National Pharmaceutical Regulatory Authority (NPRA) holds this responsibility. Thus, the *availability* of a drug could be defined more specifically as a drug that has obtained market authorisation (Blankart, Stargardt and Schreyögg, 2011). Once authorised, a drug can then be obtained through recognised channels within a country. Countries with public financing systems can decide to pay for the drug on behalf of its citizens. This is usually done through a systematic appraisal of the efficacy, safety and cost-effectiveness of the drugs, a process known as Health Technology Assessment (HTA) (Luce et al., 2010; Teerawattananon et al., 2018). In the Malaysian public health system, HTAs for reimbursement of drugs are done through the Pharmaceutical Services Programme (PSP).

The *accessibility* to drugs, then, is defined as enabling an individual to obtain and receive a drug within their financial and physical ability (Gammie, Lu and Babar, 2015). Therefore, accessibility to a drug depends on the drug's reimbursement status, price, and coverage status as determined through the HTA process.

Orphan drugs (ODs) have specific traits that distinguish them from other therapeutic areas:

1. Lack of manufacturers' interest in drug development

A rare disease is difficult to diagnose and only affects a small percentage of the population. Because of the small market, there is a lack of economic incentive to develop drugs for rare diseases. Only 10% of rare diseases have specific treatments and others have no treatment options available.

2. High price of drugs

The low prevalence of rare diseases results in the absence of economies of scale in its sale. Hence, ODs are often marketed at very high prices that frequently exceed the cost effectiveness threshold (incremental cost per benefit gained) in the HTA (Towse and Garau, 2018). There are a few factors that contribute to the extraordinary price of ODs: the manufacturers' need to recover the development expenditures of ODs, the market exclusivity (patent protection) that allows authorisation holder to set high prices, and the absence of an oversight body to control prices (Picavet, Cassiman and Simoens, 2013). Almost all rare disease patients need support from the government or other parties as the cost of treatment can easily reach millions of ringgit per year.

3. Lack of evidence base

Generally, awareness levels among physicians about rare diseases are still low compared to their familiarity with other diseases. This is mainly due to the low number of rare disease cases in clinics or hospitals, and the lack of emphasis in medical school curricula. The lack of laboratory support services and the low prevalence of rare diseases also make it difficult to collect enough samples for a proper study of the safety and efficacy of treatment. For instance, detecting a doubling in an adverse event that occurs at a rate of 1/1000 would require a sample size of 50,000.

In order to promote the development of drugs for rare diseases, some countries provide special designation for ODs that entitle manufacturers to a generous economic incentive. This includes providing tax breaks, lowered fees, research support, and a seven-year exclusivity period for emerging therapies. For drug developers, these incentives are highly attractive. In 1983, the US government legislated the Orphan Drug Act (Herder, 2017). This package includes a 50 percent discount on research costs, which equates to $30 million a year in grants and fee waivers. The introduction of such a package in the formation of the Orphan Drug Act 1983 saw the development of more than 250 ODs as compared to only 10 before its legislation. A similar regulation introduced in Europe saw 65 drugs introduced from January 2010 to July 2011. In Asia, South Korea listed 58 (48%) orphan or cancer drugs over seven years (2007-2013) through the National Health Insurance Corporation (NHIC) negotiation process. In addition, these drugs became more accessible to patients when the Risk Sharing scheme was implemented in 2013 (Kim et al., 2014).

How do rare disease patients access drugs in Malaysia?

In Malaysia, the NPRA updated their Drug Registration Guidance Document (DRGD) in September 2016 (National Pharmaceutical Regulatory Agency, 2016). This second edition included a new section for the registration of orphan products, with a special registration number or additional special alphabet for the purpose of surveillance and monitoring. However, there is no economic incentive provided for development or supply of ODs. There is also no special consideration for the listing of ODs in the national formulary, i.e. ODs have to follow the same procedures and consideration as other drugs.

The PSP, a secretariat in the Ministry of Health Medicine Formulary, reviews all evidence submitted by pharmaceutical companies and conducts in-house assessments. After a review by a technical working committee comprising of clinicians in the relevant subject area(s), the formulary listing decisions are decided by the Ministry of Health Medicines List Review Panel (MOHMLRP), which is chaired by the Director General of Health Malaysia.

Generally, ODs are at a disadvantage as the MOHMLRP rarely considers drugs that are designated for treating a small number of the population. A few drugs, however, have been successfully listed in the Ministry of Health Drug Formulary (MOHF). Since 2012, four ODs have been listed in MOHF for eligible patients in MOH facilities: Alglucosidase (Pompe disease), Idursulfase (Hunter syndrome-MPSII), Imiglucerase (Gaucher disease) and Laronidase (Hurler syndrome-MPSI). They belong to a class of drugs called enzyme replacement therapy (ERT) for treating patients with lysosomal storage disorders (LSD). Nevertheless, unlisted drugs or supplements can be accessed for a short-term period by patients via special drug approval from the Director General of Ministry of Health, subject to budget availability. Examples are Galsulfase (registered product) for MPS type VI, Elosulfase (unregistered product) for MPS type IVA and Co-enzyme Q10 (supplement).

What is the current access to OD in Malaysia?

Many rare disease patients have been wrongly diagnosed due to a lack of expertise and awareness among doctors in Malaysia. Some patients only find out their actual diagnosis after five to 20 years of suffering with the rare diseases. Unfortunately, some of these patients have to wait three to five years after diagnosis to obtain medicine, especially those who require ERT. In our recent study, we found that only about 60% of rare disease patients in Malaysia are receiving treatment (Shafie et al., 2018). It has been challenging to provide ERT for patients with confirmed diagnosis of LSD. Despite ERT being listed in the formulary, not all patients are prescribed ERT as the budget is very limited. Only 28% of LSD patients get their ERT. treatment. About half of them are subsidised by MOH and the rest are sponsored by pharmaceutical industries (Patient Assistance Programmes) and donations from the public. However, the sustainability of sponsorship and donation is not guaranteed. Some patients have already been on the waiting list for more than three years. Furthermore, newer ODs which were discovered and approved as recently as 2016 by the Food and Drug Administration (FDA), such as Nusinersen, have yet to be accessed by any spinal muscular atrophy patients.

How to improve access for OD in Malaysia?

Generally, there are two main factors that limit access to ODs in Malaysia: high price of ODs and insufficient budget to procure ODs for all eligible patients. A study published in 2011 found that the median price of ODs (EUR138.56) is higher than that of non-ODs (EUR16.55) (Picavet et al., 2011). The higher price of ODs is often attributed to the uncertainty for the pharmaceutical industry to recoup their development cost, given the small market size for ODs. Current literature shows that the price of an OD is related more closely to its rarity and what the manufacturer believes the market will bear (Picavet, Cassiman and Simoens, 2013). Efforts by health authorities to control prices, however, are often challenged by the question on the most appropriate mechanism or basis to set the price of an OD. The appropriate price should ideally be a balance between affordable pricing of the drug and securing a realistic return of investment to the industry.

Hence, we have listed a few options to remedy the issues.

Controlling High Price of OD

1. Appropriate Use of Health Technology Assessment (HTA) to Negotiate Drug Price

HTA is a technical and systematic process that evaluates the properties, impact and consequences of health technology. At present, HTA is only used in the listing process. The pricing of drugs for Ministry of Health (MOH) facilities is done separately by the Medicine Pricing Branch, after the drug has been listed in the national formulary. Consequently, the price negotiation process might not be able to benefit from the extensive evaluation conducted during the listing process. As a result, the negotiated price might not capture the actual value (benefit and risk of the drug) and uncertainties of the drug.

The use of HTA for price negotiation hinges on the ability of the process to capture the accurate value of a product. The committee members of MOHMLRP may have never encountered a particular rare disease and may have no specific knowledge of the patient experience. As such, the committee members might not be able to ascertain the accurate value of an OD. Even though opinions from rare disease experts are sought, their presence is not required in meetings on evidence deliberation or decision-making. Input from multiple disease experts and centres may be required, not just from clinicians but also nurse experts who can often provide additional context on the full care pathway for patients, beyond pharmaceutical management.

Furthermore, patients are not formally engaged in the HTA process in Malaysia. However, their involvement is critical in the case of rare diseases because the difficulty that they experience when obtaining appropriate care means that they often have no choice but to become experts in their own condition. The absence of published evidence can be partially redressed by first hand testimony on the patient experience. This can help policymakers to understand the relevance and context of unfamiliar clinical endpoints or key specificities of rare diseases and ODs, especially those that are essential to their value but are not consistently considered in national value assessments, such as disease severity, the lack of suitable alternative treatment (unmet need) and rarity.

Evidence from budget impact analysis (BIA), a tool to estimate the financial consequences of adopting a new drug, often forms the bulk of economic evidence in Malaysia's HTAs. The MOH uses BIA findings to decide affordability of the drug. However, it is important to assess the affordability keeping the total population of the patients in mind. For rare diseases, even though the unit cost is high, the total number of patients is low, resulting in a situation where total expenditure is relatively on par with other diseases.

The HTA on ODs should consider all relevant elements of value, not only evidence of efficacy, safety, and budget impact of drugs. Hence, other than BIA, elements of value such as rarity and unavailable alternatives might be unique to ODs, which are additional points to consider in the decision-making process.

In conventional HTA, various criteria are considered separately and the value of the product is formed subjectively. Recently, a new method that objectively aggregates individual criteria has been actively explored by various HTA agencies as an alternative to the conventional HTA method. The method, known as Multi-Criteria Decision Analysis (MCDA) allows clear trade-off between various criteria from different stakeholders which is useful as a support tool in complex decisions. This provides a formal framework for HTA authority to incorporate wider aspects of value criteria. In highly-priced treatment options, MCDA can be used to set the priority of allocation among the diseases. MCDA criteria can include severity of diseases, availability of treatment or alternatives, and the quality of patients' life.

Value mechanisms should be flexible to accommodate evidential uncertainty at time of HTA. Because of the rarity of rare diseases, the pool of rare disease patients is hardly enough to satisfy the sample size required for robust evidence used in HTA.

If used, the incremental cost-effectiveness ratio (ICER) thresholds should be modulated to reflect the specificities of rare diseases and ODs. Instead of a fixed threshold of cost effectiveness, the HTA agency can consider a higher threshold to reflect higher values placed on the unique characteristics of rare diseases (Lim et al., 2014). A similar modifier was applied in the United Kingdom when considering treatment that can extend patients' life within a small pool of the population (Collins and Latimer, 2013).

2. Implementing Managed Entry Agreement to Ensure Early Access at a Reasonable Price

The stringent evidence-based requirement for market access could result in delayed access to ODs. Existing evidence might not have enough statistical power to mitigate uncertainty regarding the clinical risk and utilisation pattern of the drugs. A Managed Entry Agreement (MEA) describes a range of mechanisms by which pharmaceutical firms and payers share some of the financial and clinical risk associated with the introduction of a new medicine. Financial-based MEAs refer to simple price-volume agreements (lower than official price) between the payer and supplier. Performance-based MEAs are schemes that agree on predefined utilisation pathways or expected health outcomes to be achieved. These schemes are increasingly utilised as an alternative approach to provide coverage with restrictions for drugs that may not otherwise be covered (Montilva, Xue and Degun, 2016). In Italy, in order to manage the budget impact of its introduction to the payer, betaquilina is approved for multidrug resistant tuberculosis through the use of a financial-based MEA. MEAs are still relatively new in the Asia Pacific region, with Australia being the only country that has linked MEAs with their reimbursement system. Eight ODs have been approved in Australia through this scheme.

Recently, in 2018, the Malaysia Ministry of Health introduced guidelines for the Patient Access Scheme (PASc) in order to improve access to medicines which are likely to have a high budget impact, either due to high treatment cost per patient and/or large volumes of use (economy of scale to reduce price) (Pharmacy Practice & Development Division Ministry of Health Malaysia, 2018). This scheme involves innovative pricing agreements that are designed to improve cost effectiveness and facilitate patient access to specific medicines.

On the other hand, this scheme requires high (and costly) administrative efforts and needs to be accompanied by a clear strategy as pharmaceutical firms tend to preemptively inflate the initial prices of drugs.

3. Economy of Scale through Regional Purchasing Power

The problem with low numbers of rare disease patients is that a country will never have enough patients to achieve the economies of scale required to lower drug prices. Hence, Malaysia and its neighbouring countries could establish a network to improve the regional sourcing of drugs and volume for greater purchasing power.

We can learn from other regions for best practices of pooled procurement. For example, The Organisation of Eastern Caribbean States (OECS) Pharmaceutical Procurement Service has established a small population of patients (0.7 million people) from nine OECS member states since 1986 (Organisation of Eastern Caribbean States, 2016). This pooled procurement and management of pharmaceuticals and medical supplies serves to leverage their bargaining power to achieve economies of scale. Another example is the procurement of vaccines by the Pan American Health Organisation (PAHO)'s Revolving Fund. The fund procures vaccines for 41 countries and territories in Latin America and the Caribbean using funds primarily provided by national budgets. Aggregating demand from so many countries allows PAHO's Revolving Fund to negotiate low vaccine prices for eligible countries. However, the primary challenge for such regional procurement is the collective agreement on definitions of OD or rare disease. PAHO's Revolving Fund solves this issue by only procuring WHO-prequalified vaccines.

Nevertheless, this option needs to be scrutinised more closely as the economic status among members of ASEAN are varied.

4. Compulsory or voluntary licensing on OD

Compulsory licensing is one of the flexibilities in the Doha Declaration, which is the World Trade Organization's (WTO) agreement on the Trade-Related Aspects of Intellectual Property Rights (TRIPs Agreement). The declaration allows governments to produce a patented product without the consent of the patent owner (World Trade Organization, 2001). It affirms the right of governments in developing countries to take measures to protect public health and promote access to medicines. Malaysia, as a member of WTO since 1995, has used this compulsory licensing twice; in 2003, for HIV/AIDS medicines patented by GlaxoSmithKline and Bristol-Myers Squibb (World Health Organisation, 2014) and recently, in 2017, for the hepatitis C Sofosbuvir 400mg tablet patented by Gilead Science (Ministry of Health Malaysia, 2017). This TRIPs flexibility reduced the cost of three patented drugs for HIV/AIDS and Sofosbuvir by 81% and 99% respectively. With these precedents, the government can use the same measures for ODs. Issuing compulsory licenses often ends with political rhetoric and threats of trade retaliation; nevertheless, this allows governments to negotiate price reduction or propose another method called voluntary licensing, in which the agreement between the patent holder and other manufacturers in developing countries permits the production of generic versions of a drug. This may reduce the cost of ODs as well as offer opportunities to the patent owner and the licensee.

5. Financing Drug Discovery for ODs

Pooled funding for OD discovery is one option that could reduce the risk associated with investing in OD development. Malaysia could join an international consortium to fund development of ODs. Pooled funding is a "financial investment fund in which investors commit capital to develop a portfolio of OD and receive the proceeds of these investigational drugs or intellectual property rights as they are sold to venture capitalists or licensed by pharmaceutical companies". The idea was investigated in a simulation study and is expected to yield reasonable return rates of 5% and 8% for senior and junior bondholders. This could be used as an income for countries or to negotiate lower prices for ODs. However, the investment carries higher risk for early-stage projects that could be far from market authorisation; hence, investors have no discernible royalty stream at the time of investment. As a result, the risk is much higher as projects progress from the preclinical stage into clinical trials.

Increasing Budget for OD

1. Increase Awareness Among Stakeholders

Awareness is a critical factor to increase the budget for orphan drug as national/hospital budget allocation is often decided in a restricted space of representatives e.g. parliament. Raising awareness and engaging all stakeholders is not a simple matter. They may not know that the issue exists or may not understand the implications. They also may feel that rare disease is not a big issue and only affects a few people.

This important task requires the collaboration of all parties from top to bottom, including politicians, policymakers, ministries, healthcare providers, families, the public, and patient advocacy groups.

In Malaysia, continuous efforts from patient advocacy groups in their awareness campaigns have resulted in the new government promising to allocate MYR 50 million for the specific purpose of treating rare diseases and Hepatitis C, addressing stunting among children, providing more haemodialysis screening and treatments, and improving Enhanced Primary Healthcare under strategy six (Enhancing Health and Social Welfare Protection) in the 2019 Budget. Even though these measures are far from enough to address the existing issues, it is a good start to increase activities in raising awareness among key stakeholders.

Hopefully, this ongoing effort will gain attention among policymakers so that they understand the implications of delayed treatment and consider allocation of more money to treat more patients.

2. Co-payment

Co-payment is a fixed out-of-pocket amount paid by an insured person for covered services. In the context of Malaysia's public health system, this can refer to patients who remain in the public health facilities but pay for part of their treatment themselves.

This, however, can run contrary to the statutory requirement that public services are to be provided free at the point of delivery, unless specifically provided for otherwise by statute. There can also be potential problems in getting the medicines into the public health system because of strict rules about accepting "donations".

On the other hand, all ODs are extremely expensive and ordinary people would not be able to afford ODs even if they only co-pay a small fraction of the actual cost. In addition, the treatments for rare diseases are usually lifelong and future funding cannot be guaranteed. To introduce co-payment schemes, the government should study and review the reasonable affordable cost to the patients.

3. Insurance for funding OD

Introducing rare diseases to the list of critical illnesses will result in higher cost of general insurance premium as the cost of ODs can reach millions per patient every year. Discussions between the government and insurance companies need to be held to examine the most appropriate methods to alleviate the burden of patients, for example:

- A policy specifically to cover the cost of buying non-public funded ODs (other than ERT). This could be offered through private insurance or the newly introduced B40 social insurance scheme.

- In order to improve the affordability and lower the risk of private or social insurance, the government can underwrite reinsurance schemes for specific attachment point of the drug cost, such that it is paid based on cost in public facilities.

4. Ring-fence Allocation for ODs

Ring-fence allocation refers to protection of funds for use in a specific area. This can be established as specific allocation of an existing fund or creating a trust fund that pools resources from different organisations or donors. This allows treatment security for the patients. Examples of countries adopting this approach include Australia (Life Saving Drug Program) and the United Kingdom (Cancer Drug Fund). In the United Kingdom, the fund is used (together with MEAs) as interim funding while collecting evidence for HTA prior to routine commissioning.

The financial model, however, is frequently criticised for being intrinsically unfair and unsustainable. In the Malaysian context, the MOH, as the biggest budget controller for healthcare, has to allocate the optimum required amount accordingly and reduce unnecessary or non-urgent expenses.

5. Mortgage

A mortgage is the amortisation of a high, front-end cost over time. Mortgages have been used for other consumer products for a long time. The same financial model can be applied to ODs. This allows the cost to be spread over the period during which it would accrue the benefits of the reduced downstream costs from averted diseases.

In this model, a healthcare payer enters into an agreement with a drug manufacturer, with terms that enable the payer to pay the costs of the treatment in prescribed milestones. The manufacturer, in turn, will receive revenue on the same schedule or based on agreed-upon financing measures.

This model is still at the proposal stage and has not been adopted by any country.

Conclusion & Recommendations

The Malaysian National Medicines Policy (MNMP) aims to promote equitable access and rational use of safe, effective and affordable medicines (Ministry of Health Malaysia, 2012), while simultaneously safeguarding the long-term financial sustainability of the Malaysian health system. Achieving the objective is a huge challenge for every health care system and in any therapeutic area. Ultimately, the impact is worst for rare disease patients as there are no other alternatives for treatment.

There is a need to establish a separate fit-for-purpose framework to evaluate and fund rare disease therapies, drawing on other countries' experiences in decision-making. A new financial model (as outlined here) should be explored to ensure rare disease patients receive the care that they need. This will provide assurance for the relevant industries to continue investing in such treatments, as well as ensure that funding recommendations are reflective of Malaysian values, balanced against the need for financial sustainability. The steps taken should not only ensure access to innovative treatment but should also be done in a timely manner.

All the financing options discussed above are valid options for the country. We are not dismissing any options given possible impending changes to the national health care financing system. Some of the options, however, can be pursued immediately while others might take a longer time and require more resources. Many of the options discussed above, particularly those that increase the budget, require complex structural and legislative change to the current system. Pooled drug discovery research funding, for example, requires agreement of royalty sharing and creation of sophisticated financing tools to capture the variable risk at different stages of drug development. Insurance funding and co-payment, though attractive options to increase the budget, require structural change to the current health care financing that allows its administration in public health facilities. In addition, the exact mechanism through which the insurance scheme can be implemented and managed necessitates a thorough discussion between the MOH and insurance industry. As such, in the short run, we believe that the government can consider implementing the following options:

- ☑ Appropriate use of Health Technology Assessment (HTA) to negotiate drug price
- ☑ Implementing Managed Entry Agreement (MEA) to ensure early access at reasonable price
- ☑ Increasing awareness of rare diseases among stakeholders.

In the long run, discussions and dialogues can be held with related stakeholders on the implementation of regional purchasing, co-payment and insurance intervention in the country.

Other measures that are to be carried out by the government to improve access of treatment to patients of rare diseases, such as internal funding for various rare diseases, should be transparent and inclusive. Rare diseases consist of various diseases with different treatments. At present, access to treatment varies between rare diseases, with certain diseases receiving the bulk share of government allocation. Internal distribution of funding is needed to be aligned with epidemiology and burden of care.

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